



*PG Textbook of*  
**PEDIATRICS**

VOLUME **1**  
**GENERAL PEDIATRICS  
AND NEONATOLOGY**

Piyush Gupta  
PSN Menon  
Siddarth Ramji  
Rakesh Lodha





# PG Textbook of **PEDIATRICS**



# PG Textbook of **PEDIATRICS**

## Volume 1

### GENERAL PEDIATRICS AND NEONATOLOGY

**Piyush Gupta** MD FAMS FIAP

Professor

Department of Pediatrics  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**PSN Menon** MD FIAP

Consultant and Head  
Department of Pediatrics  
Jaber Al-Ahmed Armed Forces Hospital  
Kuwait

**Siddarth Ramji** MD FNNF

Director-Professor  
Department of Neonatology  
Maulana Azad Medical College  
and Associated Lok Nayak Hospital  
New Delhi, India

**Rakesh Lodha** MD

Additional Professor  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India



JAYPEE

*The Health Sciences Publisher*

New Delhi | London | Philadelphia | Panama



**Jaypee Brothers Medical Publishers (P) Ltd.**

#### Headquarters

Jaypee Brothers Medical Publishers (P) Ltd.  
4838/24, Ansari Road, Daryaganj  
New Delhi 110 002, India  
Phone: +91-11-43574357  
Fax: +91-11-43574314  
E-mail: jaypee@jaypeebrothers.com

#### Overseas Offices

J.P. Medical Ltd.  
83, Victoria Street, London  
SW1H 0HW (UK)  
Phone: +44-20 3170 8910  
Fax: +44(0) 20 3008 6180  
E-mail: info@jpmedpub.com

Jaypee-Highlights Medical Publishers Inc.  
City of Knowledge, Bld. 237, Clayton  
Panama City, Panama  
Phone: +1 507-301-0496  
Fax: +1 507-301-0499  
E-mail: cservice@jphmedical.com

Jaypee Medical Inc.  
The Bourse  
111, South Independence Mall East  
Suite 835, Philadelphia, PA 19106, USA  
Phone: +1 267-519-9789  
E-mail: jpmed.us@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd.  
17/1-B, Babar Road, Block-B, Shaymali  
Mohammadpur, Dhaka-1207  
Bangladesh  
Mobile: +08801912003485  
E-mail: jaypeedhaka@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd.  
Bhotahity, Kathmandu, Nepal  
Phone: +977-9741283608  
E-mail: kathmandu@jaypeebrothers.com

Website: [www.jaypeebrothers.com](http://www.jaypeebrothers.com)  
Website: [www.jaypeedigital.com](http://www.jaypeedigital.com)

© 2015, Piyush Gupta

The views and opinions expressed in this book are solely those of the original contributor(s)/author(s) and do not necessarily represent those of editor(s) of the book.

All rights reserved. No part of this publication may be reproduced, stored or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission in writing of the publishers.

All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book.

Medical knowledge and practice change constantly. This book is designed to provide accurate, authoritative information about the subject matter in question. However, readers are advised to check the most current information available on procedures included and check information from the manufacturer of each product to be administered, to verify the recommended dose, formula, method and duration of administration, adverse effects and contraindications. It is the responsibility of the practitioner to take all appropriate safety precautions. Neither the publisher nor the author(s)/editor(s) assume any liability for any injury and/or damage to persons or property arising from or related to use of material in this book.

This book is sold on the understanding that the publisher is not engaged in providing professional medical services. If such advice or services are required, the services of a competent medical professional should be sought.

Every effort has been made where necessary to contact holders of copyright to obtain permission to reproduce copyright material. If any have been inadvertently overlooked, the publisher will be pleased to make the necessary arrangements at the first opportunity.

**Inquiries for bulk sales may be solicited at:** [jaypee@jaypeebrothers.com](mailto:jaypee@jaypeebrothers.com)

#### **PG Textbook of Pediatrics (Volume 1)**

First Edition: **2015**

ISBN: 978-93-5152-725-1

Printed at

**Dedicated to**  
*Children of India*  
*and*  
*Those Who Care for Them*



# Section Editors

---

**M Zulfikar Ahamed** MD DM  
Professor and Head  
Department of Pediatric Cardiology  
SAT Hospital, Government Medical College  
Thiruvananthapuram, Kerala, India  
*Cardiovascular Disorders*

**Satinder Aneja** MD FIAP  
Director-Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India  
*Neurological Disorders*

**Brijesh Arora** MD DM  
Professor  
Department of Pediatric Oncology  
Tata Memorial Hospital  
Mumbai, Maharashtra, India  
*Malignancies in Children*

**Arvind Bagga** MD FIAP FAMS  
Professor  
Division of Nephrology  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India  
*Disorders of the Kidney and Urinary Tract*

**Shripad Banavali** MD  
Professor and Head  
Medical and Pediatric Oncology  
Tata Memorial Hospital  
Mumbai, Maharashtra, India  
*Malignancies in Children*

**Raghubir Banerjee** MD  
Associate Professor  
Department of Pediatric Dermatology  
Institute of Child Health  
Kolkata, West Bengal, India  
*Common Skin Problems*

**S Balasubramanian** MD DCH MAMS FRCPCCH FIAP  
Senior Consultant and Head  
Department of Pediatrics, Kanchi Kamakoti  
Child Trust Hospital and CHILDS Trust  
Medical Research Foundation  
Chennai, Tamil Nadu, India  
*Rickettsial and Other Infections*

**Sandeep B Bavdekar** MD DCH  
Professor and Head  
Department of Pediatrics  
TN Medical College and BYL Nair  
Charitable Hospital  
Mumbai, Maharashtra, India  
*Drugs and Therapeutics*

**Vijayalakshmi Bhatia** MD FIAP  
Professor of Endocrinology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India  
*Disorders of the Endocrine Glands*

**Sanjay Chaturvedi** MD FAMS FIAPSM FIPHA  
Professor and Head  
Department of Community Medicine  
University College of Medical Sciences  
New Delhi, India  
*Vulnerable Children*

**Sudha Chaudhari** DCH FAAP  
Professor of Pediatrics  
Consultant  
Department of Pediatrics and Neonatology  
TDH Rehabilitation and Morris Child  
Development Center, KEM Hospital  
Pune, Maharashtra, India  
*Development and Developmental Delay*

**VP Choudhry** MD FIAP FIMS FICM FISHTM  
Director  
Sunflag Pahuja Center for Blood Disorders  
Sunflag Hospital, Faridabad, Haryana, India  
Head, Department of Hematology  
Paras Hospital, Faridabad, Haryana, India  
and Former Professor and Head  
Department of Hematology  
All India Institute of Medical Sciences  
New Delhi, India  
*Disorders of Hematopoietic System*

**Jaydeep Choudhury** DNB MNAMS FIAP  
Associate Professor  
Department of Pediatrics  
Institute of Child Health  
Kolkata, West Bengal, India  
*Basic Concepts of Infectious Diseases;  
Bacterial Infections*

**Pooja Dewan** MD MNAMS  
Assistant Professor  
Department of Pediatrics  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India  
*Laboratory Values and Drug Doses*

**Sandipan Dhar** MD DNB  
Professor and Head  
Department of Pediatric Dermatology  
Institute of Child Health  
Kolkata, West Bengal, India  
*Common Skin Problems*

**Ashok Kumar Dutta** MD FIAP  
Professor  
Department of Pediatrics  
School of Medical Sciences and Research  
Sharda University, Greater Noida  
Uttar Pradesh, India  
*Viral Diseases*

**KE Elizabeth** PhD MD DCH FIAP  
Professor and Head  
Pediatrics and Superintendent  
SAT Hospital, Government Medical College  
Thiruvananthapuram, Kerala, India  
*Nutrition and Nutritional Disorders*

**Apurba Ghosh** MD MRCP FRCPCCH FIAP  
Professor and Director  
Institute of Child Health  
Kolkata, West Bengal, India  
*Common Skin Problems*

**Sheffali Gulati** MD FIAP FIMS MNAMS  
Professor of Pediatrics and Chief  
Child Neurology Division  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India  
*Neuromuscular Disorders*

**Anju Gupta** MD  
Additional Professor  
Department of Pediatrics  
Advanced Pediatric Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India  
*Rheumatological Disorders*

**Neerja Gupta** MD DM  
Assistant Professor  
Division of Genetics  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India  
*Metabolic Disorders*

**Piyush Gupta** MD FAMS FIAP  
Professor  
Department of Pediatrics  
University College of Medical Sciences and  
Guru Teg Bahadur Hospital, New Delhi, India  
*Introduction to Pediatrics; Nutrition and  
Nutritional Disorders; Basic Concepts of  
Infectious Disease; Fever; Bacterial Infections;  
Viral Diseases; Protozoal Infections and  
Infestations; Fungal Infections; Rickettsial and  
Other Infections; Community Pediatrics*

**Harish S Hosalkar** MD MB MS FCPS DNB FFAOS  
Medical Director-Orthopedic Surgeon  
Center for Hip Preservation and Children's  
Orthopedics, Vista; and Faculty at San Diego  
Musculoskeletal Institute and Coastal Injury  
Specialists, San Diego, California, USA  
*Disorders of Bones and Joints*

**Monica Juneja** MD  
Professor of Pediatrics and In-charge  
of Child Development Center  
Maulana Azad Medical College and  
Associated Lok Nayak Hospital  
New Delhi, India  
*Behavior and Learning*

**Madhulika Kabra** MD  
Professor, Division of Genetics  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India  
*Metabolic Disorders*

**Ajay Kalra** MD DCH MNAMS FIAP  
Former Professor  
SN Medical College, Agra; and  
Head, Department of Pediatrics  
Rural Institute of Medical Sciences  
Saifai, Uttar Pradesh, India  
*Immunization*

**Ritabrata Kundu** MD FIAP  
Professor  
Department of Pediatrics  
Institute of Child Health  
Kolkata, West Bengal, India  
*Protozoal Infections and Infestations*

**Rakesh Lodha** MD  
Additional Professor  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India  
*Fluid and Electrolytes; Acutely Ill Child and Resuscitation; Intensive Care; Poisoning and Envenomation; Childhood Injuries*

**Rajib Malakar** MD  
Clinical Tutor  
Department of Pediatric Dermatology  
Institute of Child Health  
Kolkata, West Bengal, India  
*Common Skin Problems*

**John Matthai** DCH MD FAB FIAP  
Pediatric Gastroenterologist  
Professor and Head of Pediatrics  
PSG Institute of Medical Sciences  
Coimbatore, Tamil Nadu, India  
*Gastrointestinal Disorders*

**PSN Menon** MD MNAMS FIAP  
Consultant and Head  
Department of Pediatrics  
Jaber-Al-Ahmed Armed Forces Hospital  
Kuwait  
*Introduction to Pediatrics; Disorders of the Endocrine Glands*

**Devendra Mishra** MD  
Professor  
Department of Pediatrics  
Maulana Azad Medical College and  
Associated Lok Nayak Hospital  
New Delhi, India  
*Behavior and Learning*

**MKC Nair** PhD MD MMed Sc MBA MA FIAP FIACAM  
Vice Chancellor  
Kerala University of Health Sciences, Thrissur;  
Formerly Professor of Pediatrics and  
Director, Child Development Center  
Medical College  
Thiruvananthapuram, Kerala, India  
*Adolescent Development; Health Issues in Adolescence; Care of the Adolescents*

**Anand Pandit** MD FRCPCH  
Honorary Professor and Director  
Department of Pediatrics and Neonatology  
TDH Rehabilitation Center and Morris Child  
Development Center, KEM Hospital  
Pune, Maharashtra, India  
*Development and Developmental Delay*

**AK Patwari** MD DCH MNAMS FIAP FAMS  
Professor and Head  
Department of Pediatrics  
Hamdard Institute of Medical Sciences and  
Research, and HAH Centenary Hospital  
Hamdard University, New Delhi, India  
*Diarrheal Illnesses*

**Shubha R Phadke** MD DM  
Professor and Head  
Department of Medical Genetics  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India  
*Genetics and Genetic Disorders*

**Siddarth Ramji** MD FNNF  
Director-Professor  
Department of Neonatology  
Maulana Azad Medical College  
and Associated Lok Nayak Hospital  
New Delhi, India  
*Neonatal Physiology and Organization of Care; Normal Newborn; Disorders of Weight and Gestation; High-risk Newborn; Neonatal Infections; Neurological Problems (of The Newborn Infant); Respiratory Problems (of The Newborn Infant); Neonatal Malformations*

**Amit Rawat** MD PDCC MNAMS  
Associate Professor  
Pediatric Allergy and Immunology Unit  
Department of Pediatrics  
Advanced Pediatric Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India  
*Immunity, Immune Disorders and Allergy*

**A Riyaz** MD DCH DNB DM  
Pediatric Gastroenterologist  
Professor and Head of Pediatrics  
Government Medical College  
Calicut, Kerala, India  
*Gastrointestinal Disorders*

**Anju Seth** MD  
Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India  
*Growth: Normal and Abnormal*

**GR Sethi** MD FIAP  
Director-Professor and Head  
Department of Pediatrics  
Maulana Azad Medical College and  
Associated Lok Nayak Hospital  
New Delhi, India  
*Respiratory Diseases*

**Suvasini Sharma** MD DM  
Assistant Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India  
*Neurological Disorders*

**Kirti Singh** MD DNB FRCS  
Director Professor  
Glaucoma and CL LV Division  
Guru Nanak Eye Center  
Maulana Azad Medical College  
and Associated Hospitals  
New Delhi, India  
*Common Eye Abnormalities*

**Surjit Singh** MD DCH FRCP FRCPCH FAMS  
Professor of Pediatrics and In-charge  
Allergy Immunology Unit  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India  
*Immunity, Immune Disorders and Allergy; Rheumatological Disorders*

**Varinder Singh** MD FRCPCH  
Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India  
*Respiratory Diseases*

**Aditi Sinha** MD DNB  
Assistant Professor  
Division of Pediatric Nephrology  
All India Institute of Medical Sciences  
New Delhi, India  
*Disorders of the Kidney and Urinary Tract*

**S Srinivasan** MD DCH  
Professor  
Department of Pediatrics  
Mahatma Gandhi Medical College  
and Research Institute  
Pillayarkuppam, Puducherry, India  
*Cardiovascular Disorders*

**Soumya Swaminathan** MD FIAP FASc FNAsc FAMS  
Director  
National Institute for Research in Tuberculosis  
Chennai, Tamil Nadu, India  
*Mycobacterial Infections*

**J Andoni Urtizberea** MD  
Professor and Consultant Myologist  
Neuromuscular Unit, Hospital Marin  
Hendaye, France  
*Neuromuscular Disorders*

**Vipin M Vashishtha** MD FIAP  
Convener  
Indian Academy of Pediatrics Advisory  
Committee on Vaccines and Immunization  
Practices; Director and Consultant Pediatrician  
Mangla Hospital and Research Center  
Bijnor, Uttar Pradesh, India  
*Immunization*

**Surender K Yachha** MD DM  
Professor and Head  
Department of Pediatric Gastroenterology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India  
*Hepatobiliary Diseases*



# Authors

---

**B Adhisivam** DCH DNB

Associate Professor  
Division of Neonatology  
Department of Pediatrics  
Jawaharlal Institute of Postgraduate  
Medical Education and Research  
Puducherry, India

**Keshavmurthy A Adya** MD

Assistant Professor  
Department of Dermatology  
Venereology and Leprosy  
Shri BM Patil Medical College  
Hospital and Research Center  
BLDE University  
Bijapur, Karnataka, India

**Kamran Afzal** MD

Associate Professor  
Division of Nephrology  
Department of Pediatrics  
JLN Medical College  
Aligarh Muslim University  
Aligarh, Uttar Pradesh, India

**Bharat Agarwal** MD DNB DCH

Head, Department of Pediatric Hematology  
and Oncology, Bai Jerbai Wadia  
Hospital for Children  
Mumbai, Maharashtra, India

**Indira Agarwal** MD FISI

Professor and Head  
Pediatric Unit and Pediatric Nephrology  
Christian Medical College  
Vellore, Tamil Nadu, India

**KN Agarwal** MD MD FIAP FAMS FNA

Former Professor and Director  
Institute of Medical Sciences  
Banaras Hindu University  
Varanasi, Uttar Pradesh, India  
Former Director  
SGPGIMS, Lucknow; and  
Professor of Pediatrics, UCMS  
Bhairwah, Nepal

**Meenal Agarwal** MD DM

Assistant Professor  
Department of Medical Genetics  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Prakash Agarwal** MS MCh

Professor and Head  
Pediatric Surgery  
Sri Ramachandra University  
Chennai, Tamil Nadu, India

**Ramesh Agarwal** MD DM

Additional Professor  
Newborn Health Knowledge Center  
Division of Neonatology  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Sikha Agarwal** MD

Registrar, Department of Pediatrics  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Mandar V Agashe** MS

Honorary Assistant Professor  
Department of Orthopedics  
KJ Somaiya Medical College  
Mumbai, Maharashtra, India  
Consultant Pediatric Orthopedic Surgeon  
Center for Pediatric Orthopedic Care (CPOC)  
Dr Agashe's Hospital, Mumbai  
Visiting Pediatric Orthopedic Specialist  
Fortis Healthcare Hospital and Godrej  
Memorial Hospital  
Mumbai, Maharashtra, India

**Prachi Agashe** DNB ICO

Director and Consultant Ophthalmologist  
Iconic Eye Hospital  
Mumbai, Maharashtra, India  
and Consultant Pediatric Ophthalmologist  
and Squint Specialist  
Advanced Eye Hospital and Institute  
Navi Mumbai, Maharashtra, India

**Kiran Aggarwal** DCH FAMS

Former Unit Head  
Department of Pediatrics  
North Delhi Municipal Corporation Medical  
College and Hindu Rao Hospital  
New Delhi, India

**Richa Aggarwal** MD DNB

Assistant Professor  
Department of Obstetrics and Gynecology  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Satish Kumar Aggarwal** MS MCh

Director-Professor  
Department of Pediatric Surgery  
Maulana Azad Medical College and  
Associated Lok Nayak and GB Pant Hospitals  
New Delhi, India

**Shagun Aggarwal** MD DM

Assistant Professor  
Department of Medical Genetics  
Nizam's Institute of Medical Sciences  
Hyderabad, Telangana, India

**M Zulfikar Ahamed** MD DM

Professor and Head  
Department of Pediatric Cardiology  
SAT Hospital, Government Medical College  
Thiruvananthapuram, Kerala, India

**Jasmina Ahluwalia** MD

Associate Professor  
Department of Hematology  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Ramandeep S Ahuja** MD DM

Assistant Professor  
Department of Cardiology  
Maulana Azad Medical College  
and GB Pant Hospital  
New Delhi, India

**Kunal Ahya** MD F Neonat

Consulting Neonatologist  
Ankur Institute of Child Health  
Ahmedabad, Gujarat, India

**Sheila Aiyer** MD

Associate Professor  
Department of Pediatrics  
Government Medical College  
Vadodara, Gujarat, India

**Sayed Mohammed Akbar** MBBS

Lecturer  
Department of Pediatric Surgery  
Malabar Medical College  
Calicut, Kerala, India

**Seema Alam** MD

Professor  
Department of Pediatric Hepatology  
Institute of Liver and Biliary Sciences  
New Delhi, India

**Ravi Ambey** MD

Assistant Professor  
Department of Pediatrics  
GR Medical College  
Gwalior, Madhya Pradesh, India

**Kimberly Amburgey** MS CGC

Genetic Counselor  
Hospital for Sick Children  
Department of Pediatrics  
Division of Neurology  
Toronto, Ontario, Canada

**AK Amitava** MS

Professor of Strabismology  
Institute of Ophthalmology  
JN Medical College  
Aligarh Muslim University  
Aligarh, Uttar Pradesh, India

**Satinder Aneja** MD

Director-Professor  
Department of Pediatrics  
Lady Hardinge Medical College, and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**B Anjaiah** MD DCH

Director  
Rajiv Gandhi Institute of Medical Sciences  
Ongole, Prakasam District  
Andhra Pradesh, India

**Abhishek Somasekhara Aradhya** MD

Senior Resident  
Department of Pediatrics  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Andrew C Argent** MD  
Professor  
Pediatric Intensive Care Unit  
Red Cross War Memorial Children's Hospital  
Cape Town, South Africa

**Brijesh Arora** MD DM  
Professor  
Department of Pediatric Oncology  
Tata Memorial Hospital  
Mumbai, Maharashtra, India

**JS Arora** MD  
General Secretary  
National Thalassemia Welfare Society  
Federation of Indian Thalassemia  
New Delhi, India

**Rahul Arora** MD DNB  
Senior Resident  
Department of Dermatology and STD  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Ritu Arora** MD DNB  
Director Professor  
Maulana Azad Medical College  
and Associated Guru Nanak Eye Center  
New Delhi, India

**Shilpa Khanna Arora** MD  
Assistant Professor  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
and Ram Manohar Lohia Hospital  
New Delhi, India

**Archana Dayal Arya** MD  
Senior Consultant  
Pediatric and Adolescent Endocrinologist  
Institute of Child Health  
Sir Ganga Ram Hospital  
New Delhi, India

**Ravindra Arya** MD DM  
Assistant Professor of Neurology and Pediatrics  
Comprehensive Epilepsy Center  
Division of Neurology  
Cincinnati Children's Hospital Medical Center  
Cincinnati, Ohio, USA

**Sugandha Arya** MD  
Consultant  
Department of Pediatrics  
Vardhman Mahavir Medical College  
and Safdarjung Hospital  
New Delhi, India

**Stephanie Austin** MS MA CGC  
Genetic Counselor and Clinical Research  
Coordinator, Duke University Medical Center  
Durham, North Carolina, USA

**Neeraj Awasthy** MD  
Consultant Pediatric Cardiologist  
Fortis Escorts Heart Institute  
New Delhi, India

**Yee Aye** MD MBBS  
Fellow in Pediatric Infectious Diseases  
Department of Pediatrics  
Los Angeles County and University of  
Southern California Medical Center  
Maternal Child and Adolescent Program  
University of Southern California  
Los Angeles, California, USA

**Arvind Bagga** MD FIAP FAMS  
Professor  
Division of Nephrology  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Sulochana Putali Bai** MD  
Consultant, Microbiologist  
Kanchi Kamakoti CHILDS Trust Hospital  
Chennai, Tamil Nadu, India

**Anurag Bajpai** MD FRACP  
Pediatric and Adolescent Endocrinologist  
Regency Hospital Limited  
Kanpur, Uttar Pradesh, India  
Fortis CDOC, Fortis Memorial  
Research Institute  
Gurgaon, Haryana, India

**Duraisamy Balaguru** MBBS DCH MRCP FAAP  
FACC FSCAI  
Associate Professor of Pediatrics  
Associate Director of Fellowship Program  
Division of Pediatric Cardiology  
UT-Houston Medical School  
Houston, Texas, USA

**Suma Balan** MD MRCP CCST  
Assistant Professor  
Consultant Pediatrician and  
Pediatric Rheumatologist  
Amrita Institute of Medical Sciences  
Kochi, Kerala, India

**S Balasubramanian** MD DCH MAMS FRCPC FIAP  
Senior Consultant and Head  
Department of Pediatrics  
Kanchi Kamakoti CHILDS Trust Hospital  
and The CHILDS Trust Medical Research  
Foundation  
Chennai, Tamil Nadu, India

**Manish Balde** DCH FN  
Consultant Neonatologist  
The Cradle, Apollo Hospital  
Gurgaon, Haryana, India

**Shripad Banavali** MD  
Professor and Head  
Medical and Pediatric Oncology  
Tata Memorial Hospital  
Mumbai, Maharashtra, India

**Biswajit Bandyopadhyay** DNB F PED CARD  
Head of the Department  
Senior Consultant Pediatric Cardiologist  
Rabindranath Tagore International  
Institute of Cardiac Sciences  
Kolkata, West Bengal, India

**Raghubir Banerjee** MD  
Associate Professor  
Department of Pediatric Dermatology  
Institute of Child Health  
Kolkata, West Bengal, India

**SR Banerjee** MD DCH FIAP  
Professor and Head  
Department of Pediatrics  
Islamia Hospital  
Kolkata, West Bengal, India

**Sushmita Banerjee** FRCPC  
Consultant  
Department of Pediatrics  
Calcutta Medical Research Institute  
and Department of Nephrology  
Institute of Child Health  
Kolkata, West Bengal, India

**Akash Bang** MD DNB FPCC  
Associate Professor  
Department of Pediatrics  
Mahatma Gandhi Institute of Medical Sciences  
Wardha, Maharashtra, India

**Arun Bansal** MD MRCPC MAMS  
Additional Professor  
Department of Pediatrics  
Advanced Pediatric Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Deepak Bansal** MD DNB MAMS  
Professor  
Hematology Oncology Unit  
Department of Pediatrics  
Advanced Pediatric Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Arun Kumar Baranwal** MD PgDip MNAMS  
Additional Professor and Head  
Department of Pediatrics  
All India Institute of Medical Sciences  
Patna, Bihar, India

**Maitreyi Basu** MD  
Professor  
Department of Pediatrics  
CSS College of Obstetrics,  
Gynecology and Child Health  
Kolkata, West Bengal, India

**Srikanta Basu** MD MNAMS FIAP  
Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**Sriparna Basu** MD DCH FRCPI FRCPC  
Associate Professor  
Department of Pediatrics  
Institute of Medical Sciences  
Banaras Hindu University  
Varanasi, Uttar Pradesh, India

**Prerna Batra** MD  
Associate Professor  
Department of Pediatrics  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Sumathi Bavanandam** MD DCH DM  
Assistant Professor  
Pediatric Gastroenterology  
Institute of Child Health  
and Hospital for Children  
Madras Medical College  
Chennai, Tamil Nadu, India

**Ashish Bavdekar** DCH DNB  
Associate Professor  
Consultant Pediatric Gastroenterologist  
Department of Pediatrics, KEM Hospital  
Pune, Maharashtra, India

**Sandeep B Bavdekar** MD DCH

Professor and Head  
Department of Pediatrics  
TN Medical College and BYL Nair  
Charitable Hospital  
Mumbai, Maharashtra, India

**Nidhi Bedi** MD

Assistant Professor  
Department of Pediatrics  
Vardhman Mahavir Medical College  
and Safdarjung Hospital  
New Delhi, India

**Govind Benakatti** MD DM

Chief Consultant, PICU  
Dr Bidari's Ashwini Hospital  
Ashwini Institute of Child Health  
and Research Center  
Bijapur, Karnataka, India

**Monica Bhagat** MS DNB

Fellow, Division of Pediatric Surgical Oncology  
Department of Surgical Oncology  
Tata Memorial Hospital  
Mumbai, Maharashtra, India

**Utpal Bhalala** MD FAAP

Assistant Professor  
Department of Anesthesiology  
Critical Care Medicine and Pediatrics  
The Johns Hopkins University School of  
Medicine, and Attending Physician  
Pediatric Intensive Care Unit  
Bloomberg Children's Center  
The Johns Hopkins Hospital  
Baltimore, Maryland, USA

**Anil Kumar Bhalla** MD

Professor  
Child Growth and Anthropology Unit  
Department of Pediatrics  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Lalit Bharadia** MD DNB PDCC

Consultant Pediatric Gastroenterologist  
Fortis Escorts Hospital  
Jaipur, Rajasthan, India

**VK Bhardwaj** MD DM

Professor and Head  
Department of Pediatrics  
NSCB Government Medical College  
Jabalpur, Madhya Pradesh, India

**Santosh K Bhargava** MD FIAP FNNF

Former Professor and Head  
Department of Pediatrics  
Safdarjung Hospital and University  
College of Medical Sciences  
New Delhi, India

**Aruna Bhat** DCH MRCPCH

Consultant Pediatric Rheumatologist  
Narayana Health City  
Bengaluru, Karnataka, India

**B Vishnu Bhat** MD

Professor and Head  
Department of Neonatology  
Jawaharlal Institute of Postgraduate  
Medical Education and Research  
Puducherry, India

**Swarna Rekha Bhat** MD

Senior Consultant  
Pediatrics and Neonatology  
Mazumdar Shaw Medical Center  
Narayana Hridayalaya, Narayana Health  
Bengaluru, Karnataka, India

**Vidyut Bhatia** MD

Consultant Pediatric Gastroenterologist  
Indraprastha Apollo Hospital  
New Delhi, India

**Vijayalakshmi Bhatia** MD FIAP

Professor of Endocrinology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Shinjini Bhatnagar** MD FIAP

Professor and Dean, Clinical Research  
Head, Pediatric Biology Center  
Translational Health Science  
and Technology Institute  
Gurgaon, Haryana, India

**Veereshwar Bhatnagar** MS MCh

Professor  
Department of Pediatric Surgery  
All India Institute of Medical Sciences  
New Delhi, India

**Maitryee Bhattacharya** MD DM

Professor and Head  
Department of Hematology  
Nil Ratan Sircar Medical College  
and Hospital  
Kolkata, West Bengal, India

**Subhasish Bhattacharyya** MD DCH DNB MNAMS

Professor of Pediatrics  
Department of Pediatrics  
Program Director  
Pediatric Center of Excellence in Pediatric  
HIV Care, Medical College  
Kolkata, West Bengal, India

**Anuj Bhatti** MD DM

Lecturer  
Department of Pediatrics  
Government Medical College  
Jammu, Jammu and Kashmir, India

**Nisha Bhavani** MD DNB

Clinical Additional Professor  
Department of Endocrinology  
Amrita Institute of Medical Sciences  
Kochi, Kerala, India

**Swati Y Bhawe** MD DCH FCPS FIAP FAAP

Executive Director  
Association of Adolescent  
and Child Care in India  
Mumbai, Maharashtra, India  
Former Professor of Pediatrics  
BJ Medical College and Sasson Hospital  
Pune, Maharashtra, India

**LH Bidari** MD

Director  
Dr Bidari's Ashwini Hospital  
Ashwini Institute of Child Health  
and Research Center  
Bijapur, Karnataka, India

**S Bindusha** MD

Assistant Professor  
Department of Pediatrics  
Government Medical College  
Thiruvananthapuram, Kerala, India

**Vishnu Biradar** MD PDCC

Consultant Pediatric Gastroenterologist  
Deenanath Mangeshkar Hospital  
Pune, Maharashtra, India

**Priya Bishnoi** MD

Senior Resident  
Department of Dermatology  
Manipal Hospital  
Bengaluru, Karnataka, India

**Rishi Bolia** MD PDCC

Fellow  
Department of Pediatric Gastroenterology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Reeta Bora** MD DM

Associate Professor (Neonatal Unit)  
Department of Pediatrics  
Assam Medical College and Hospital  
Dibrugarh, Assam, India

**Anuradha Bose** MD MRCP FRCPCH

Professor of Pediatrics  
Department of Community Health  
Christian Medical College  
Vellore, Tamil Nadu, India

**Meenakshi Bothra** MD

Senior Resident  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Shobha Broor** MD FAMS

Professor and Head  
Department of Microbiology  
Faculty of Health and Medicine  
SGT University, Budhera  
Gurgaon, Haryana, India

**A Bush** MD FRCP FRCPCH FERS

Professor of Pediatric Respiriology  
National Heart and Lung Institute  
Consultant Pediatric Chest Physician  
Royal Brompton and Harefield NHS  
Foundation Trust, UK

**Lavjay Butani** MD MACM

Professor of Pediatrics and  
Chief of Pediatric Nephrology  
University of California Davis Medical Center  
Sacramento, California, USA

**Chandrakanta** MD

Associate Professor in Pediatrics  
King George's Medical University  
Lucknow, Uttar Pradesh, India

**Raghuvamsi Chaitra** MD IDPCCM

Senior Resident  
Department of Pediatric  
Critical Care  
Apollo Children's Hospital  
Chennai, Tamil Nadu, India

**Arunaloke Chakrabarti** MD Dip NB FAMS FNAsc

FIDSA  
Professor and Head  
Department of Medical Microbiology  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Biswaroop Chakrabarty** MD DM

Assistant Professor  
Child Neurology Division  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Jaya Chakravarty** MD

Associate Professor  
Department of Medicine  
Institute of Medical Sciences  
Banaras Hindu University  
Varanasi, Uttar Pradesh, India

**Jagdish Chandra** MD FIAP

Director-Professor and Head  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**Aparna Chandrasekaran** MD DM

Consultant Neonatologist  
Kanchi Kamakoti CHILDS Trust Hospital  
Chennai, Tamil Nadu, India

**Manigandan Chandrasekaran** MD DCH FRCPC

Consultant Neonatologist  
Cloudnine Hospital  
Chennai, Tamil Nadu, India

**Sudha Rao Chandrashekhar** MD

Professor and Chief  
Division of Pediatric Endocrinology  
and Neonatology  
Bai Jerbai Wadia Hospital for Children  
Mumbai, Maharashtra, India

**Mammen Chandy** MD FRACP FRCPA FRCP

Director  
Tata Medical Center  
Kolkata, West Bengal, India

**Pallab Chatterjee** DCH MD DNB

Visiting Consultant  
Pediatric Pulmonology  
Apollo Gleneagles Hospitals  
Kolkata, West Bengal, India

**Pranab Chatterjee** MBBS

Resident  
Department of Community Medicine  
University College of Medical Sciences  
New Delhi, India

**Sukanta Chatterjee** MD

Professor  
Department of Pediatrics  
KPC Medical College  
Kolkata, West Bengal, India

**Tathagata Chatterjee** MD DM MNAMS FUICC FISHTM

Professor and Head  
Department of Immunohematology  
and Transfusion Medicine  
Armed Forces Medical College  
Pune, Maharashtra, India

**Sanjay Chaturvedi** MD FAMS FIAPSM FIPHA

Professor and Head  
Department of Community Medicine  
University College of Medical Sciences  
New Delhi, India

**Swasti Chaturvedi** MD FRACP MSC

Consultant Pediatric Nephrologist  
National University Health System  
Singapore

**Sudha Chaudhari** DCH FAAP

Professor of Pediatrics; Consultant,  
Department of Pediatrics and Neonatology;  
TDH Rehabilitation and Morris Child  
Development Center, KEM Hospital  
Pune, Maharashtra, India

**Suman Chaurasia** MD

Senior Research Officer  
Newborn Health Knowledge Center  
Division of Neonatology  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Deepak Chawla** MD DM

Associate Professor  
Department of Pediatrics  
Government Medical College and Hospital  
Chandigarh, India

**Harish Chellani** MD DCH

Consultant and Professor  
Department of Pediatrics  
Vardhman Mahavir Medical College  
and Safdarjung Hospital  
New Delhi, India

**Jagdish Chinnappa** MD

Consultant Pediatrician  
Manipal Hospital  
Bengaluru, Karnataka, India

**Girish Chinnaswamy** MD MRCP

Associate Professor, Pediatric Oncology  
Department of Medical Oncology  
Tata Memorial Hospital  
Mumbai, Maharashtra, India

**Shashi Ajit Chiplonkar** MSc, PhD

Honorary Senior Scientist  
Hirabai Cowasji Jehangir Medical  
Research Institute  
Pune, Maharashtra, India

**AJ Chitkara** MD, DNB, FIAP

Consultant and Head  
Department of Pediatrics  
Max Superspecialty Hospital  
New Delhi, India

**Anita Choudhary** MD DM

Assistant Professor  
Department of Pediatrics  
SPMCHI, SMS Medical College  
Jaipur, Rajasthan, India

**VP Choudhry** MD FIAP FIMS FIAACM FISHTM

Director  
Sunflag Pahuja Center for Blood  
Disorders, Sunflag Hospital  
Faridabad, Haryana, India  
Head  
Department of Hematology, Paras Hospital  
Faridabad, Haryana, India;  
and Formerly Professor and Head  
Department of Hematology  
All India Institute of Medical Sciences  
New Delhi, India

**Jaydeep Choudhury** DNB MNAMS FIAP

Associate Professor  
Department of Pediatrics  
Institute of Child Health  
Kolkata, West Bengal, India

**Nabajyoti Choudhury** MBBS PhD MBA

Additional Director and Head  
Department of Transfusion Medicine  
Fortis Memorial Research Institute  
Gurgaon, Haryana, India

**Panna Choudhury** MD FIAP FAMS

Former Consultant Pediatrician  
Lok Nayak Hospital, and President  
Indian Academy of Pediatrics  
New Delhi, India

**Michael Lim Teik Chung** MSc FRCPC FRCP FAMS

Consultant  
Division of Pediatric  
Pulmonology and Sleep  
Department of Pediatrics  
National University Hospital  
Singapore

**Prisca Colaco** MD

Professor  
Department of Pediatrics  
MGM Medical College  
Navi Mumbai, Maharashtra, India

**Karobi Lahiri Coutinho** MS

Consultant Vitreoretinal Surgeon  
and Pediatric Ophthalmologist  
Bombay Hospital Institute of Medical Sciences  
Mumbai, Maharashtra, India

**S Criton** MD

Professor and Head  
Department of Dermatology  
Amala Institute of Medical Sciences  
Thrissur, Kerala, India

**Tarangini D** MD

Fellow  
Pediatric Hemato-oncology and  
Bone Marrow Transplant Unit  
Institute of Child Health  
Sir Ganga Ram Hospital  
New Delhi, India

**Preeti Dabadghao** MD DM

Additional Professor  
Department of Endocrinology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Aashima Dabas** MD

Assistant Professor  
Department of Pediatrics  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**JP Dadhich** MD FNNF

National Coordinator  
Breastfeeding Promotion Network of India  
New Delhi, India

**Ashwin Dalal** MD DM

Head, Diagnostics Division  
Center for DNA Fingerprinting  
and Diagnostics  
Hyderabad, Telangana, India

**Bharat Dalvi** MD DM FACC

Pediatric Cardiologist  
Glenmark Cardiac Center  
Mumbai, Maharashtra, India



**Samir H Dalwai** MD DCH DNB FCPS LLB

Developmental Pediatrician  
Director

New Horizons Child Development Center  
Mumbai, Maharashtra, India

**Vibhawari S Dani** MD DCH

Ex-Dean and Professor of Pediatrics  
Government Medical College  
Nagpur, Maharashtra, India

**Anirban Das** MD

Fellow

Pediatric Hematology-oncology Unit  
Department of Pediatrics  
Advanced Pediatric Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Bikramjit Das** MD DM

Senior Resident  
Newborn Unit  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Rashmi Ranjan Das** MD FCCP

Assistant Professor  
Department of Pediatrics  
All India Institute of Medical Sciences  
Bhubaneswar, Odisha, India

**Deepashree Daulatabad** MD

Senior Resident  
Department of Dermatology and STD  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Devi Dayal** MD

Additional Professor  
Pediatric Endocrinology Unit  
Department of Pediatrics  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Rajeshwar Dayal** MD FAMS FIAP DNB

Professor and Head  
Department of Pediatrics  
SN Medical College  
Agra, Uttar Pradesh, India

**Anuradha De** MD

Professor  
Department of Microbiology  
Lokmanya Tilak Municipal Medical  
College and Hospital  
Mumbai, Maharashtra, India

**Koushik Sinha Deb** MD

Assistant Professor  
Department of Psychiatry  
All India Institute of Medical Sciences  
New Delhi, India

**Meena Desai** MD

Honorary Consultant  
Division of Pediatric Endocrinology  
Bai Jerbai Wadia Hospital for Children  
Institute of Child Health and Research Center  
Mumbai, Maharashtra, India

**Pooja Dewan** MD MNAMS

Assistant Professor  
Department of Pediatrics  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Sandipan Dhar** MD DNB

Professor and Head  
Department of Pediatric Dermatology  
Institute of Child Health  
Kolkata, West Bengal, India

**Bhavna Dhingra** MD DNB

Assistant Professor  
Department of Pediatrics  
All India Institute of Medical Sciences  
Bhopal, Madhya Pradesh, India

**Dhulika Dhingra** MD

Consultant Pediatrician  
St Stephens Hospital  
Gurgaon, Haryana, India

**Chhaya Divecha** MD DCH

Assistant Professor  
Department of Pediatrics  
Seth GS Medical College and KEM Hospital  
Mumbai, Maharashtra, India

**Krishna Kumar Diwakar** MD DNB FRCPCH

Professor and Head  
Department of Neonatology  
Malankara Orthodox Syrian Church  
Medical College  
Kochi, Kerala, India

**James J Dowling** MD PhD

Clinician  
Division of Neurology  
Scientist  
Genetics and Genome Biology Program  
Hospital for Sick Children  
Toronto, Ontario, Canada

**AP Dubey** MD FIAP

Director Professor  
Department of Pediatrics  
Maulana Azad Medical College  
and Associated Lok Nayak Hospital  
New Delhi, India

**Rachana Dubey** MD DNB MNAMS

DM Fellow  
Child Neurology Division  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Swati Dublith** MD

Assistant Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**David W Dunn** MD

Professor of Psychiatry and Neurology  
Director  
Child and Adolescent Psychiatry Clinics  
Department of Psychiatry and Neurology  
Riley Hospital for Children  
Indiana University Medical Center  
Indianapolis, Indiana, USA

**Ashok Kumar Dutta** MD FIAP

Professor of Pediatrics  
School of Medical Sciences and Research  
Sharda University  
Greater Noida, Uttar Pradesh, India

**Sourabh Dutta** MD

Professor  
Newborn Unit  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Umesh Dyamenahalli** MD FACC CMQ

Associate Professor of Pediatrics  
Director, Cardiovascular ICU  
Associate Chief of Pediatric Cardiology  
University of Chicago Medicine  
Comer Children's Hospital  
Chicago, Illinois, USA

**Maha Elhassan** MBBS

Fellow  
Division of Pediatric Endocrinology  
University of Michigan  
Ann Arbor, Michigan, USA

**Abhay Elhence** MS DNB MNAMS MCh

Associate Professor  
Department of Orthopedics  
All India Institute of Medical Sciences  
Jodhpur, Rajasthan, India

**KE Elizabeth** PhD MD DCH FIAP

Professor and Head  
Department of Pediatrics; and Superintendent  
SAT Hospital, Government Medical College  
Thiruvananthapuram, Kerala, India

**Refika Ersu** MD

Professor  
Division of Pediatric Pulmonology  
Marmara University  
Istanbul, Turkey

**Emily F Fishman** MD

Fellow  
Neonatal-Perinatal Medicine  
Department of Pediatrics  
Division of Newborn Medicine  
Washington University  
St Louis, Missouri, USA

**Elsie Jazmin Foglio** DO

Pediatric Gastroenterology Fellow  
Department of Pediatrics  
Yale University School of Medicine  
New Haven, Connecticut, USA

**Joana Manuel Ferreira Freitas** MD

Consultant Pediatric Orthopedic  
Pediatric Spine Deformities  
and Trauma Surgeon  
S. João Medical Center  
Porto, Portugal

**Vikram Gagneja** DNB FNB FCCM

Senior Consultant and Intensivist  
Max Superspecialty Hospital  
New Delhi, India

**Mona P Gajre** MD

Professor  
Department of Pediatrics  
LTM Medical College and  
LTM General Hospital  
Mumbai, Maharashtra, India

**Preeti M Galagali** MD PGDAP

Director and Consultant  
Adolescent Health Specialist  
Bangalore Adolescent Care  
and Counseling Center  
Bengaluru, Karnataka, India

**R Ganesh** MBBS DNB MNAMS MRCPCH

Consultant Pediatrician  
Kanchi Kamakoti CHILDS Trust Hospital  
and The CHILDS Trust Medical  
Research Foundation  
Chennai, Tamil Nadu, India

**Sandra C Ganesh** DNB

Consultant  
Department of Pediatric Ophthalmology  
and Strabismus, Aravind Eye Hospital  
Coimbatore, Tamil Nadu, India

**Nupur Ganguly** DCH DNB FIAP

Associate Professor  
Department of Pediatrics  
Institute of Child Health  
Kolkata, West Bengal, India

**Sutapa Ganguly** MD

Professor of Pediatrics and Principal  
CSS College of Obstetrics  
Gynecology and Child Health  
Kolkata, West Bengal, India

**Ajay Gaur** MD PhD FIAP

Associate Professor and Head  
Department of Pediatrics  
GR Medical College  
Gwalior, Madhya Pradesh, India

**Manjyot Manish Gautam** MD

Associate Professor  
Department of Dermatology  
Dr DY Patil Medical College  
and Research Center  
Navi Mumbai, Maharashtra, India

**Renu George** MD

Professor and Head  
Department of Dermatology  
Venereology and Leprosy  
Christian Medical College  
Vellore, Tamil Nadu, India

**Apurba Ghosh** MD MRCP FRCPH FIAP

Professor and Director  
Institute of Child Health  
Kolkata, West Bengal, India

**Debabrata Ghosh** MD DNB DM

Associate Professor  
Division of Pediatric Neurology  
Nationwide Children's Hospital  
Ohio State University College of Medicine  
Columbus, Ohio, USA

**Tushar Godbole** DNB MNAMS PDCC

Assistant Professor in Pediatrics  
Dr Vasantrao Pawar Medical College  
Nashik, Maharashtra, India  
Consultant Pediatric Endocrinologist  
Harmony Health Hub  
Nashik, Maharashtra, India

**Amit Goel** MD DNB DM MNAMS

Assistant Professor  
Department of Gastroenterology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Daniel YT Goh** MMed FRCPCH FCCP FAMS

Associate Professor  
Chair, Khoo Teck Puat - National University  
Children's Medical Institute  
and Head of Pediatrics  
Yong Loo Lin School of Medicine  
National University of Singapore  
and National University Hospital  
Singapore

**Sunil Gomer** MD FIAP

Director-Professor  
Department of Pediatrics  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Jatinder S Goraya** MD FRCP

Assistant Professor  
Division of Pediatric Neurology  
Department of Pediatrics  
Dayanand Medical College and Hospital  
Ludhiana, Punjab, India

**Geeta M Govindaraj** MD DCH DNB

Additional Professor of Pediatrics  
Government Medical College  
Calicut, Kerala, India

**Manisha Goyal** MD

Division of Genetics  
Genetic and Metabolic Lab  
Department of Pediatrics  
Lok Nayak Hospital and  
Maulana Azad Medical College  
New Delhi, India

**Tarang Goyal** MD

Professor  
Department of Dermatology  
Venereology and Leprology  
Muzaffarnagar Medical College and Hospital  
Muzaffarnagar, Uttar Pradesh, India

**Shivani Grover** MBBS

Resident  
Institute of Ophthalmology  
JN Medical College  
Aligarh Muslim University  
Aligarh, Uttar Pradesh, India

**Lokesh Guglani** MD FAAP

Assistant Professor of Pediatrics  
Pulmonary Medicine Division  
The Carman and Ann Adams  
Department of Pediatrics  
Children's Hospital of Michigan  
Detroit, Michigan, USA

**Ashima Gulati** MD

Fellow  
Pediatric Nephrology  
Yale University School of Medicine  
and Yale-New Haven Hospital  
New Haven, Connecticut, USA

**Sheffali Gulati** MD FIAP FIMS MNAMS

Professor of Pediatrics; and  
Chief, Child Neurology Division  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Ashish Gulia** MS MCh

Associate Professor  
Orthopedic Oncology  
Bone and Soft Tissue Services  
Tata Memorial Hospital  
Mumbai, Maharashtra, India

**Anju Gupta** MD

Additional Professor  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Ankur Gupta** MD DM

Assistant Professor  
Department of Cardiology  
Advanced Cardiac Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Dhiren Gupta** MD

Senior Consultant  
Pediatric Intensive Care Unit  
Sir Ganga Ram Hospital  
New Delhi, India

**Neeraj Gupta** DCH DNB

Consultant  
Pediatric Intensive Care Unit  
Sir Ganga Ram Hospital  
New Delhi, India

**Neeraj Gupta** MD DM

Assistant Professor  
Department of Pediatrics  
All India Institute of Medical Sciences  
Jodhpur, Rajasthan, India

**Neerja Gupta** MD DM

Assistant Professor  
Division of Genetics  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Piyush Gupta** MD FAMS FIAP

Professor  
Department of Pediatrics  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Priyanka Gupta** MD

Assistant Professor of Pediatrics  
North Delhi Municipal Corporation  
Medical College and Associated  
Hindu Rao Hospital  
New Delhi, India

**Samir Gupta** DM MD FRCPCH FRCPI

Professor of Neonatology  
University of Durham  
Co-Director  
Research and Development  
University Hospital of North Tees  
Stockton-on-Tees, UK

**Shalu Gupta** MD

Associate Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**Shuchita Gupta** MD

Senior Research Officer  
Newborn Health Knowledge Center  
Division of Neonatology  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**SK Gupta** MS DNB FRCS FAMS

Professor of Surgery  
Department of General Surgery  
Institute of Medical Sciences  
Banaras Hindu University  
Varanasi, Uttar Pradesh, India

**Sunil Kumar Gupta** MBBS MD PhD

Consultant Pediatrician and Neonatologist  
and Scientist of Environmental Medicine  
Krishna Ram Hospital and Research Center  
Jaipur, Rajasthan, India

**Swati Gupta** MD

Clinical Associate  
Lilavati Hospital and Research Center  
Mumbai, Maharashtra, India

**Vijay Gupta** MD

Senior Registrar  
Department of Neonatology  
Christian Medical College  
Vellore, Tamil Nadu, India

**Vineeta Gupta** MD DNB MAMS FRCPCH

Associate Professor  
Department of Pediatrics  
Institute of Medical Sciences  
Banaras Hindu University  
Varanasi, Uttar Pradesh, India

**Omkar P Hajirnis** MD DNB MRCPC

Clinical Fellow in Pediatric Neurology  
Jaslok Hospital and Research Center  
Mumbai, Maharashtra, India

**Pankaj Hari** MD

Professor  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Kamlesh Harish** MD

Senior Specialist and Head  
Department of Pediatrics  
ESI Hospital  
New Delhi, India

**Rekha Harish** MD FIAP

Professor and Head  
Department of Pediatrics  
Government Medical College  
Jammu, Jammu and Kashmir, India

**Hemlata** DNB PDCC

Senior Resident  
Department of Anesthesiology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Puja Hingorani** MS DNB FCPS

Associate Professor of Ophthalmology  
Mahatma Gandhi Institute of  
Medical Sciences, Sewagram  
Wardha, Maharashtra, India

**Ravi Hiremagalore** MD

Consultant Pediatric Dermatologist  
Adjunct Faculty, Center for Human Genetics  
Bengaluru  
Department of Pediatrics  
and Dermatology, Manipal Hospital  
Bengaluru, Karnataka, India

**Paul Hofman** MD

Professor  
Director of Maurice and Nessie  
Paykel CRU Liggins Institute  
University of Auckland  
Auckland, New Zealand

**James Homans** MD MPH

Associate Professor of Clinical Pediatrics  
Division of Infectious Diseases  
Department of Pediatrics  
Keck School of Medicine of University  
of Southern California  
Los Angeles, California, USA

**Harish S Hosalkar** MD MB MS FCPS DNB FAAOS

Medical Director-Orthopedic Surgeon  
Center for Hip Preservation and  
Children's Orthopedics, Vista; and  
Faculty at San Diego Musculoskeletal Institute  
and Coastal Injury Specialists  
San Diego, California, USA

**Khalid Hussain** MD

Reader and Honorary Consultant  
Pediatric Endocrinologist  
Developmental Endocrinology Research Group  
Clinical and Molecular Genetics Unit  
UCL Institute of Child Health  
Great Ormond Street  
Children's Hospital NHS Foundation Trust  
London, UK

**Riaz I** DCH DNB

Assistant Professor  
Department of Pediatrics  
Government Medical College  
Thiruvananthapuram, Kerala, India

**Arun C Inamadar** MD DVD FRCP

Professor and Head  
Department of Dermatology  
Venereology and Leprosy  
Shri BM Patil Medical College  
Hospital and Research Center  
BLDE University  
Bijapur, Karnataka, India

**Aspi Irani** MD DCH

Consultant Pediatrician  
Nanavati Hospital and Research Center  
Mumbai, Maharashtra, India

**Parvathi U Iyer** MD

Director  
Pediatric Intensive Cardiac Care  
Fortis Escorts Heart Institute  
New Delhi, India

**Rajalakshmi Iyer** MD

Senior Resident  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Mary Iype** MD DM MNAMS FIMS

Additional Professor  
Department of Pediatric Neurology  
Government Medical College  
Thiruvananthapuram, Kerala, India

**Barath Jagadisan** MD PDCC

Associate Professor  
Department of Pediatrics  
Jawaharlal Institute of Postgraduate  
Medical Education and Research  
Puducherry, India

**Ashish Jain** MD DNB MNAMS DM

Assistant Professor  
Department of Pediatrics  
Maulana Azad Medical College and  
Associated Lok Nayak Hospital  
New Delhi, India

**Dipty Jain** MD MSC

Professor and Head  
Department of Pediatrics  
Government Medical College  
Akola, Maharashtra, India

**Divya Jain** MD

Assistant Professor  
Department of Ophthalmology  
Pondicherry Institute of Medical Sciences  
Puducherry, India

**Manish Jain** MD MBA DCA

Senior Technical Advisor  
John Snow India Pvt Ltd  
New Delhi, India

**Naveen Jain** MD DM

Professor  
Department of Neonatology  
Kerala Institute of Medical Sciences  
Thiruvananthapuram, Kerala, India

**Puneet Jain** MD DM

Consultant, Pediatric Neurology  
Department of Neonatal  
Pediatric and Adolescent Medicine  
BL Kapur Superspecialty Hospital  
New Delhi, India

**Rahul Jain** MD

Assistant Professor  
Department of Pediatrics  
Chacha Nehru Bal Chikitsalaya  
New Delhi, India

**Sandeep Jain** DNB FIAP

Consultant  
Department of Pediatric  
Hematology and Oncology  
Rajiv Gandhi Cancer Institute  
and Research Center  
New Delhi, India

**Shreepal Jain** MD FNB

Consultant Pediatric Cardiologist  
Jaslok Hospital  
Fortis Raheja Hospital  
Mumbai, Maharashtra, India

**Suksham Jain** MD DM

Associate Professor  
Department of Pediatrics  
Government Medical College  
and Hospital  
Chandigarh, India

**Vandana Jain** MD

Additional Professor  
Division of Pediatric Endocrinology  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Vikas Jain** MD PDCC

Fellow  
Department of Pediatric Gastroenterology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Nishant Jaiswal** MBBS

Scientist C, ICMR Advanced Center  
for Evidence Based Child Health  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Mamta Jajoo** DNB MNAMS

Assistant Professor  
Department of Pediatrics  
Chacha Nehru Bal Chikitsalaya  
New Delhi, India

**Anil B Jalan** MD DCH MCPS

Chief Scientific Research Officer  
Navi Mumbai Institute of Research  
in Mental and Neuro Handicap  
Navi Mumbai, Maharashtra, India

**Ashok Jaryal** MD

Additional Professor  
Department of Physiology  
All India Institute of Medical Sciences  
New Delhi, India

**Kana Ram Jat** MD FCCP

Assistant Professor  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Prashant Jauhari** MD DM

Division of Pediatric Neurology  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Kumutha Jayaraman** MD DCH

Professor and Head  
Department of Neonatology  
Institute of Child Health and  
Hospital for Children  
Chennai, Tamil Nadu, India

**V Jayaraman** MS MCH PHD

Former Professor of Burns, Plastic  
and Reconstructive Surgery  
Kilpauk Medical College  
Chennai, Tamil Nadu, India

**Ganesh S Jevalikar** MD DNB PDCC

Consultant  
Division of Endocrinology and Diabetes  
Medanta—The Medicity Hospital  
Gurgaon, Haryana, India

**Urmila Jhamb** MD

Director-Professor  
In-charge PICU  
Department of Pediatrics  
Maulana Azad Medical College  
and Associated Lok Nayak Hospital  
New Delhi, India

**Rajesh Joshi** MD DNB

Professor  
Department of Pediatrics  
Division of Pediatric Endocrinology  
Bai Jerbai Wadia Hospital for Children  
Mumbai, Maharashtra, India

**Monica Juneja** MD

Professor of Pediatrics and In-charge  
of Child Development Center  
Maulana Azad Medical College  
and Associated Lok Nayak Hospital  
New Delhi, India

**Rajnish Juneja** MD DM

Professor  
Department of Cardiology  
Cardiothoracic Center  
All India Institute of Medical Sciences  
New Delhi, India

**Venkatadass K** MD

Consultant Pediatric Orthopedic Surgeon  
Department of Orthopedics  
Ganga Hospital  
Coimbatore, Tamil Nadu, India

**Vidya K** MD

Assistant Professor  
Department of Pathology  
Vydehi Institute of Medical Sciences  
Bengaluru, Karnataka, India

**AKM Iqbal Kabir** MBBS MD PhD

Senior Scientist and Senior Consultant  
Dhaka Hospital, International Center for  
Diarrheal Diseases Research, Bangladesh  
(ICDDR, B), Dhaka, Bangladesh

**Madhulika Kabra** MD

Professor  
Division of Genetics  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**SK Kabra** MD

Professor  
Pediatric Pulmonology Division  
All India Institute of Medical Sciences  
New Delhi, India

**Lalitha Kailas** MD DCH

Professor and Head  
Department of Pediatrics  
Government Medical College  
Thiruvananthapuram, Kerala, India

**Shruti Kakkar** MD

Assistant Professor  
Department of Pediatrics  
Dayanand Medical College and Hospital  
Ludhiana, Punjab, India

**Ajay Kalra** MD DCH MNAMS FIAP

Former Professor  
SN Medical College, Agra, Uttar Pradesh, India  
and Head, Department of Pediatrics  
Rural Institute of Medical Sciences  
Saifai, Uttar Pradesh, India

**Suprita Kalra** MD

Major  
Pediatrician, Military Hospital  
Jalandhar, Punjab, India

**Veena Kamat** MD

Professor and Head  
Department of Community Medicine  
Kasturba Medical College  
Manipal, Karnataka, India

**Mahesh Kamate** MD DM

Associate Professor of Pediatric Neurology  
KLE University JN Medical College and  
In-charge, Child Development Clinic  
KLES Prabhakar Kore Hospital  
Belgaum, Karnataka, India

**Nutan Kamath** MD

Professor  
Department of Pediatrics  
Kasturba Medical College  
Manipal University  
Mangaluru, Karnataka, India

**Vijay HD Kamath** MS FNBE

Consultant Spine Surgeon  
Spinal Disorders Services  
Department of Orthopedics  
Bangalore Baptist Hospital  
Bengaluru, Karnataka, India

**Swati Kanakia** MD DCH PHD

Pediatric Hematologist Oncologist  
Kanakia Health Care, Lilavati Hospital and  
Research Center; and Raheja Fortis Hospital  
Lion Tarachand Bappa Hospital  
Mumbai, Maharashtra, India

**Preeti Kandasamy** MD PDF

Fellow  
Department of Child and Adolescent Psychiatry  
National Institute of Mental Health  
and Neurosciences  
Bengaluru, Karnataka, India

**Gagandeep Kang** MD PhD FRCPath FAAM FASc FNAsc

Professor and Head  
Division of Gastrointestinal Sciences  
Christian Medical College  
Vellore, Tamil Nadu, India

**Sujata Kanhere** DNB DCH MNAMS FRCPC

Professor and Chief  
Pediatric Neurology Division  
Department of Pediatrics and Neonatology  
KJ Somaiya Medical College, Hospital  
and Research Center  
Mumbai, Maharashtra, India

**Atul M Kanikar** MBBS DCH

Pediatrician and Adolescent Care Specialist  
Dr Kanikar Hospital  
Nasik, Maharashtra, India

**Madhuri Kanitkar** MD FIAP

Consultant Pediatric Nephrologist  
and Deputy Director General  
(Planning and Training)  
Armed Forces Medical Services  
New Delhi, India

**Lakshminarayanan Kannan** MD DM

Fellow in Pediatric Epilepsy and EEG  
Department of Neurology  
The Royal Children's Hospital  
Melbourne, Australia

**BRJ Kannan** MD DM DNB

Chief Pediatric Cardiology Consultant  
Vadmalayan Hospital  
Madurai, Tamil Nadu, India

**Sonal Kansra** MD MRCPCH

Consultant in Pediatric Respiratory Medicine  
Sheffield Children's Hospital, NHS Trust  
Sheffield, UK

**Shruti Kant** MD

Assistant Professor  
Department of Emergency Medicine  
Division of Pediatric Emergency Medicine  
University of California San Francisco, UCSF  
Benioff Children's Hospital  
San Francisco, California, USA

**Amrinder Jit Kanwar** MD FAMS FRCP

Professor and Head  
Department of Dermatology  
Sharda Hospital, Greater Noida  
Uttar Pradesh, India



**Vikramjit S Kanwar** MRCP MBA FAAP

Chief, Division of Pediatric Hematology Oncology; Director, Melodies Center for Childhood Cancer and Blood Disorders and Professor, Department of Pediatrics Albany Medical Center Albany, New York, USA

**Umesh Kapil** MD

Professor  
Public Health Nutrition  
Department of Human Nutrition  
All India Institute of Medical Sciences  
New Delhi, India

**Akshay Kapoor** MD

Consultant Pediatric Gastroenterologist  
Indraprastha Apollo Hospital  
New Delhi, India

**Gauri Kapoor** MD PhD

Director and Head  
Department of Pediatric Hematology Oncology  
Rajiv Gandhi Cancer Institute  
and Research Center  
New Delhi, India

**Seema Kapoor** DNB

Professor, Division of Genetics, Genetic and Metabolic Laboratory, Department of Pediatrics Maulana Azad Medical College and Associated Lok Nayak Hospital  
New Delhi, India

**Sneh Kapoor** PhD

Fellow  
Department of Psychiatry  
All India Institute of Medical Sciences  
New Delhi, India

**Tanuja Karande** MD

Consultant  
Division of Pediatric Cardiology  
Kokilaben Dhirubhai Ambani Hospital  
Mumbai, Maharashtra, India

**Prathibha Karanth** PhD

Former Professor and Head  
Department of Speech–Language Pathology  
All India Institute of Speech and Hearing  
Mysuru, Karnataka, India

**Sakshi Karkra** MD

Department of Pediatric Gastroenterology Hepatology and Liver Transplantation  
Medanta—The Medicity Hospital  
Gurgaon, Haryana, India

**Archana Kashyap** MD

Senior Resident  
Department of Pediatrics  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Srinivas G Kasi** MD

Consultant Pediatrician  
Kasi Clinic  
Bengaluru, Karnataka, India

**Satyendra Katewa** DCH DNB

Consultant  
Pediatric Hematology Oncology, and Bone Marrow Transplant Unit  
Fortis Memorial Research Institute  
Gurgaon, Haryana, India

**Apjit Kaur** MS

Professor and Chief  
Oculoplasty Unit  
Department of Ophthalmology  
King George's Medical University  
Lucknow, Uttar Pradesh, India

**Harsheen Kaur** MBBS

Research Fellow  
Pediatrics Intensive Care Unit  
Mayo Clinic  
Rochester, USA

**Satnam Kaur** MD

Assistant Professor  
Department of Pediatrics  
Maulana Azad Medical College and Associated Lok Nayak Hospital  
New Delhi, India

**Savleen Kaur** MS

Senior Resident  
Postgraduate Institute of Medical Education and Research  
Chandigarh, India

**Jaya Shankar Kaushik** MD DNB MNAMS

DM Fellow, Child Neurology Division  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Rajesh Khadgawat** MD

Additional Professor  
Department of Endocrinology and Metabolism  
All India Institute of Medical Sciences  
New Delhi, India

**Satish V Khadilkar** MD DM DNBE FIAN

Professor and Head  
Department of Neurology  
Grant Medical College and Sir JJ Group of Hospitals  
Mumbai, Maharashtra, India

**Rajni Khajuria** PhD

Ex-Research Associate  
Genetics Unit  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Anita Khalil** MD FIAP FAMS

Former Director-Professor  
Pediatrics, Maulana Azad Medical College and Consultant Pediatric Cardiologist  
The Heart Center  
New Delhi, India

**Sumaira Khalil** DNB

Assistant Professor  
Department of Pediatrics  
Maulana Azad Medical College and Associated Lok Nayak Hospital  
New Delhi, India

**Amir Maroof Khan** MD

Assistant Professor  
Department of Community Medicine  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Mohammad Imran Khan** MBBS MSc PhD

Director  
Coalition against Typhoid  
Sabin Vaccine Institute  
Washington DC, USA

**Sujoy Khan** MBBS FRCP CCT FRCPath

Consultant Immunologist  
Department of Allergy and Immunology  
Apollo Gleneagles Hospital  
Kolkata, West Bengal, India

**Rajeev Khanna** MD, PDCC

Assistant Professor  
Department of Pediatric Hepatology  
Institute of Liver and Biliary Sciences  
New Delhi, India

**VK Khanna** MD

Senior Consultant  
Department of Pediatrics  
Institute of Child Health  
Sir Ganga Ram Hospital  
New Delhi, India

**Ilin Kinimi** MD

Consultant Pediatrician and Pediatric Pulmonologist  
Department of Pediatric Pulmonology and Sleep Medicine  
Manipal Hospital  
Bengaluru, Karnataka, India

**Priya S Kishnani** MD

Professor of Pediatrics  
Division Chief, Medical Genetics  
Duke University, Medical Center  
Durham, North Carolina, USA

**Niranjan Kissoon** MD FRCP(C) FAAP FCCM FACP

Vice President  
Medical Affairs  
BC Children's Hospital BCCH and UBC Professor—Acute and Critical Care in Global Child Health  
Vancouver, British Columbia, Canada

**Neelam Kler** MD

Professor and Chairperson  
Department of Neonatology  
Sir Ganga Ram Hospital  
New Delhi, India

**Girisha KM** MD DM

Professor and Head  
Department of Medical Genetics  
Kasturba Medical College  
Manipal University  
Manipal, Karnataka, India

**Harikrishnan KN** MD

Senior Resident  
Department of Pediatrics  
Jawaharlal Institute of Postgraduate Medical Education and Research  
Puducherry, India

**Vyunkta Raju KN** DM

Assistant Professor of Pediatric Neurology  
Indira Gandhi Institute of Child Health  
Bengaluru, Karnataka, India

**Gurpreet Singh Kochar** MD DM

Consultant Pediatric Neurologist  
SPS Apollo Hospital  
Ludhiana, Punjab, India

**Ramesh Konanki** MD DM

Consultant Pediatric Neurologist  
Rainbow Hospital for Women and Children  
Hyderabad, Telangana, India

**Nageswara Rao Koneti** MD DM  
Consultant Pediatric Cardiologist  
CARE Hospital  
Hyderabad, Telangana, India

**Suja Koshy** MSc PhD  
Associate Professor and Head  
Department of Human Development  
SVT College of Home Science  
SNDT Women's University  
Mumbai, Maharashtra, India

**Suresh Kotagal** MD  
Consultant in Neurology  
Pediatrics and Sleep Medicine Professor  
Department of Neurology, Mayo Clinic  
Rochester, Minnesota, USA

**Srikanth KP** MD  
Senior Resident  
Division of Pediatric Gastroenterology  
Hepatology and Nutrition  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Sriram Krishnamurthy** MD  
Associate Professor  
Department of Pediatrics  
Jawaharlal Institute of Postgraduate  
Medical Education and Research  
Puducherry, India

**Ketki V Kudalkar** MSc  
Senior Scientific Research Officer  
and Laboratory Incharge  
Navi Mumbai Institute of Research  
in Mental and Neurological Handicap  
Navi Mumbai, Maharashtra, India

**Atul A Kulkarni** MD  
Assistant Professor  
Ashwini Rural Medical College  
Solapur, Maharashtra, India

**Madhuri Kulkarni** MD DCH PGD  
Former Professor and Head  
Department of Pediatrics and  
Former Dean In-charge  
LTM Medical College and LTMG Hospital  
Mumbai, Maharashtra, India

**Nikhil Kulkarni** MD  
DM Registrar  
Department of Neonatology  
St John's Medical College Hospital  
Bengaluru, Karnataka, India

**Shilpa Kulkarni** MD DNB  
Associate Professor in Pediatrics  
Bai Jerbai Wadia Hospital for Children  
Consultant Pediatric Neurologist  
Dr Balabhai Nanavati Hospital  
Mumbai, Maharashtra, India

**Snehal Kulkarni** MD DM DNB FACC  
Chief, Division of Pediatric Cardiology  
Kokilaben Dhirubhai Ambani Hospital  
Mumbai, Maharashtra, India

**Sucheta Kulkarni** DOMS DNB  
Head of Medical Retina and ROP Services  
HV Desai Eye Hospital  
Pune, Maharashtra, India

**Arun Kumar** MD MRCP FRCPC  
Consultant Pediatrician  
Croydon University Hospital Croydon  
Surrey, UK

**Ashok Kumar** MD FNNF FIAP FAMS  
Professor and Head  
Department of Pediatrics  
Institute of Medical Sciences  
Banaras Hindu University  
Varanasi, Uttar Pradesh, India

**Atin Kumar** MD DNB MNAMS  
Additional Professor  
Department of Radiology  
All India Institute of Medical Sciences  
New Delhi, India

**Jyoti Kumar** MD DNB MNAMS  
Professor  
Department of Radiodiagnosis  
Maulana Azad Medical College  
and Associated Lok Nayak Hospital  
New Delhi, India

**Mala Kumar** MD  
Professor in Pediatrics  
NICU In-charge  
King George's Medical University  
Lucknow, Uttar Pradesh, India

**Meet Kumar** MD  
Fellow  
Department of Hematology  
Nil Ratan Sircar Medical College and Hospital  
Kolkata, West Bengal, India

**Praveen Kumar** MD DM  
Head, Neonatal Unit and Professor  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Praveen Kumar** MD  
Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**Puneet Kumar** MD  
Consultant Pediatrician  
Kumar Child Clinic  
Dwarka, New Delhi, India

**R Krishna Kumar** MD DM FACC FAHA  
Clinical Professor and Head  
Department of Pediatric Cardiology  
Amrita Institute of Medical Sciences  
Kochi, Kerala, India

**R Ramesh Kumar** MD DNB MNAMS FPCC DM  
Assistant Professor  
Pediatric Critical Care Units  
JIPMER, Women and Children Hospital  
Puducherry, India

**R Suresh Kumar** MD DM FSCAI  
Senior Consultant and Head  
Department of Pediatric Cardiology  
Frontier Life Line and Dr KM Cherian  
Heart Foundation  
Chennai, Tamil Nadu, India

**Rakesh Kumar** MD  
Associate Professor  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Rashmi Kumar** MD FNASc  
Professor and Head  
Department of Pediatrics  
King George's Medical University  
Lucknow, Uttar Pradesh, India

**Sathish Kumar** MD DCH  
Consultant Pediatric Rheumatologist  
Professor of Pediatrics  
Christian Medical College  
Vellore, Tamil Nadu, India

**Sobha Kumar** MD  
Additional Professor  
Department of Pediatrics, SAT Hospital  
Government Medical College  
Thiruvananthapuram, Kerala, India

**Virendra Kumar** MD PDCDM  
Director Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**Shaveta Kundra** MD  
Associate Professor  
Department of Pediatrics  
Christian Medical College and Hospital  
Ludhiana, Punjab, India

**Ritabrata Kundu** MD FIAP  
Professor  
Department of Pediatrics  
Institute of Child Health  
Kolkata, West Bengal, India

**PA Kurkure** MD FIAP  
Professor Emeritus  
Pediatric Oncology and Head  
Division of Pediatric Oncology  
Department of Medical Oncology  
Tata Memorial Hospital  
Mumbai, Maharashtra, India

**K Anil Kuruvilla** MD  
Professor and Head  
Child Health and Neonatology Department  
Associate Director  
Christian Medical College and Hospital  
Vellore, Tamil Nadu, India

**Chandrakant Lahariya**  
MD DNB MNAMS PGDHHM FICMCB MBA  
Formerly Assistant Professor  
Department of Community Medicine  
GR Medical College  
Gwalior, Madhya Pradesh, India

**Michael W Lawlor** MD PhD  
Assistant Professor  
Medical College of Wisconsin  
Department of Pathology and  
Laboratory Medicine  
Division of Pediatric Pathology  
Milwaukee, Wisconsin, USA

**P Leelakumari** DCH DNB Mphil  
Additional Professor  
Department of Pediatrics  
SAT Hospital  
Government Medical College  
Thiruvananthapuram, Kerala, India

**Aparna Limaye** MD DCH DABP  
Consultant Pediatric Endocrinologist  
and Clinical Fellow  
Department of Pediatric Endocrinology  
Bai Jerbai Wadia Hospital for Children  
Mumbai, Maharashtra, India

**Lokesh Lingappa** MD DM MRCPC  
Consultant Pediatric Neurologist  
Rainbow Children's Hospital  
Hyderabad, Telangana, India

**Rakesh Lodha** MD  
Additional Professor  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**MR Lokeshwar** MD DCH FIAP  
Former Professor  
Department of Pediatrics  
LTMG Hospital and Medical College  
and Consultant Pediatrician  
and Pediatric Hematologist  
Shushrusha Citizens Cooperative Hospital Ltd  
Lilavati Hospital and Research Center  
Mumbai, Maharashtra, India

**Subhash Lokre** MD  
Consultant Dermatologist  
General Hospital  
Bengaluru, Karnataka, India

**Newton Luiz** MD DCH DNB  
Consultant Pediatrician  
Dhanya Mission Hospital  
Thrissur, Kerala, India

**Deenadayalan M** DNB FNB  
Consultant in Pediatric Hematology  
Oncology and Bone Marrow Transplant  
Apollo Hospitals  
Chennai, Tamil Nadu, India

**Jayashree M** MD DNB  
Additional Professor  
Department of Pediatrics  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Manu Madhok** MD MPH  
Associate Professor of Pediatrics  
University of Minnesota; and  
Director  
Pediatric Emergency Medicine  
Fellowship Program  
Division of Emergency Medicine  
Children's Hospitals and Clinics of Minnesota  
Minneapolis, USA

**Manisha Madkaikar** MD  
Scientist E  
National Institute of Immunohematology  
Indian Council of Medical Research  
KEM Hospital  
Mumbai, Maharashtra, India

**S Mahadevan** MD PhD MNAMS  
Professor of Pediatrics and Dean  
Head, Pediatric Critical Care Units  
JIPMER, Women and Children Hospital  
Puducherry, India

**Amita Mahajan** MD MRCPC CCST  
Senior Consultant  
Pediatric Hematology and Oncology  
Indraprastha Apollo Hospital  
New Delhi, India

**Vidushi Mahajan** DNB  
Assistant Professor  
Department of Pediatrics  
Government Medical College and Hospital  
Chandigarh, India

**Manoranjan Mahapatra** MD FICP FISTM FIACM  
Professor  
Department of Hematology  
All India Institute of Medical Sciences  
New Delhi, India

**Sunita Bijarnia Mahay** DCH DNB  
Associate Professor  
Ganga Ram Institute of Postgraduate  
Medical Education and Research  
and Senior Consultant  
Clinical and Metabolic Geneticist  
Center of Medical Genetics  
Sir Ganga Ram Hospital  
New Delhi, India

**Anu Maheshwari** MD  
Associate Professor  
Department of Pediatrics  
North Delhi Municipal Corporation  
Medical College  
New Delhi, India

**Sunita Maheshwari** ABP ABPC  
Senior Consultant  
Pediatric Cardiologist and Academic Professor  
Narayana Hrudayalaya  
Bengaluru, Karnataka, India

**Rajib Malakar** MD  
Clinical Tutor  
Department of Pediatric Dermatology  
Institute of Child Health  
Kolkata, West Bengal, India

**Prahbhjot Malhi** PhD  
Professor (Child Psychology)  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Priya Mary Mammen** DPM DNB  
Professor of Psychiatry  
Child and Adolescent Psychiatry Unit  
Department of Psychiatry  
Christian Medical College  
Vellore, Tamil Nadu, India

**Kausik Mandal** MD DM  
Assistant Professor  
Department of Medical Genetics  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Swati Manerkar** MD  
Assistant Professor  
Department of Neonatology  
Lokmanya Tilak Municipal Medical  
College and General Hospital  
Mumbai, Maharashtra, India

**Mamta Manglani** MD DCH  
Professor and Head  
Department of Pediatrics  
Chief, Division of Hematology-Oncology  
Program Director  
Pediatric Center of Excellence for HIV Care  
Lokmanya Tilak Municipal Medical  
College, and General Hospital  
Mumbai, Maharashtra, India

**Mukta Mantan** MD DNB  
Professor  
Department of Pediatrics  
Maulana Azad Medical College and  
Associated Lok Nayak Hospital  
New Delhi, India

**Aditi Manudhane** MS DNB  
Senior Resident  
Guru Nanak Eye Center  
Maulana Azad Medical College  
and Associated Hospitals  
New Delhi, India

**Ben J Marais** MD  
Professor and Deputy Director  
Marie Bashir Institute for Infectious  
Diseases and Biosecurity  
Center for Research Excellence in Tuberculosis  
and Infectious Diseases  
Clinician  
The Children's Hospital at Westmead  
University of Sydney, Australia

**Yogesh S Marfatia** MD  
Professor  
Department of Skin and Veneral Disease  
Medical College  
Vadodara, Gujarat, India

**RK Marwaha** MD (Late)  
Ex-Professor and Chief-Hematology/  
Oncology Unit, Department of Pediatrics  
Advanced Pediatric Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Sarah Mathai** DCH DNBE PhD  
Pediatric Endocrinologist  
Associate Professor  
Department of Pediatrics  
Christian Medical College and Hospital  
Vellore, Tamil Nadu, India

**Sheila S Mathai** MD DNB DM  
Professor and Head  
Department of Pediatrics and Neonatology  
Armed Forces Medical College  
Pune, Maharashtra, India

**Joseph I Mathew** MD  
Associate Professor  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**T Mathivanan** MS MCH  
Former Professor and Head  
Department of Plastic  
Reconstructive and Burn Surgery  
Kilpauk Medical College  
Chennai, Tamil Nadu, India

**Amit M Mathur** MD MRCP  
Professor of Pediatrics  
Division of Newborn Medicine, Washington  
University School of Medicine  
Medical Director  
Neonatal Intensive Care Unit  
St Louis Children's Hospital  
St Louis, Missouri, USA

**NB Mathur** MD  
Director Professor and Head  
Department of Neonatology  
Maulana Azad Medical College and  
Associated Lok Nayak Hospital  
New Delhi, India

**John Matthai** DCH MD FAB FIAP  
Pediatric Gastroenterologist  
Professor and Head  
Department of Pediatrics  
PSG Institute of Medical Sciences  
Coimbatore, Tamil Nadu, India

**Mignon I McCulloch** MD  
Associate Professor  
Pediatric Intensive Care Unit  
Red Cross War Memorial  
Children's Hospital  
Cape Town, South Africa

**AK Meena** MD DM  
Professor  
Department of Neurology  
Nizam's Institute of Medical Sciences  
Hyderabad, Telangana, India

**Babu Lal Meena** MD  
Division of Pediatric Gastroenterology  
Hepatology and Nutrition  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Sumit Mehndiratta** MD  
Junior Specialist  
Department of Pediatrics  
Maulana Azad Medical College and  
Associated Lok Nayak Hospital  
New Delhi, India

**Amarjeet Mehta** MD  
Professor  
Pediatric Medicine  
Sir Padampat Mother and  
Child Health Institute  
SMS Medical College  
Jaipur, Rajasthan, India

**Manju Mehta** DM SP PhD  
Professor of Clinical Psychology  
Department of Psychiatry  
All India Institute of Medical Sciences  
New Delhi, India

**Parang N Mehta** MD  
Consultant Pediatrician  
Mahavir General Hospital  
Surat, Gujarat, India

**Rajesh Mehta** MD FIAP  
Medical Officer  
Child and Adolescent Health  
WHO South East Asia Regional Office  
New Delhi, India

**Vibhu Mendiratta** MD  
Professor  
Department of Dermatology  
Lady Hardinge Medical College and  
Associated Kalwati Saran Children's Hospital  
New Delhi, India

**P Ramesh Menon** MD  
Assistant Professor  
Department of Pediatrics  
Institute of Maternal and Child Health  
Calicut, Kerala, India

**PSN Menon** MD MNAMS FIAP  
Consultant and Head  
Department of Pediatrics  
Jaber-Al-Ahmed Armed Forces Hospital  
Kuwait

**Ram K Menon** MD  
David Murray Cowie Research Professor  
of Pediatrics and Communicable Diseases  
Professor of Pediatrics  
Professor of Molecular and  
Integrative Physiology  
Director-Pediatric Endocrinology  
CS Mott Children's Hospital University  
of Michigan Med School  
Michigan, USA

**Shina Menon** MD  
Consultant Pediatric Nephrologist  
Apollo Center for Advanced Pediatrics  
Indraprastha Apollo Hospital  
New Delhi, India

**Devendra Mishra** MD  
Professor  
Department of Pediatrics  
Maulana Azad Medical College  
and Associated Lok Nayak Hospital  
New Delhi, India

**OP Mishra** MD MAMS FIAP  
Professor  
Department of Pediatrics  
Institute of Medical Sciences  
Banaras Hindu University  
Varanasi, Uttar Pradesh, India

**Pravas Mishra** MD DM  
Additional Professor  
Department of Hematology  
All India Institute of Medical Sciences  
New Delhi, India

**Ruchi Mishra** MD  
Specialist cum Assistant Professor  
Department of Pediatrics  
ESI Postgraduate Institute of Medical  
Sciences and Research  
New Delhi, India

**Smita Mishra** MD FDNB  
Associate Director  
Department of Pediatric Cardiology  
Jaypee Hospital  
Noida, Uttar Pradesh, India

**Kirtida Mistry** MBChD DCH MRCPCH  
Assistant Professor (Pediatrics)  
Children's National Medical Center  
The George Washington University  
Washington DC, USA

**Monjori Mitra** DCH DNB FIAP  
Associate Professor  
Institute of Child Health  
Kolkata, West Bengal, India

**Manoj Modi** MD DNB  
Consultant Neonatologist  
Sir Ganga Ram Hospital  
New Delhi, India

**Neelam Mohan** MD  
Director  
Department of Pediatric Gastroenterology,  
Hepatology and Liver Transplantation  
Medanta—The Medicity Hospital  
Gurgaon, Haryana, India

**Niranjan Mohanty** MD  
Professor of Pediatrics  
Postgraduate Institute of Pediatrics  
SCB Medical College  
Utkal University  
Bhubaneswar, Odisha, India

**Rakesh Mondal** MD DNB PDSR MNAMS  
Professor and Pediatric Rheumatologist  
Medical College  
Kolkata, West Bengal, India

**Jayashree Mondkar** MD  
Professor and Head  
Department of Neonatology  
Lokmanya Tilak Municipal Medical  
College and General Hospital  
Mumbai, Maharashtra, India

**Mari Mori** MD  
Medical Biochemical Genetics Fellow  
Duke University Medical Center  
Durham, North Carolina, USA

**Asha Moudgil** MD FASN  
Professor of Pediatrics  
Medical Director  
Kidney Transplant  
Children's National Medical Center  
The George Washington University  
Washington DC, USA

**Dhrubojyoti Mridha** MD  
Assistant Professor of Pediatrics  
CSS College of Obstetrics,  
Gynecology and Child Health  
Kolkata, West Bengal, India

**Sangeeta Mudaliar** DNB MRCPCH  
Consultant  
Department of Pediatrics  
Hematology and Oncology  
Bai Jerbai Wadia Hospital for Children  
Mumbai, Maharashtra, India

**M Zulf Mughal** MBChB FRCPCH FRCP  
Consultant in Pediatric  
Bone Disorders and Honorary Clinical  
Professor in Child Health  
Royal Manchester Children's Hospital  
Central Manchester University Hospitals  
Manchester, UK



**Sharmila Banerjee Mukherjee** MD

Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**Devdeep Mukherjee** DCH

Registrar  
Institute of Child Health  
Kolkata, West Bengal, India

**Kanya Mukhopadhyay** MD DNB DM

Professor of Neonatology  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Khushnuma Mullanfiroze** MD

Fellow in Pediatric Hematology-Oncology  
Bai Jerbai Wadia Hospital for Children  
Mumbai, Maharashtra, India

**Nandini Mundkur** MD

Director  
Consultant in Developmental Pediatrics  
Center for Child Development and Disabilities  
Bengaluru, Karnataka, India

**Mamta Muranjan** MD

Additional Professor of Pediatrics  
In-charge of the Genetic Clinic  
Seth GS Medical College and KEM Hospital  
Consultant in Clinical Genetics  
PD Hinduja National Hospital  
and Research Center  
Mumbai, Maharashtra, India

**Srinivas Murki** MD DM

Consultant Neonatologist  
Fernandez Hospital  
Hyderabad, Telangana, India

**Philip G Murray** MBChB PhD MRCPCH

Clinical Lecturer  
Department of Pediatric Endocrinology  
Royal Manchester Children's Hospital  
Manchester, UK

**Srinivas Murthy** MD FAAP FRCPC

Consultant Pediatrician  
British Columbia Children's Hospital and  
The University of British Columbia  
Faculty of Medicine  
Department of Pediatrics Child  
and Family Research Institute  
Vancouver, British Columbia, Canada

**Karthik Muthusamy** MD DM DNB

Associate Professor and Pediatric Neurologist  
Department of Neurological Sciences  
Christian Medical College  
Vellore, Tamil Nadu, India

**Ankush Mutreja** MS DNB FICO FAICO

Senior Resident  
Guru Nanak Eye Center  
Maulana Azad Medical College  
and Associated Hospitals  
New Delhi, India

**Deepthi Mutreja** MD DNB

Assistant Professor  
Department of Hematology  
All India Institute of Medical Sciences  
New Delhi, India

**Karthi N** MD DM

Assistant Professor  
Registrar, Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Shakil Ahmed Nagori** MDS

Department of Oral and Maxillofacial Surgery  
Center for Dental Education and Research  
All India Institute of Medical Sciences  
New Delhi, India

**Akash Nahar** MD MPH

Assistant Professor  
Division of Oncology  
St Christopher's Hospital of Children  
Drexel University College of Medicine  
Philadelphia, USA

**Ronak Naik** MD DNB FACC

Assistant Professor  
Division of Pediatric Cardiology  
Department of Pediatrics  
University of Tennessee Health Science Center  
Le Bonheur Children's Hospital  
Memphis, Tennessee, USA

**Tripty Naik** MD

Assistant Professor  
Department of Pediatrics  
Pt JNM Medical College  
Raipur, Chhattisgarh, India

**MKC Nair** PhD MD MMed Sc MBA MA FIAP FIACAM

Vice-Chancellor  
Kerala University of Health Sciences, Thrissur  
Formerly Professor of Pediatrics and Director  
Child Development Center, Medical College  
Thiruvananthapuram, Kerala, India

**Muralidharan Nair** MD DM

Professor and Head  
Department of Neurology  
Sree Chitra Tirunal Institute for  
Medical Sciences and Technology  
Thiruvananthapuram, Kerala, India

**Ruchi Nimish Nanavati** MD IBCLC

Professor and Head  
Department of Neonatology  
Seth GS Medical College and KEM Hospital  
Mumbai, Maharashtra, India

**Chhavi Nanda** DCH DNB MNAMS

Assistant Professor  
Department of Pediatrics  
Shri Guru Ram Rai Institute of  
Medical and Health Sciences  
Dehradun, Uttarakhand, India

**Nigam Prakash Narain** MD PhD MRCP

Professor and Head  
Department of Pediatrics  
Patna Medical College  
Patna, Bihar, India

**Tarun Narang** MD

Assistant Professor  
Department of Dermatology  
Venereology and Leperology  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Kirti M Naranje** MD

Assistant Professor  
Department of Neonatology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Kalpana Narendran** DNB

Chief, Department of Pediatric  
Ophthalmology and Strabismus  
Aravind Eye Hospital  
Coimbatore, Tamil Nadu, India

**Gaurav Narula** MD DNB

Associate Professor (Pediatric Oncology)  
Department of Medical Oncology  
Tata Memorial Center  
Mumbai, Maharashtra, India

**Patanjali Dev Nayar** MPH

Medical Officer  
South-East Asia Regional Office  
World Health Organization  
New Delhi, India

**Tipu Nazeer** MD

Professor of Pathology  
Director Surgical Pathology and  
Hematopathology Fellowship  
Albany Medical College  
Albany, New York, USA

**Ujjwal Nene** MA PhD

Consultant Psychologist  
Morris Child Development Center  
and TDH Rehabilitation Center  
KEM Hospital  
Pune, Maharashtra, India

**Daniel K Ng** MD FRCPCH

Consultant  
Department of Pediatrics  
Kwong Wah Hospital  
Hong Kong SAR, China

**Stephanie Nguyen** MD MAS

Assistant Professor of Pediatrics  
Section of Pediatric Nephrology  
University of California Davis Medical Center  
Sacramento, California, USA

**Somashekhar Nimbalkar** MD

Professor  
Department of Pediatrics  
Pramukhswami Medical College  
Anand, Gujarat, India

**S Nivedhana** MD

Consultant Microbiologist  
Kanchi Kamakoti CHILDS Trust Hospital  
Chennai, Tamil Nadu, India

**Narayanan P** MD

Associate Professor  
Department of Pediatrics  
Jawaharlal Institute of Postgraduate  
Medical Education and Research  
Puducherry, India

**Raja Padidela** MD

Consultant Pediatric Endocrinology  
and Honorary Senior Lecturer  
Royal Manchester Children's Hospital  
Central Manchester University Hospitals  
Manchester, UK

**C Padmapriyadarsini** DNB MS  
Deputy Director  
Department of Clinical Research  
National Institute for Research in Tuberculosis  
Chennai, Tamil Nadu, India

**Priyanka Pal** MD  
Associate Professor and In-charge  
Pediatric Rheumatology  
Institute of Child Health  
Kolkata, West Bengal, India

**Deepika Pandhi** MD MNAMS  
Associate Professor  
Department of Dermatology and STD  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Anand Pandit** MD FRCPCH  
Honorary Professor and Director  
Department of Pediatrics and Neonatology  
TDH Rehabilitation Center and  
Morris Child Development Center  
KEM Hospital  
Pune, Maharashtra, India

**Satish V Pandya** MD FIAP PGDAP PGDGC  
Consultant Pediatrician  
Varun Children Hospital  
Vadodara, Gujarat, India

**Ankit Parakh** MD DNB MNAMS EDPRM  
Consultant Pediatric Pulmonologist  
BL Kapur Memorial Hospital  
New Delhi, India

**H Paramesh** MD FAAP FIAP FIAMS FIAA FICAAI  
Pediatric Pulmonologist and Environmentalist  
Medical Director  
Lakeside Medical Center and Hospital  
Bengaluru, Karnataka, India

**Deepak A Parikh** MD  
Professor and Head  
Department of Pediatric Dermatology  
Bai Jerbai Wadia Hospital for Children  
Mumbai, Maharashtra, India

**Ketan Parikh** MS MCh  
Consultant Pediatric Surgeon and  
Pediatric Laparoscopist  
Jaslok Hospital  
Seven Hills Hospital  
and LH Hiranandani Memorial Hospital,  
Mumbai, Maharashtra, India

**Ruchi Parikh** DNB  
Fellow, Pediatric Endocrinology  
Division of Pediatric Endocrinology  
Bai Jerbai Wadia Hospital for Children  
Institute of Child Health and Research Center  
Mumbai, Maharashtra, India

**Veena R Parmar** MD  
Former Professor and Head  
Department of Pediatrics  
Government Medical College and Hospital  
Chandigarh, India

**Dinesh S Pashankar** MD MRCP  
Pediatric Gastroenterologist  
Associate Professor of Pediatrics  
Department of Pediatrics  
Yale University School of Medicine  
New Haven, Connecticut, USA

**Gouri Rao Passi** MD DNB MNAMS  
Consultant  
Department of Pediatrics  
In-charge  
Pediatric Neurology Clinic  
Choithram Hospital and Research Center  
Indore, Madhya Pradesh, India

**Leena Patel** MD FRCPCH MHPed MD FAME SFHEA  
Senior Lecturer in Child Health  
University of Manchester Medical School and  
Hon Consultant Pediatric Endocrinologist  
Royal Manchester Children's Hospital  
Manchester, UK

**Hema Patel** MD FAAN  
Professor  
Clinical Neurology  
Section of Pediatric Neurology  
Department of Neurology  
Director of the Pediatric Epilepsy  
Monitoring Unit and Ketogenic Diet Clinic  
Riley Hospital for Children  
Indiana University Medical Center  
Indianapolis, Indiana, USA

**HP Pati** MD FIMS FISHTM  
Professor  
Department of Hematology  
All India Institute of Medical Sciences  
New Delhi, India

**AK Patwari** MD MNAMS FIAP FAMS  
Professor and Head  
Department of Pediatrics  
Hamdard Institute of Medical  
Sciences and Research, and  
HAH Centenary Hospital  
Hamdard University  
New Delhi, India

**Nandini Paul** MSc  
PhD Scholar  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Sarah Paul** MD  
Professor  
Department of Pediatrics  
PSG Institute of Medical Sciences  
Coimbatore, Tamil Nadu, India

**Vinod K Paul** MD PhD  
Professor and Head  
Department of Pediatrics  
All India Institute of Medical Sciences  
New Delhi, India

**Katrina Peariso** MD PhD  
Neurocritical Care Fellow  
Neurocritical Care Program  
University of Cincinnati Neuroscience Institute  
Cincinnati, Ohio, USA

**Harish K Pemde** MD FIAP  
In-charge  
Center for Adolescent Health  
Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**Shubha R Phadke** MD DM  
Professor and Head  
Department of Medical Genetics  
Sanjay Gandhi Postgraduate  
Institute of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Pranay Phukan** MD FICOG  
Associate Professor  
Department of Obstetrics and Gynecology  
Assam Medical College and Hospital  
Dibrugarh, Assam, India

**R Bhanu Vikraman Pillai** MD FAAP  
Consultant in Pediatric Gastroenterology  
Amrita Institute of Medical  
Sciences and Research  
Kochi, Kerala, India

**Suman Rao PN** MD DM  
Professor and Head  
Department of Neonatology  
St John's Medical College Hospital  
Bengaluru, Karnataka, India

**Banani Poddar** MD DNB  
Professor  
Department of Critical Care Medicine  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**N Pooranagangadevi** MBBS PGDPH  
Scientist  
Department of Clinical Research  
National Institute for Research in Tuberculosis  
Chennai, Tamil Nadu, India

**Shakuntala Prabhu** MD DCH FRCPCH  
Professor  
Seth GS Medical College  
Head  
Department of Pediatrics and Division  
of Pediatric Cardiology  
Bai Jerbai Wadia Hospital for Children  
Mumbai, Maharashtra, India

**Nirmalya D Pradhan** MD  
Resident  
Pediatric Oncology  
Department of Medical Oncology  
Tata Memorial Center  
Mumbai, Maharashtra, India

**Sunil Pradhan** MD DM FRCP FAMS FNAsc  
Professor  
Department of Neurology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Baldev S Prajapati** MD FIAP MNAMS FICMCH  
Professor  
Department of Pediatrics  
GCS Medical College,  
Hospital and Research Center  
Ahmedabad, Gujarat, India

**Rajal B Prajapati** MD D Ped  
Professor  
Smt NHL Municipal Medical College  
Sheth VS General Hospital  
Ahmedabad, Gujarat, India

**Anand Prakash** MD DNB FNB  
Pediatric Hematologist-Oncologist  
Associate Professor  
Department of Pediatrics  
St John's Medical College Hospital  
Bengaluru, Karnataka, India

**Asuri N Prasad** MD FRCPC FRCPE  
Professor in Pediatrics and  
Clinical Neurosciences  
Section of Pediatric Neurology  
Department of Pediatrics, Faculty of Medicine  
Western University and  
Schulich School of Medicine and Dentistry  
London, Ontario, Canada

**Chitra Prasad** MD FRCPC FCCMG FACMG  
Associate Professor  
Genetics, Metabolism and Pediatrics  
Western University  
Director of Metabolic Clinic  
and Newborn Screening  
London Health Sciences Center  
Ontario, Canada

**Maya Prasad** MD  
Assistant Professor  
Pediatric Oncology  
Tata Memorial Hospital  
Mumbai, Maharashtra, India

**Rajniti Prasad** MD MAMS FIAP  
Associate Professor  
Department of Pediatrics  
Institute of Medical Sciences  
Banaras Hindu University  
Varanasi, Uttar Pradesh, India

**Tejo Oleti Pratap** MD DM  
Consultant Neonatologist  
Fernandez Hospital, Hyderguda  
Hyderabad, Telangana, India

**Leena Priyambada** MD  
Assistant Professor  
Department of Pediatrics  
Christian Medical College  
Vellore, Tamil Nadu, India

**Bindu PS** MD DNB DM  
Additional Professor  
Department of Neurology  
National Institute of Mental Health  
and Neurosciences  
Bengaluru, Karnataka, India

**Ratna Dua Puri** MD DM  
Professor  
Ganga Ram Institute of Postgraduate  
Medical Education and Research  
Center of Medical Genetics  
Sir Ganga Ram Hospital  
New Delhi, India

**Sajid Qureshi** MS DNB FICS FAIS  
Professor  
Division of Pediatric Surgical Oncology  
Department of Surgical Oncology  
Tata Memorial Hospital  
Mumbai, Maharashtra, India

**Nita Radhakrishnan** MD  
Fellow  
Pediatric Hematology-Oncology  
and Bone Marrow Transplantation  
Institute for Child Health  
Sir Ganga Ram Hospital  
New Delhi, India

**S Radhakrishnan** MD DM  
Head and Director  
Department of Pediatric and  
Congenital Heart Diseases  
Escorts Heart Institute and Research Center  
New Delhi, India

**Palany Raghupathy** MD DCH FRCP  
Professor of Pediatric Endocrinology  
Indira Gandhi Institute of Child Health  
Bengaluru, Karnataka, India

**Ruchi Rai** MD  
Professor  
Department of Pediatrics  
Motilal Nehru Medical College  
Allahabad, Uttar Pradesh, India

**Neena Raina** PhD  
Regional Advisor  
Child and Adolescent Health (CAH)  
WHO South-East Asia Regional Office  
New Delhi, India

**Rupesh Raina** MD  
Consultant  
Pediatric Nephrology  
Akron Children's Hospital and  
Cleveland Clinic (Medina)  
Cleveland, Ohio, USA

**Dinesh Raj** MD  
Consultant  
Department of Pediatrics  
Holy Family Hospital  
New Delhi, India

**R Benedict Raj** MS MCh FCPS  
Chief Pediatric Cardiac Surgeon  
and Associate Professor  
Amrita Institute of Medical Sciences  
and Research Center  
Ernakulam, Kerala, India

**Revathi Raj** DCH MRCP FRCPath  
Consultant in Pediatric Hematology  
Oncology and Bone Marrow Transplant  
Apollo Hospitals  
Chennai, Tamil Nadu, India

**B Bhaskar Raju** MD  
Former Professor and Head  
Department of Pediatric Gastroenterology  
Institute of Child Health and  
Hospital for Children  
Chennai, Tamil Nadu, India

**Geetha Ramachandran** PhD  
Scientist and Head  
Department of Biochemistry  
and Clinical Pharmacology  
National Institute for Research in Tuberculosis  
Chennai, Tamil Nadu, India

**P Ramachandran** MD DNB  
Professor of Pediatrics  
Sri Ramachandra Medical College  
Chennai, Tamil Nadu, India

**VG Ramachandran** PhD DMV  
Professor of Microbiology  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**K Mathangi Ramakrishnan**  
MB FRCS MCh DSc FAMS  
Former Professor of Burns, Plastic  
and Reconstructive Surgery  
Kilpauk Medical College, Chennai  
Chief of Plastic Surgery and Burns  
Chairperson, The CHILDS Trust  
Medical Research Foundation  
Kanchi Kamakoti CHILDS Trust Hospital  
Chennai, Tamil Nadu, India

**Mahesh Babu Ramamurthy** MD FCPS MRCP  
Senior Consultant and Head  
Division of Pediatric Pulmonology and Sleep  
Department of Pediatrics  
National University Hospital  
Singapore

**Venkateswaran Ramesh** MBBS FRCPC DCH  
Consultant Pediatric Neurologist  
and Honorary Clinical Lecturer  
Great North Children's Hospital  
Newcastle University Hospitals NHS Trust  
Newcastle upon Tyne, UK

**Siddarth Ramji** MD FNNF  
Director-Professor  
Department of Neonatology  
Maulana Azad Medical College and  
Associated Lok Nayak Hospital  
New Delhi, India

**Prajnya Ranganath** MD DM  
Assistant Professor and Head  
Department of Medical Genetics  
Nizam's Institute of Medical Sciences, and  
Adjunct Faculty, Diagnostics Division  
Center for DNA Fingerprinting and Diagnostics  
Hyderabad, Telangana, India

**Rajeev Ranjan** MD  
Senior Resident  
Department of Psychiatry  
All India Institute of Medical Sciences  
New Delhi, India

**Suchitra Ranjit** MD FCCM  
Head  
Department of Pediatric Critical Care  
and Emergency Medicine  
Apollo Children's Hospital  
Chennai, Tamil Nadu, India

**MS Ranjith** MD DCH  
Senior Consultant Pediatric Cardiologist  
Dr Mehta's Children's Hospital  
and Kavery Hospital  
Chennai, Tamil Nadu, India

**Anand Prahalad Rao** MD DNB FPR (EULAR)  
Consultant Pediatric Rheumatologist  
Manipal Hospital and Indira Gandhi  
Institute of Child Health  
Bengaluru, Karnataka, India

**Chandrika Rao** MD PGDAP PGDMLAE  
Professor and Head  
Department of Pediatrics  
MS Ramaiah Medical College and Hospitals  
Bengaluru, Karnataka, India

**G Raghurama Rao** MD  
Professor and Head  
Department of Dermatology and Venerology  
GSL Medical College  
Rajahmundry, Andhra Pradesh, India

**P Syamasundar Rao** MD FAAP FACC FSCAI  
Professor of Pediatrics and Medicine  
Director  
Pediatric Cardiology Fellowship Programs  
Emeritus Chief of Pediatric Cardiology  
University of Texas-Houston Medical School  
Children's Memorial, Hermann Hospital  
Houston, Texas, USA

**Rakesh Rao** MD  
Assistant Professor of Pediatrics  
Division of Newborn Medicine  
Department of Pediatrics  
Washington University School of Medicine  
St Louis, Missouri, USA

**SD Subba Rao** DCH DNB  
Former Professor and Head  
Department of Pediatrics  
St John's Medical College Hospital; and  
Consultant Pediatrician Manipal Hospital  
Bengaluru, Karnataka, India

**Narendra Rathi** MD DNB FIAP  
Consultant Pediatrician  
Rathi Children Hospital, Civil lines  
Akola, Maharashtra, India

**SR Rathinam** FAMS PhD  
Professor and Head of Uveitis Service  
Aravind Eye Hospital and Postgraduate Institute  
of Ophthalmology  
Madurai, Tamil Nadu, India

**ATK Rau** MD DHA  
Pediatric Hematologist-Oncologist  
Professor  
Department of Pediatrics  
MS Ramaiah Medical College  
Bengaluru, Karnataka, India

**Janani Ravi** MBBS  
Pediatrician  
Mehta Children Hospital  
Chennai, Tamil Nadu, India

**KG Ravikumar** MD MRCP FRCPCH  
Consultant Pediatric Endocrinologist  
Kanchi Kamakoti CHILDS Trust Hospital  
Chennai, Tamil Nadu, India

**Yaddanapudi Ravindranath** MBBS  
Professor of Pediatrics  
Georgie Ginopolos Chair of  
Pediatric Cancer and Hematology  
Wayne State University School of Medicine  
Division of Hematology/Oncology  
Children's Hospital of Michigan  
Detroit, Michigan, USA

**Amit Rawat** MD PDCC  
Associate Professor  
Pediatric Allergy and Immunology Unit  
Department of Pediatrics  
Advanced Pediatric Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**KR Bharath Kumar Reddy** MD DMLE  
Consulting Pediatric Pulmonologist  
Department of Pediatric Pulmonology and Sleep  
Indira Gandhi Institute of Child Health  
and Bhagwan Mahaveer Jain Institute  
of Pulmonology and Sleep  
Bengaluru, Karnataka, India

**Nikhil Rishikeshi** DOMS FPOS  
Head  
Pediatric Ophthalmology  
HV Desai Eye Hospital  
Pune, Maharashtra, India

**A Riyaz** MD DCH DNB DM  
Pediatric Gastroenterologist  
Professor and Head of Pediatrics  
Government Medical College  
Calicut, Kerala, India

**Manoj Kumar Rohit** MD DM MNAMS  
Additional Professor  
Department of Cardiology  
Advanced Cardiac Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Ajoy Roychoudhury** MDS  
Professor and Head  
Department of Oral and Maxillofacial Surgery  
Center for Dental Education and  
Research (CDER)  
All India Institute of Medical Sciences  
New Delhi, India

**Sunanda Roychoudhury** MDS FIBO  
Professor and Head  
Department of Orthodontics and  
Dentofacial Orthopedics  
Shri Bankey Bihari Dental College  
Ghaziabad, Uttar Pradesh, India

**Bruce K Rubin** MD MEngr MBA FRCP  
Jessie Ball du Pont  
Distinguished Professor and Chair  
Department of Pediatrics  
Professor of Biomedical Engineering  
Virginia Commonwealth University  
School of Medicine  
Children's Hospital of Richmond  
Virginia, USA

**CA Rupar** PhD FCCMG  
Associate Professor  
Departments of Biochemistry and Pediatrics  
Schulich School of Medicine and Dentistry  
Western University, Chair  
Division of Clinical Biochemistry  
Department of Biochemistry  
Western University, Canada

**Paul Russell** MD  
Professor of Psychiatry and Head  
Child and Adolescent Psychiatry Unit  
Department of Psychiatry  
Christian Medical College  
Vellore, Tamil Nadu, India

**Madhu S** MDS  
Associate Professor  
Department of Pedodontics  
Government Dental College  
Kozhikode, Kerala, India

**Pradeep S** MBBS  
Resident  
SVP Postgraduate Institute of Pediatrics  
SCB Medical College  
Cuttack, Odisha, India

**Srinivas S** MD DCH DNB PDCC  
Consultant Pediatric Gastroenterologist  
Kanchi Kamakoti CHILDS Trust Hospital  
Apollo Children's Hospital  
Chennai, Tamil Nadu, India

**Yamuna S** DNB DCH PGDAP  
Consultant Pediatrician and  
Adolescent Physician  
Child and Adolescent Clinic  
Chennai, Tamil Nadu, India

**Tapas Kumar Sabui** MD  
Professor and Head  
Department of Pediatrics  
Medical College  
Kolkata, West Bengal, India

**S Sacchidanand** MD DVD DHA FRCP  
Registrar (Evaluation)  
Rajiv Gandhi University of Health Sciences  
Bengaluru, Karnataka, India  
Former Professor and Head  
Department of Dermatology  
Bangalore Medical College and  
Research Institute, BMCRI  
Bengaluru, Karnataka, India

**Anupam Sachdeva** MD  
Chairman  
Department of Pediatrics; and  
Academics Director  
Pediatric Hematology and BMT Unit  
Institute of Child Health  
Sir Ganga Ram Hospital  
New Delhi, India

**Karan Singh Sagar** MD  
Public Health and Immunization Specialist  
Geneva, Switzerland

**Rajesh Sagar** MD  
Professor  
Department of Psychiatry  
All India Institute of Medical Sciences  
New Delhi, India

**Abhijeet Saha** MD  
Associate Professor  
Department of Pediatrics  
Division of Pediatric Nephrology  
Postgraduate Institute of Medical  
Education and Research and Associated  
Dr Ram Manohar Lohia Hospital  
New Delhi, India

**Abhijit Saha** MD  
Department of Dermatology  
Burdwan Medical College  
Burdwan, West Bengal, India

**Sushant Sahastrabudhe** MBBS MPH  
Enteric and Diarrheal Diseases Program Leader  
International Vaccine Institute  
Seoul, Republic of Korea

**Manisha Sahay** MD DNB MAMS  
Professor and Head  
Department of Nephrology  
Osmania Medical College and General Hospital  
Hyderabad, Telangana, India

**Jitendra Kumar Sahu** MD DM  
Assistant Professor  
Division of Pediatric Neurology  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India



**Biman Saikia** MD  
Additional Professor  
Department of Immunopathology  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Shiv Sajan Saini** MD DM  
Assistant Professor  
Newborn Unit  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Jayanth Sundar Sampath** MSc FRCS  
Consultant Pediatric Orthopedic  
Surgeon and Director  
Bangalore Institute of Movement  
Research and Analysis  
Bengaluru, Karnataka, India

**Thangavelu Sangaralingam** MD DNB MRCP  
Former Assistant Professor  
Institute of Child Health  
Madras Medical College  
Chennai, Tamil Nadu, India  
Head, Department of Pediatrics  
Mehta Children's Hospital  
Chennai, Tamil Nadu, India

**Chitra Sankar** MD  
Consultant Pediatrician  
Bangalore Children Hospital  
Bengaluru, Karnataka, India

**Janani Sankar** DNB PhD MAMS  
Senior Consultant  
Kanchi Kamakoti CHILDS Trust Hospital  
Chennai, Tamil Nadu, India

**M Jeeva Sankar** MD DM  
Assistant Professor  
Department of Pediatrics  
WHO Collaborating Center for Training  
and Research in Newborn Care  
ICMR Center for Advanced Research  
in Newborn Health  
Newborn Health Knowledge Center  
All India Institute of Medical Sciences  
New Delhi, India

**VS Sankaranarayanan** MD DCH DM MAMS  
Former Professor and Head  
Department of Pediatric Gastroenterology  
Madras Medical College, and  
Institute of Child Health  
Head and Senior Consultant  
Pediatric Gastroenterologist  
Kanchi Kamakoti CHILDS Trust Hospital  
Chennai, Tamil Nadu, India

**Naveen Sankhyan** MD DM  
Assistant Professor  
Neurology Unit  
Department of Pediatrics  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Indumathy Santhanam** MD DCH  
Professor and Head  
Pediatric Emergency Department  
Institute of Child Health  
Madras Medical College  
Chennai, Tamil Nadu, India

**Vijaya Sarathi** MD DM  
Assistant Professor  
Department of Endocrinology  
Vydehi Institute of Medical Sciences  
and Research Center  
Bengaluru, Karnataka, India

**Neha Sareen** MSc  
Research Scholar  
Department of Human Nutrition  
All India Institute of Medical Sciences  
New Delhi, India

**Yogesh Kumar Sarin** MD  
Director Professor and Head  
Department of Pediatric Surgery  
Maulana Azad Medical College and  
Associated Lok Nayak Hospital  
New Delhi, India

**Rashmi Sarkar** MD MNAMS  
Professor  
Department of Dermatology  
Maulana Azad Medical College and  
Associated Lok Nayak Hospital  
New Delhi, India

**Moinak Sen Sarma** MD PDCC  
Fellow  
Department of Pediatric Gastroenterology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Navaneetha Sasikumar** MD DM  
Consultant Cardiologist  
Narayana Hrudayalaya  
Guwahati, Assam, India

**Veeraraja B Sathenahalli** MD  
Assistant Professor  
Bapuji Child Health Institute  
and Research Center  
Davangere, Karnataka, India

**Sharada Sathish** DCH DNB  
Fellow Pediatric Emergency Medicine  
Institute of Child Health  
Madras Medical College  
Chennai, Tamil Nadu, India

**Malathi Sathiyasekaran** MD DCH DM MNAMS  
Senior Consultant Pediatric Gastroenterologist  
Kanchi Kamakoti CHILDS Trust Hospital  
Chennai, Tamil Nadu, India

**Sujata Sawhney** MD MRCP CCST  
Senior Consultant  
Rheumatologist Institute of Child Health  
Sir Ganga Ram Hospital  
New Delhi, India

**Anita Saxena** MD DM FACC FAMS  
Professor  
Department of Cardiology  
All India Institute of Medical Sciences  
New Delhi, India

**Pranjali Saxena** MD  
Department of Pediatrics  
Lala Lajpat Rai Memorial Medical College  
Meerut, Uttar Pradesh, India

**Renu Saxena** MD  
Head  
Department of Hematology  
All India Institute of Medical Sciences  
New Delhi, India

**Alison Scott** MBChB MRCPCH MSc  
Specialty Registrar in  
Pediatric Respiratory Medicine  
Sheffield Children's Hospital NHS Trust  
Sheffield, UK

**Julius Xavier Scott** MD DCH  
Professor of Pediatrics and Head  
Division of Pediatric Hematology  
and Oncology  
Sri Ramachandra Medical University  
Chennai, Tamil Nadu, India

**S Arivu Selvan** MS  
Professor and Head  
Department of Anatomy  
Government Medical College  
Kozhikode, Kerala, India

**Sankar Sengupta** MD  
Professor and Head  
Department of Microbiology  
Institute of Child Health and  
Chief-Clinical Quality and Academics  
The Calcutta Medical Research Institute  
Kolkata, West Bengal, India

**Senthil Senniappan** MD MRCPCH MSc PhD  
Consultant Pediatric Endocrinologist  
Alder Hey Children's Hospital  
Liverpool, UK

**Anju Seth** MD  
Professor  
Department of Pediatrics  
Lady Hardinge Medical College and Associated  
Kalawati Saran Children's Hospital  
New Delhi, India

**Tulika Seth** MD  
Additional Professor  
Department of Hematology  
All India Institute of Medical Sciences  
New Delhi, India

**GR Sethi** MD  
Director-Professor and Head  
Department of Pediatrics  
Maulana Azad Medical College and  
Associated Lok Nayak Hospital  
New Delhi, India

**Manpreet Sethi** MD  
Consultant  
Department of Pediatrics  
Pushpanjali Crosslay Hospital  
Ghaziabad, Uttar Pradesh, India

**Sidharth Kumar Sethi** MD  
Consultant  
Pediatric Nephrology  
Kidney and Urology Institute  
Medanta—The Medicity Hospital  
Gurgaon, Haryana, India

**Dheeraj Shah** MD FIAP MNAMS  
Associate Professor  
Department of Pediatrics  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Ira Shah** MD DCH FCPS DNB  
In-charge Pediatric HIV, TB and Liver Clinic  
and Associate Professor of Pediatrics  
Bai Jerbai Wadia Hospital for Children  
Mumbai, Maharashtra, India

**Manish K Shah** MD

Associate Dermatologist  
Bai Jerbai Wadia Hospital for Children  
Mumbai, Maharashtra, India

**Nalini S Shah** MD DM

Professor and Head  
Department of Endocrinology  
Seth GS Medical College and KEM Hospital  
Mumbai, Maharashtra, India

**Nishant Shah** MD FACC

Pediatric Cardiologist  
Fellowship Program Director  
Division of Cardiology  
Department of Pediatrics  
Penn State Hershey Medical Center  
Penn State College of Medicine  
Hershey, Pennsylvania, USA

**Nitin Shah** MD DCH

Professor of Pediatrics and  
Consultant Pediatrician  
PD Hinduja Hospital  
Mumbai, Maharashtra, India

**Pratima Shah** MD DPed

Former Professor  
SBK Medical College  
Gujarat, India

**Raju C Shah** MD DPed FIAP

Former Professor and Head of Pediatrics  
GCS Medical College  
Ahmedabad, Gujarat, India

**Sajani K Shah** MS

Consultant Ophthalmologist  
Iladevi Cataract and IOL Research Center  
Raghudeep Eye Hospital  
Ahmedabad, Gujarat, India

**Venkat Shankar** MD MBA FAAP FCCP

Associate Professor of Pediatrics  
George Washington University  
School of Medicine  
Division Chief  
Divisions of Critical Care Medicine  
and Respiratory Care  
Director  
Pediatric ECMO and VAD  
Children's National Health System  
Washington DC, USA

**Naresh P Shanmugam** DCH DNB FRCPCH

Consultant Pediatric Hepatologist  
and Gastroenterology  
Institute of Liver Diseases and Transplantation  
Global Hospital and Health City  
Chennai, Tamil Nadu, India

**JN Sharma** MD

Professor and Head  
Department of Pediatrics  
North Eastern Indira Gandhi Regional  
Institute of Health and Medical Sciences  
Shillong, Meghalaya, India

**Jyoti Sharma** MD DNB

Consultant Pediatric Nephrologist  
King Edward Memorial Hospital  
Pune, Maharashtra, India

**MC Sharma** MD, FRCPath

Professor  
Department of Pathology  
All India Institute of Medical Sciences  
New Delhi, India

**Meghna Sharma** MD

Senior Resident  
Department of Pediatrics  
Government Medical College and Hospital  
Chandigarh, India

**Neetu Sharma** MD

Assistant Professor  
Department of Pediatrics  
GR Medical College  
Gwalior, Madhya Pradesh, India

**Pradeep Sharma** MD DM

Senior Consultant  
SPS Apollo Hospitals  
Ludhiana, Punjab, India

**Pradeep Sharma** MD FAMS

Professor of Ophthalmology  
Dr Rajendra Prasad Center  
for Ophthalmic Sciences  
All India Institute of Medical Sciences  
New Delhi, India

**Pramod Sharma** MD

Professor  
Department of Pediatrics  
Umaid Hospital for Women and Children  
Dr SN Medical College  
Jodhpur, Rajasthan, India

**Rajni Sharma** MD

Consultant Pediatric Endocrinologist  
BL Kapur Superspecialty Hospital  
New Delhi, India

**Sangeeta Sharma** MD

Head  
Department of Pediatrics  
National Institute of Tuberculosis  
and Respiratory Diseases  
New Delhi, India

**Shilpa Sharma** MS MCh DNB PhD

Assistant Professor  
Department of Pediatric Surgery  
All India Institute of Medical Sciences  
New Delhi, India

**Suvasini Sharma** MD DM

Assistant Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**Lazina Sharmin** MBBS FCPS

Assistant Professor  
Department of Pediatrics  
Enam Medical College and Hospital  
Savar, Bangladesh

**Upender Shava** MD PDCC

Fellow  
Department of Pediatric Gastroenterology  
Sanjay Gandhi Postgraduate  
Institute of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Subhash Chandra Shaw** MD DM

Pediatrician and Neonatologist  
Command Hospital, Eastern Command  
Kolkata, West Bengal, India

**Niranjan Shendurnikar** MD FIAP

Consultant Pediatrician  
KG Patel Children Hospital  
Vadodara, Gujarat, India

**VS Akbar Sherif** MS MCh

Former Professor and Head  
Department of Pediatric Surgery  
Medical College  
Principal, Malabar Medical College  
Calicut, Kerala, India

**Anita Shet** MD PhD

Associate Professor  
Department of Pediatrics  
St John's Medical College Hospital  
Bengaluru, Karnataka, India

**Kshitij Sheth** DNB MD FNB

Pediatric Cardiologist  
Glenmark Cardiac Center  
Mumbai, Maharashtra, India

**Preeti Sheth** MD FRGUHS

Registrar  
Bangalore Medical College and  
Research Institute  
Bengaluru, Karnataka, India

**Savitri Shrivastava** MD DM FAMS FACC FACA FICC

Director  
Pediatric and Congenital Heart Diseases  
Fortis Escorts Heart Institute  
New Delhi, India

**Anupam Sibal** MD FIMSA FIAP FRCP FRCPC FAAP

Group Medical Director  
Apollo Hospitals Group  
Senior Consultant  
Pediatric Gastroenterologist and Hepatologist  
Indraprastha Apollo Hospital  
New Delhi, India

**Sirisharani Siddaiahgari** MD DNB MRCPC

Consultant Pediatric Hematologist-Oncologist  
Rainbow Children's Hospital  
Hyderabad, Telangana, India

**Anna Simon** MD

Professor and Head  
Department of Pediatrics  
Christian Medical College  
Vellore, Tamil Nadu, India

**Daljit Singh** MS MCH

Professor  
Department of Neurosurgery  
Maulana Azad Medical College and  
Associated GB Pant Hospital  
New Delhi, India

**Digvijay Singh** MD

Associate Consultant  
Medanta Division of Ophthalmology  
Medanta—The Medicity Hospital  
Gurgaon, Haryana, India

**Hukum Singh** MS MCh

Associate Professor  
Department of Neurosurgery  
Maulana Azad Medical College and  
Associated GB Pant Hospital  
New Delhi, India

**Kirti Singh** MD DNB FRCS

Director Professor  
Glaucoma and CL LV Division  
Guru Nanak Eye Center  
Maulana Azad Medical College  
and Associated Hospitals  
New Delhi, India

**Kuldeep Singh** MD DM FAMS  
Additional Professor and Head  
Department of Pediatrics  
All India Institute of Medical Sciences  
Jodhpur, Rajasthan, India

**Manoj Kumar Singh** MD  
Lecturer  
Department of Pediatrics  
SN Medical College  
Agra, Uttar Pradesh, India

**Meenu Singh** MD FCCP FIAP  
Professor of Pediatrics  
In-charge Pediatric Pulmonology  
Asthma and Allergy Clinics  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Neha Singh** MD  
Fellow  
Department of Hematopathology  
All India Institute of Medical Sciences  
New Delhi, India

**Preeti Singh** MD  
Assistant Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**Ramandeep Singh** DCH MD FRCPCH  
Consultant Pediatric Oncologist  
Department of Medical Oncology  
Max Superspecialty Hospital  
New Delhi, India

**Surjit Singh** MD DCH FRCP FRCPCH FAMS  
Professor of Pediatrics and In-charge  
Allergy Immunology Unit  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Tejinder Singh** MD DNB FIAP MA MSc  
Professor  
Department of Pediatrics  
Christian Medical College and Hospital  
Ludhiana, Punjab, India

**Varinder Singh** MD FRCPCH  
Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**Kamal Kumar Singhal** DCH MD  
Assistant Professor  
Department of Pediatrics  
Lady Hardinge Medical College and  
Associated Kalawati Saran Children's Hospital  
New Delhi, India

**Rashi Singhal** MD  
Assistant Professor  
Department of Pediatrics  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Ravish Singhal** DNB  
Fellow in Neonatology  
Department of Pediatrics  
Government Medical College and Hospital  
Chandigarh, India

**Swati Singhal** MD MRCPCH  
Staff Registrar  
Department of Child Development  
KK Hospital, Singapore

**Tanu Singhal** MD  
Consultant  
Pediatrics and Infectious Disease  
Kokilaben Dhirubhai Ambani Hospital  
Mumbai, Maharashtra, India

**Pratibha Singh** MD FIAP FAMS  
Chief  
Pediatric Neurology and Neurodevelopment  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Sunit Singh** MD FIAP FAMS  
Professor and Head  
Pediatric Emergency and Intensive Care  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Aditi Sinha** MD DNB  
Assistant Professor  
Division of Pediatric Nephrology  
All India Institute of Medical Sciences  
New Delhi, India

**Rajiv Sinha** MD FRCPCH  
Associate Professor  
Department of Pediatrics  
Institute of Child Health  
Kolkata, West Bengal, India

**Shalini Sinha** MS MCh  
Assistant Professor  
Department of Pediatric Surgery  
Maulana Azad Medical College  
and Associated Lok Nayak Hospital  
New Delhi, India

**Sunil K Sinha** MD PhD FRCPCH FRCP  
Professor  
Department of Neonatology  
James Cook University Hospital  
Middlesbrough, UK  
University of Durham  
Stockton-on-Tees, UK

**Somu Sivabalan** MD DNB MNAMS FCCP FIAP  
Consultant Pediatrician and Pulmonologist  
Sundaram Medical Foundation  
Dr Rangarajan Memorial Hospital  
Chennai, Tamil Nadu, India

**K Sivakumar** MD DCH DNB DM DNB  
Head  
Department of Pediatric Cardiology and  
Senior Consultant  
Institute of Cardiovascular Diseases  
The Madras Medical Mission  
Chennai, Tamil Nadu, India

**S Sivasankaran** MD DM MNAMS  
Professor of Cardiology  
Sree Chitra Tirunal Institute for  
Medical Sciences and Technology  
Medical College  
Thiruvananthapuram, Kerala, India

**Praveen C Sobti** MD DCH FIMSA  
Professor (Pediatric Hemato-oncology)  
Christian Medical College and Hospital  
Ludhiana, Punjab, India

**Vishal Sondhi** MD  
Assistant Professor  
Department of Pediatrics  
Armed Forces Medical College  
Pune, Maharashtra, India

**Samatha Sonnappa** MD DCH MRCP FRCPCH PhD  
Respiratory, Critical Care and Anesthesia  
(Portex Unit)  
UCL Institute of Child Health and  
Great Ormond Street Hospital  
for Children, NHS Trust  
London, UK

**Prashant Sood** MD  
Senior Research Officer  
Department of Medical Microbiology  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Vikrant Sood** MD  
Senior Resident  
Department of Pediatric Hepatology  
Institute of Liver and Biliary Sciences  
New Delhi, India

**Shoba Srinath** MD DPM  
Professor of Child and Adolescent Psychiatry  
Department of Child and Adolescent Psychiatry  
National Institute of Mental Health  
and Neurosciences  
Bengaluru, Karnataka, India

**Arathi Srinivasan** DNB  
Junior Consultant  
Department of Pediatric  
Hematology and Oncology  
Kanchi Kamakoti CHILDS Trust Hospital  
Chennai, Tamil Nadu, India

**S Srinivasan** MD  
Professor and Head  
Department of Pediatrics  
Mahatma Gandhi Medical College  
and Research Institute  
Puducherry, India

**V Srinivasan** MS MCH  
Professor of Plastic  
Reconstructive and Microsurgery  
Sri Ramachandra Medical College  
Chennai, Tamil Nadu, India

**Vijay Srinivasan** MD FAAP  
Assistant Professor  
Department of Anesthesiology  
Critical Care and Pediatrics  
Perelman School of Medicine  
University of Pennsylvania  
and Attending Physician  
The Children's Hospital of Philadelphia  
Philadelphia, Pennsylvania, USA

**Anshu Srivastava** MD DM  
Additional Professor  
Department of Pediatric Gastroenterology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**RN Srivastava** DCH FIAP FAMS FRCP  
Consultant Pediatric Nephrologist  
Apollo Indraprastha Hospital  
New Delhi, India

**Gopinath Musuwadi Subramanian**  
MD DNB DM DNB FRACP  
Consultant Staff Specialist  
in Pediatric Neurology  
John Hunter Children's Hospital  
New Lambton Heights  
New South Wales, Australia

**NK Subramanya** MD  
Professor  
Department of Pediatrics  
Vydehi Institute of Medical Sciences  
Bengaluru, Karnataka, India

**Annapurna Sudarsanam** MD MRCPCH FRACP  
Staff Specialist Pediatrician  
Goulburn Base Hospital  
New South Wales, Australia

**Nidhi Sugandhi** MD  
Assistant Professor  
Department of Pediatric Surgery  
Postgraduate Institute of Medical Education  
and Research and Associated RML Hospital  
New Delhi, India

**Shaila Sukthankar** MD FRCPCH  
Consultant Pediatrician  
Royal Manchester Children's Hospital  
Central Manchester University Hospitals  
Manchester, UK

**Praveen Suman** MD  
Senior Consultant  
Developmental Pediatrician  
Department of Pediatrics  
Sir Ganga Ram Hospital  
Director  
Child Development  
New Delhi, India

**Shyam Sundar** MD FRCP FAMS FNA  
Professor  
Department of Medicine  
Institute of Medical Sciences  
Banaras Hindu University  
Varanasi, Uttar Pradesh, India

**Karthick Sundaram** MD  
Consultant  
Department of Pediatrics  
Institute of Liver Diseases  
and Transplantation  
Global Hospital and Health City  
Chennai, Tamil Nadu, India

**Soumya Sundaram** MD DM  
Assistant Professor  
Department of Neurology  
Sree Chitra Tirunal Institute for  
Medical Sciences and Technology  
Thiruvananthapuram, Kerala, India

**Venkataseshan Sundaram** MD DM  
Assistant Professor  
Newborn Unit  
Department of Pediatrics  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Amita Suneja** MD FICMCH MNAMS  
Professor  
Department of Obstetrics and Gynecology  
University College of Medical Sciences  
and Guru Teg Bahadur Hospital  
New Delhi, India

**Deepti Suri** MD  
Assistant Professor  
Pediatric Allergy Immunology Unit  
Department of Pediatrics  
Advanced Pediatric Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Archana Swami** MD MRCP  
Consultant  
Department of Pediatrics  
Hematology/Oncology  
Bai Jerbai Wadia Hospital  
Mumbai, Maharashtra, India

**Soumya Swaminathan** MD FIAP FASc FNAsc FAMS  
Director  
National Institute for Research  
in Tuberculosis  
Chennai, Tamil Nadu, India

**Zaki Syed** MD FCPS FICMCH  
Associate Professor  
Department of Pediatrics  
Employees State Insurance Corporation  
Medical College  
Gulbarga, Karnataka, India

**B Talukdar** DCH MD  
Former Director-Professor and Head  
Department of Pediatrics  
Chacha Nehru Bal Chikitsalaya  
New Delhi, India

**Parag M Tamhankar** MD DNB DCH FCPS DM  
Assistant Director and Divisional Head  
ICMR Genetic Research Center  
National Institute for Research in  
Reproductive Health  
Mumbai, Maharashtra, India

**Nirav Thacker** MD  
Registrar  
Department of Pediatric Oncology  
Tata Memorial Hospital  
Mumbai, Maharashtra, India

**Rhishikesh Thakre** DM MD DNB FCPS  
Consultant Neonatologist and Director  
Neonatal Intensive Care Unit  
Neo Clinic and Hospital  
Aurangabad, Maharashtra, India

**Anup Thakur** MD DNB  
Assistant Professor and Associate Consultant  
Department of Neonatology  
Institute of Child Health  
Sir Ganga Ram Hospital  
New Delhi, India

**BR Thapa** MD  
Professor and Head  
Division of Pediatric Gastroenterology  
Hepatology and Nutrition  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Maya Thomas** DCH MD DM  
Professor and Pediatric Neurologist  
Department of Neurological Sciences  
Christian Medical College and Hospital  
Vellore, Tamil Nadu, India

**Niranjan Thomas** MD  
Professor  
Department of Neonatology  
Christian Medical College and Hospital  
Vellore, Tamil Nadu, India

**Soumya Tiwari** MD  
Assistant Professor of Pediatrics  
Kalawati Saran Children's Hospital and  
Lady Hardinge Medical College  
New Delhi, India

**Munesh Tomar** MD FNB  
Senior Consultant  
Department of Pediatric Cardiology  
and Congenital Heart Diseases  
Medanta—The Medicity Hospital  
Gurgaon, Haryana, India

**Sidharth Totadri** MD  
Registrar  
Pediatric Hematology-Oncology Unit  
Department of Pediatrics  
Advanced Pediatric Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Amita Trehan** MD  
Additional Professor  
Pediatric Hematology-Oncology  
Advanced Pediatric Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Piyush Tripathi** MSc  
Research Scholar  
Department of Pediatrics  
King George's Medical University  
Lucknow, Uttar Pradesh, India

**Shalini Tripathi** MD  
Assistant Professor  
Department of Pediatrics  
King George's Medical University  
Lucknow, Uttar Pradesh, India

**Koushik Tripathy** MS  
Senior Resident  
Dr Rajendra Prasad Center  
for Ophthalmic Sciences  
All India Institute of Medical Sciences  
New Delhi, India

**Shamik Trivedi** MD  
Fellow in Neonatal/Perinatal Medicine  
Division of Newborn Medicine  
Washington University School of Medicine  
St Louis Children's Hospital  
St Louis, Missouri, USA



**Milind S Tullu** MD DCH DNB FCPS MNAMS FIAP  
Additional Professor  
Department of Pediatrics  
Seth GS Medical College and KEM Hospital  
Mumbai, Maharashtra, India

**Vrajesh Udani** MD DABNP DABCN  
Section of Child Neurology and Epilepsy  
PD Hinduja National Hospital  
Mumbai, Maharashtra, India

**Sunil Udgire** DNB DCH  
Fellow  
Department of Pediatric Hematology-Oncology  
Bai Jerbai Wadia Hospital  
Mumbai, Maharashtra, India

**Anaita Udwadia-Hegde** MD MRCPCH  
Consultant Pediatric Neurologist  
Jaslok Hospital and Research Center  
Mumbai, Maharashtra, India

**Jeeson C Unni** MD DCH FIAP  
Editor-in-Chief  
Indian Academy of Pediatrics  
Drug Formulary and Pediatrician  
Dr Kunhalu's Nursing Home  
Cochin, Kerala, India

**Amit Upadhyay** MD DM  
Professor and Head  
Department of Pediatrics  
LLRM Medical College  
Meerut, Uttar Pradesh, India

**J Andoni Urtizberea** MD  
Professor and Consultant Myologist  
Neuromuscular Unit, Hospital Marin  
Hendaye, France

**Susan Uthup** MD DNB DM DNB FISI  
Additional Professor and  
Chief of Pediatric Nephrology  
Department of Pediatrics  
SAT Hospital  
Government Medical College  
Thiruvananthapuram, Kerala, India

**Kheya Ghosh Uttam** MD  
Associate Professor and NICU  
In-charge  
Institute of Child Health  
Kolkata, West Bengal, India

**Zeynep Seda Uyan** MD  
Associate Professor  
Division of Pediatric Pulmonology  
Kocaeli University, Kocaeli, Turkey

**Neelam Vaid** MS DNB  
Associate Professor  
Department of ENT  
KEM Hospital  
Pune, Maharashtra, India  
Head of the Audiology and  
Cochlear Implant Program  
KEM Hospital  
Pune, Maharashtra, India

**Pankaj C Vaidya** MD  
Assistant Professor  
Department of Pediatric Medicine  
Advanced Pediatrics Center  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Sunil Vaidya** MD DCH  
Professor and Head  
Department of Pediatrics  
Ashwini Rural Medical College  
Solapur, Maharashtra, India

**Balu Vaidyanathan** MD DM FACC  
Clinical Professor  
Pediatric Cardiology  
Amrita Institute of Medical Sciences  
Kochi, Kerala, India

**Neelam Varma** MD FISHTM  
Professor and Head, Hematology  
Chairperson, Pathology  
Postgraduate Institute of Medical  
Education and Research  
Chandigarh, India

**Resham J Vasani** MD DNB FCPS DDV  
Assistant Professor  
Department of Dermatology  
KJ Somaiya Medical College  
and Research Center  
Mumbai, Maharashtra, India

**Abhay R Vasavada** MS FRCS  
Consultant Ophthalmologist  
Iladevi Cataract and IOL Research Center  
Raghudeep Eye Hospital  
Ahmedabad, Gujarat, India

**Vipin M Vashishtha** MD FIAP  
Convener, Indian Academy of Pediatrics  
Advisory Committee on Vaccines  
and Immunization Practices  
Director and Consultant Pediatrician  
Mangla Hospital and Research Center  
Bijnor, Uttar Pradesh, India

**Anil Vasudevan** MD DNB  
Associate Professor  
Department of Pediatric Nephrology  
St John's Medical College Hospital  
Bengaluru, Karnataka, India

**Pradeep Venkatesh** MS DNB  
Professor Ophthalmology  
Dr Rajendra Prasad Center for  
Ophthalmic Sciences  
All India Institute of Medical Sciences  
New Delhi, India

**Sumitra Venkatesh** DCH DNB  
Assistant Professor  
Division of Pediatric Cardiology  
Department of Pediatrics  
Bai Jerbai Wadia Hospital for Children  
Mumbai, Maharashtra, India

**Kannan Venkatnarayan** MD DNB MNAMS DM  
Associate Professor  
Department of Pediatrics  
Command Hospital and Armed  
Forces Medical College  
Pune, Maharashtra, India

**Anupam Verma** MD PDCC  
Additional Professor  
Department of Transfusion Medicine  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**IC Verma** FRCP FAAP FAMS FIAP  
Professor and Director  
Center of Medical Genetics  
Sir Ganga Ram Hospital  
New Delhi, India

**Priya Verma** MBBS  
Resident  
Department of Pediatrics  
Patna Medical College  
Patna, Bihar, India

**Rohit Verma** MD  
Assistant Professor  
Department of Psychiatry  
All India Institute of Medical Sciences  
New Delhi, India

**Joseph John Vettukattil**  
MD DNB FRCP FRCPCH CCST  
Co-Director and Division Chief  
The Congenital Heart Center  
Helen De Vos Children's Hospital  
Grand Rapids, Michigan, USA

**M Vijayakumar** MD  
Additional Professor  
Department of Pediatrics  
Government Medical College  
Kozhikode, Kerala, India

**M Vijayakumar** MD DCH DM FIAP  
Head  
Department of Pediatric Nephrology  
Mehta Children's Hospital, Chetpet  
Chennai, Tamil Nadu, India

**IB Vijayalakshmi** MD DM DSc  
Professor of Pediatric Cardiology  
Sri Jayadeva Institute of Cardiovascular  
Sciences and Research  
Bengaluru, Karnataka, India

**D Vijayasekaran** MD PhD FIAP  
Former Professor  
Pediatrics and Respiratory Diseases  
Madras Medical College; and  
Pediatric Pulmonologist  
Sree Balaji Medical College, KKCTH and  
Apollo Children's Hospital  
Chennai, Tamil Nadu, India

**Anju Virmani** MD  
Senior Consultant Pediatric Endocrinologist  
Apollo, Max, Pentamed  
and Sunderlal Jain Hospitals  
New Delhi, India

**V Viswanathan** MBBS DCH MRCP PhD  
Consultant Pediatric Neurologist  
Kanchi Kamakoti CHILDS Trust and  
Apollo Children's Hospitals  
Chennai, Tamil Nadu, India

**Tushar Vora** MD MRes  
Associate Professor  
Pediatric Medical Oncology  
Tata Memorial Hospital  
Mumbai, Maharashtra, India

**Praveen VP** MD DM  
Clinical Additional Professor  
Department of Endocrinology  
Amrita Institute of Medical Sciences  
Kochi, Kerala, India

**Arpita K Vyas** MBChB DCH  
Assistant Professor  
Pediatric Endocrinology  
Department of Pediatrics College  
of Human Medicine  
Michigan State University, Michigan, USA

**Bhawna Wadhwa** MD  
Skin Specialist  
Department of Dermatology  
Lok Nayak Hospital  
New Delhi, India

**Nishant Wadhwa** DCH DNB  
Senior Consultant and Chief  
Division of Pediatric Gastroenterology  
and Hepatology  
Institute of Child Health  
Sir Ganga Ram Hospital  
New Delhi, India

**Yogesh Waikar** MD DNB  
Consultant Pediatric Gastroenterologist  
and Hepatologist  
Superspecialty Children Clinics  
Nagpur, Maharashtra, India

**Mandeep Walia** MD  
Assistant Professor  
Department of Pediatrics  
Maulana Azad Medical College  
and Associated Lok Nayak Hospital  
New Delhi, India

**Vinit Warthe** MD  
Assistant Professor  
Department of Pediatrics  
Government Medical College  
Akola, Maharashtra, India

**Sanjay Wazir** MD DM  
Consultant Neonatologist  
The Cradle, Apollo Hospital  
Gurgaon, Haryana, India

**Ronald W Williams** MD  
Assistant Professor  
Department of Pediatrics  
Virginia Commonwealth University  
School of Medicine  
Children's Hospital of Richmond  
Virginia, USA

**Erica Winnicki** MD  
Assistant Professor of Pediatrics  
Section of Pediatric Nephrology  
University of California Davis Medical Center  
Sacramento, California, USA

**Michael A Wood** MD  
Associate Professor of Pediatrics  
Division of Pediatric Endocrinology  
University of Michigan  
Ann Arbor, Michigan, USA

**Surender Kumar Yachha** MD DM  
Professor and Head  
Department of Pediatric Gastroenterology  
Sanjay Gandhi Postgraduate Institute  
of Medical Sciences  
Lucknow, Uttar Pradesh, India

**Dinesh Yadav** MD  
Consultant Pediatrician  
Vivekanand Hospital  
Bhadra, Rajasthan, India  
Formerly, Assistant Professor of Pediatrics  
Sri Aurobindo Institute of Medical Sciences  
Indore, Madhya Pradesh, India

**Rakhil S Yadav** MD DM  
Assistant Professor  
Department of Neurology  
Grant Medical College and  
Sir JJ Group of Hospitals  
Mumbai, Maharashtra, India

**Satya Prakash Yadav** DCH DNB  
Consultant Pediatric Hematology-Oncology  
and Bone Marrow Transplant Unit  
Fortis Memorial Research Institute  
Gurgaon, Haryana, India

**Ada Y Yip** MB ChB MRCPCH  
Associate Consultant  
Department of Pediatrics  
Kwong Wah Hospital  
Hong Kong SAR, China

**Sangeetha Yoganathan** MD DNB DM  
Assistant Professor  
Department of Neurological Sciences  
Christian Medical College and Hospital  
Vellore, Tamil Nadu, India

**Margaret Zacharin** MB D Med Sci FRACP  
Professor  
Pediatric Endocrinology  
Royal Children's Hospital  
Melbourne, Australia

# Preface

---

In the last decade, many textbooks of pediatrics have been published in India. However, most were targeted towards undergraduates and general practitioners. The number of students opting for postgraduate courses in pediatrics is on the rise. Currently, most postgraduates in pediatrics augment their knowledge by reading and referencing to textbooks published abroad. Many of the Western textbooks are very detailed and provide an important amalgamation of clinical pediatrics with the major advances in genetics, genomics, physiology, diagnosis, imaging, and therapeutics. However, the “state-of-the-art” on the care of the normal and ill neonate, child, or adolescent as presented in these textbooks differ from that practiced in India or South Asia. While these books provide a detailed description of most disorders seen in children, they unfortunately do not provide both evidence-based medicine and astute personal clinical experiences from India. The focus is missing on the core issues relevant in the Indian context, i.e., growth, nutrition, immunization, development, newborn and adolescent health, and programmatic and social issues in child health. The need for a comprehensive postgraduate textbook, which can be adapted to Indian needs, has been recognized and expressed for some time now.

Rapid strides in medicine and technological advances in biological sciences were witnessed in the last decade. Advances in preventive and therapeutic care have opened new prospects for care of children. However, substantial improvements in quality of life have been limited to those with access to healthcare. Poverty, ignorance, war, bioterrorism, misplaced priorities and the lack of political will have prevented many children throughout the world, benefitting from these significant advances. Despite advances in infectious diseases, newer vaccines and preventive neonatal care, mortality and morbidity continue to be unacceptably high. Our priorities for care of children are often different from the developed world. Also, medical advances and good clinical practice must always be coupled with effective advocacy. These aspects need to be addressed in a postgraduate textbook, as current postgraduates are the future decision makers in our country.

It is our earnest wish and hope that the postgraduate textbook will help to fill the long-felt vacuum. It attempts to provide the essential information that postgraduates throughout India need to capture to effectively address the health problems that our children and youth may face in the times to come. Our objective is to be comprehensive yet concise and reader friendly, embracing both the new advances in science as well as the time-honored art of pediatric practice. Both Indian and international experts in respective fields have provided the details that have been further scrutinized for exposition and usefulness to pediatric postgraduates by a chosen team of eminent academicians. We have liberally included tables, line diagrams, images, clinical photographs, illustrative figures, flow charts and algorithms in the main text. The book is divided into 10 major Parts and further arranged into 51 Sections and Annexures to cover all aspects of postgraduate pediatric curriculum. Themes which have major public health relevance for India are extensively covered. It is almost impossible to cover all pediatric problems with the same degree of detail, and hence a careful balance has been made in the details of description of diseases and their management to the needs of the students, and to keep the book to a manageable size. Summary points “In A Nutshell” are provided at the end of each chapter. Selected recent references—mostly leading articles, reviews and position statements—are provided for more detailed information, if desired by the student or the teacher.

Some kind of overlap is unavoidable in a book of this magnitude, with 725 plus minds working on more than 600 chapters simultaneously. We have strived hard to minimize it. We have also tried our best to keep all the chapters on an even keel despite the unavoidable diversity of disciplines, thoughts, experience, and expressive capabilities of the distinguished authors and section editors, from all over the globe. The book would not have been possible but for the support that we received from these erudite contributors. We are indebted to them for their knowledge, introspection, and judgment during the entire process. Together we have worked hard to produce a compilation that will be helpful to those who desire to learn more about child health in India and thus provide better care for children.

**Piyush Gupta**  
**PSN Menon**  
**Siddarth Ramji**  
**Rakesh Lodha**





# Acknowledgments

---

## ACKNOWLEDGMENTS FROM AUTHORS

### 2.1 Gene, Genome and Genetic Basis of Diseases

I have written similar chapters on basics of genetics and molecular medicine for three editions (8th, 9th and 10th) of the *API Textbook of Medicine* published by the Association of Physicians of India, Mumbai. I am grateful to Ms Smrithi for drawing the figures in this chapter.  
*Girisha KM*

### 3.1.1 Inborn Errors of Metabolism

We are grateful to our patients, their families, students, residents and colleagues for their help. We thank Dr Charushree Prasad for critically reviewing the chapter and providing suggestions.

*Chitra Prasad, CA Rupar*

### 9.1 Poisoning

I wish to acknowledge the help and support given to me by Dr Paul Nixon.

*P Ramesh Menon*

### 12.2 Assessment of the Newborn

We acknowledge the efforts of Dr Aliza Mittal in taking clinical photographs for the chapter.

*Harish Chellani, Sugandha Arya*

### 18.5 CNS Malformations

We gratefully acknowledge the help of Professors Sandeep Agarwal and M Srinivas by contributing the photographs for this chapter.

*Nidhi Sugandhi, Veereshwar Bhatnagar*

### 23.1 Basic Concepts of Vaccination

I have immensely benefitted from the interactions with many eminent vaccine experts, epidemiologists, academicians and public health program managers. A few of the concepts presented in this chapter could have been (knowingly and unknowingly) borrowed, developed and influenced by my interactions with national and international experts in these areas. I would like to acknowledge their teaching and influence. The opinions expressed in the chapter are solely of mine and should not be attributed to any institution/organization; I have been affiliated in the past or at present.

*Chandrakant Lahariya*

### 23.5 Adverse Events Following Immunization

I have borrowed heavily from my earlier publication (Vashishtha VM, Kalra A. Adverse Events following Immunization (AEFI), Vaccine Safety and Misinformation against Vaccination. Mumbai: Tree Life Media; 2014.) after due permission from the authors.

*Ajay Kalra*

### 23.13 Typhoid Fever Vaccines

We would like to thank Dr Leon Ochiai for the continuous guidance and encouragement and Dr Vittal Mogasale for constructive suggestions during the review process.

*Sushant Sahastrabuddhe, Mohammad Imran Khan*

### 31.19 HIV and Acquired Immunodeficiency Syndrome

We thank Dr Shubhangi Parkar, Dean (Incharge) of Seth GS Medical College and KEM Hospital, for granting permission to publish this manuscript.

*Milind S Tullu, Chhaya Divecha*

### 37.1 Applied Anatomy and Physiology of Liver and Biliary Tract

Special thanks to Dr Vijayshri Bhide, GI and Liver Pathologist, Department of Pathology, Deenanath Mangeshkar Hospital, Pune for sharing liver histology pictures.

*Vishnu Biradar*

### 40.39 Surgical Considerations in Congenital Heart Diseases

Acknowledgement and thanks to my teachers for their contribution and help me in gaining appropriate knowledge and skills to choose, offer and perform the correct operative procedure to scores of unfortunate children born with simple and complex congenital heart defects.

*R Benedict Raj*

#### 40.40 Preventive Cardiology in the Young

This publication was made possible by grant number 1 D43 HD065249 from the Fogarty International Center and the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the National Institutes of Health.

*S Sivasankaran*

#### 42.11 Status Epilepticus

We wish to acknowledge the help and support provided by Lisa Garrity, Pharm D.

*Ravindra Arya, Katrina Peariso*

#### 42.24 Childhood Ataxia

I wish to acknowledge that a significant part of the discussion on genetic and inherited metabolic disorders associated with ataxia was included in a prior work on the same subject published for e-medicine. The material has been modified considerably to fit into a pertinent discussion on childhood ataxia. I also wish to acknowledge and thank contributors to the prior work; Professor Cheryl Greenberg (MD FRCPC), Division of Genetics and Metabolism, University of Manitoba; Dr Chitra Prasad (MD FRCPC FCCMG), Genetics and Metabolic Disorders, Program of South-Western Ontario; Professor M Jog (MD FRCPC), Division of Clinical Neurosciences, University of Western Ontario.

*Asuri N Prasad*

#### 47.1 Common Visual Problems

I wish to acknowledge the contribution of Dr Ankush Mutreja in preparation of Flow charts 1 to 5 included in this chapter.

*Kirti Singh*

#### 48.11 Cutaneous Manifestations of Collagen Vascular Diseases

I acknowledge Dr Ipsa Niyant Pandya, postgraduate student, Department of Skin and Veneral Diseases, Baroda Medical College, Vadodara, Gujarat for her invaluable contribution.

*Yogesh S Marfatia*

### FROM THE EDITORIAL DESK

**Ms Anju Kumari:** Secretarial assistance.

**Dr Sakshi Sachdeva:** Editorial assistance.

We would like to extend our thanks and appreciation to Shri Jitendar P Vij (Group Chairman) and Mr Ankit Vij (Group President) for their vision and belief in this project; Mr Tarun Duneja (Director-Publishing), Mr KK Raman (Production Manager), Ms Samina Khan (Exec. Assistant to Director-Publishing), Mr Sunil Kumar Dogra (Production Executive) and Mr Neelambar Pant (Production Coordinator), for their unflinching support and tireless work. We would also like to thank the entire staff of M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi, India, especially Ms Shalu Mann (Medical Editor); Mr Gurnam Singh (Sr Proofreader); Mr Sarvesh Kumar, Ms Kamlesh Rawat, Mr Gyanendra Kumar (Proofreaders); Mr Rajesh Kumar, Mrs Yashu Kapoor, Mr Rakesh Kumar (Typesetters); Mr Satender Singh, Mr Sumit Kumar, Mr Rohan Prasad (Graphic Designers); and Mr Joginder Kumar for delivery of the proofs.

# Contents

## Volume 1: General Pediatrics and Neonatology

### PART I: Pediatrics—Yesterday, Today, Tomorrow

#### Section 1: INTRODUCTION TO PEDIATRICS

**Section Editors** Piyush Gupta, PSN Menon

1.1	Evolution of Pediatrics	1
	<i>KN Agarwal</i>	
1.2	20 Milestones in the History of Pediatrics	5
	<i>Santosh K Bhargava</i>	
1.3	Status of Child Health	8
	<i>RN Srivastava</i>	
1.4	Millennium Development Goals for Child Health	11
	<i>Raju C Shah, Pratima Shah, Kunal Ahya</i>	
1.5	Evidence-based Care in Pediatrics	16
	<i>Joseph L Mathew</i>	

### PART II: Basic Sciences as Applied to Pediatrics

#### Section 2: GENETICS AND GENETIC DISORDERS

**Section Editor** Shubha R Phadke

2.1	Gene, Genome and Genetic Basis of Diseases	20
	<i>Girisha KM</i>	
2.2	Patterns of Inheritance	26
	<i>Prajnya Ranganath, Shubha R Phadke</i>	
2.3	Clinical Dysmorphology: An Approach to Bedside Diagnosis	33
	<i>Ratna Dua Puri</i>	
2.4	Chromosomal Disorders	39
	<i>Shagun Aggarwal, Ashwin Dalal</i>	
2.5	Management of Genetic Disorders and Genetic Counseling	49
	<i>Shubha R Phadke</i>	
2.6	Prevention of Genetic Disorders	56
	<i>Neerja Gupta, Madhulika Kabra</i>	

#### Section 3: METABOLIC DISORDERS

**Section Editors** Madhulika Kabra, Neerja Gupta

3.1	Approach to Inborn Errors of Metabolism	61
	<i>Chitra Prasad, CA Rupar</i>	
3.2	Defects of Amino Acid Metabolism	70
	<i>Anil B Jalan, Ketki V Kudalkar</i>	

3.3	Urea Cycle Disorders	79
	<i>Sunita Bijarnia-Mahay</i>	
3.4	Organic Acidemias	86
	<i>Neerja Gupta</i>	
3.5	Fatty Acid Oxidation Defects	93
	<i>Manisha Goyal, Seema Kapoor</i>	
3.6	Mitochondrial Disorders	98
	<i>Sheffali Gulati, Biswaroop Chakrabarty</i>	
3.7	Peroxisomal Disorders	103
	<i>Madhulika Kabra, Neerja Gupta</i>	
3.8	Lysosomal Storage Disorders	106
	<i>IC Verma</i>	
3.9	GM1 and GM2 Gangliosidosis	114
	<i>Parag M Tamhankar</i>	
3.10	Gaucher Disease	117
	<i>Mamta Muranjan</i>	
3.11	Niemann-Pick Disease	127
	<i>Ashwin Dalal</i>	
3.12	Fabry Disease	131
	<i>Ratna Dua Puri</i>	
3.13	Defects of Carbohydrate Metabolism	135
	<i>Kausik Mandal</i>	
3.14	Glycogen Storage Diseases	141
	<i>Priya S Kishnani, Stephanie Austin</i>	
3.15	Pompe Disease	145
	<i>Mari Mori, Priya S Kishnani</i>	
3.16	Mucopolysaccharidoses	149
	<i>Girisha KM</i>	
3.17	Approach to Hypoglycemia	154
	<i>Meenakshi Bothra, Vandana Jain</i>	
3.18	Porphyrias	161
	<i>Meenal Agarwal, Shubha R Phadke</i>	
3.19	Newborn Screening	165
	<i>Seema Kapoor, Madhulika Kabra</i>	

#### Section 4: IMMUNITY, IMMUNE DISORDERS AND ALLERGY

**Section Editors** Surjit Singh, Amit Rawat

4.1	Basics of Immunology	169
	<i>Amit Rawat, Biman Saikia</i>	

4.2	Laboratory Diagnosis of Immune-mediated Diseases <i>Biman Saikia, Deepti Suri</i>	176	7.4	Pediatric Advanced Life Support (PALS) <i>Banani Poddar</i>	253
4.3	Primary Immunodeficiency Disorders <i>Manisha Madkaikar</i>	184	<b>Section 8: INTENSIVE CARE</b>		
4.4	Therapy for Primary Immunodeficiency Disorders <i>Revathi Raj, Surjit Singh</i>	191	<b>Section Editor</b> Rakesh Lodha		
4.5	Intravenous Immunoglobulin <i>Sujoy Khan, Surjit Singh</i>	193	8.1	Pediatric Intensive Care Unit <i>Dhiren Gupta, Neeraj Gupta, Manpreet Sethi</i>	264
4.6	Approach to a Child with Allergic Disorder <i>H Paramesh</i>	198	8.2	Shock <i>Srinivas Murthy, Niranjan Kissoon</i>	268
<b>Section 5: FLUID AND ELECTROLYTES</b>			8.3	Acute Respiratory Distress Syndrome <i>Venkat Shankar</i>	274
<b>Section Editor</b> Rakesh Lodha			8.4	Respiratory Failure <i>Lokesh Guglani</i>	281
5.1	Body Fluids <i>Raghuvamsi Chaitra, Suchitra Ranjit</i>	201	8.5	Mechanical Ventilation <i>Dinesh Raj, Rakesh Lodha</i>	288
5.2	Maintenance Fluid Therapy <i>Banani Poddar, Kirti M Naranje</i>	206	8.6	Sedation and Analgesia <i>Venkat Shankar</i>	297
5.3	Acid-Base Equilibrium <i>Dinesh Raj, Rakesh Lodha</i>	210	<b>Section 9: POISONING AND ENVENOMATION</b>		
5.4	Abnormalities of Acid-Base Balance <i>Dinesh Raj, Rakesh Lodha</i>	214	<b>Section Editor</b> Rakesh Lodha		
5.5	Sodium and Related Disorders <i>Andrew C Argent, Mignon I McCulloch</i>	220	9.1	Clinical Approach to a Poisoned Child <i>P Ramesh Menon</i>	302
5.6	Potassium <i>Virendra Kumar</i>	225	9.2	Poisonings by Common Drugs <i>Indumathy Santhanam, Sharada Sathish</i>	308
5.7	Magnesium Balance <i>Virendra Kumar</i>	229	9.3	Hydrocarbon Poisoning <i>Jayashree M, Karthi N</i>	315
<b>Section 6: DRUGS AND THERAPEUTICS</b>			9.4	Poisoning in the Household <i>Narayanan P, Harikrishnan KN</i>	318
<b>Section Editor</b> Sandeep B Bavdekar			9.5	Corrosive Poisoning <i>Urmila Jhamb</i>	326
6.1	Principles of Drug Therapy <i>Sandeep B Bavdekar</i>	231	9.6	Snakebite <i>S Mahadevan, R Ramesh Kumar</i>	331
6.2	Administration of Medications <i>Jeeson C Unni</i>	236	9.7	Scorpion Sting <i>S Mahadevan, R Ramesh Kumar</i>	341
<b>PART III: Intensive Care and Emergencies</b>			<b>Section 10: CHILDHOOD INJURIES</b>		
<b>Section 7: ACUTELY ILL CHILD AND RESUSCITATION</b>			<b>Section Editor</b> Rakesh Lodha		
<b>Section Editor</b> Rakesh Lodha			10.1	Trauma: Stabilization, Triage and Transport <i>Shruti Kant, Manu Madhok</i>	348
7.1	Assessment and Triage <i>Jayashree M, Sunit Singh</i>	241	10.2	Drowning/Submersion Injuries <i>Arun Bansal</i>	354
7.2	Cardiopulmonary Resuscitation <i>Utpal Bhalala, Vijay Srinivasan</i>	245	10.3	Animal Related Injuries <i>Arun Kumar Baranwal</i>	357
7.3	Basic Life Support (BLS) <i>Shalu Gupta</i>	249	10.4	Pediatric Burns <i>K Mathangi Ramakrishnan, V Jayaraman, T Mathivanan, V Srinivasan</i>	361
			10.5	Cold Injuries <i>Manu Madhok, Shruti Kant</i>	370

## PART IV: The Newborn Infant

### Section 11: NEONATAL PHYSIOLOGY AND ORGANIZATION OF CARE

**Section Editor** Siddarth Ramji

11.1	Fetal Physiology and Growth	376
	<i>Deepak Chawla</i>	
11.2	Maternal Influence on the Fetus	380
	<i>Jayashree Mondkar, Swati Manerkar</i>	
11.3	Transition of the Fetus to Newborn	383
	<i>Siddarth Ramji</i>	
11.4	Neonatal Mortality and Morbidities: An Overview	386
	<i>Aparna Chandrasekaran, M Jeeva Sankar</i>	
11.5	Organization of Neonatal Care	392
	<i>Subhash Chandra Shaw, Vinod K Paul</i>	

### Section 12: NORMAL NEWBORN

**Section Editor** Siddarth Ramji

12.1	Delivery Room Care of the Newborn	396
	<i>Siddarth Ramji</i>	
12.2	Assessment of the Newborn	401
	<i>Harish Chellani, Sugandha Arya</i>	
12.3	Care of the Normal Newborn	408
	<i>Somashekhar Nimbalkar</i>	
12.4	Maintenance of Temperature	412
	<i>Suksham Jain, Ravish Singhal</i>	
12.5	Breastfeeding and Lactation Management	417
	<i>NB Mathur</i>	

### Section 13: DISORDERS OF WEIGHT AND GESTATION

**Section Editor** Siddarth Ramji

13.1	Low Birthweight: Classification and Etiology	422
	<i>Ruchi Nimish Nanavati</i>	
13.2	Prematurity and Intrauterine Growth Restriction	427
	<i>Ashok Kumar, Sriparna Basu</i>	
13.3	Feeding of Low Birthweight	432
	<i>Kanya Mukhopadhyay</i>	
13.4	Long-term Outcome of Low Birthweight	437
	<i>Suman Rao PN, Nikhil Kulkarni</i>	
13.5	Postmaturity	442
	<i>Reeta Bora, Pranay Phukan</i>	
13.6	Large for Gestational Age	445
	<i>Rhishikesh Thakre</i>	
13.7	Multiple Gestations	449
	<i>Mamta Jajoo</i>	

### Section 14: HIGH-RISK NEWBORN

**Section Editor** Siddarth Ramji

14.1	Recognition of High-Risk Neonate	453
	<i>Niranjan Thomas, Vijay Gupta</i>	
14.2	Birth Injuries	462
	<i>Neeraj Gupta</i>	
14.3	Jaundice in the Newborn	469
	<i>Sheila S Mathai, Kannan Venkatnarayan</i>	
14.4	Infant of Diabetic Mother	479
	<i>Srinivas Murki, Tejo Oleti Pratap</i>	
14.5	Neonatal Hypoglycemia	483
	<i>Shiv Sajjan Saini, Praveen Kumar</i>	
14.6	Anemia and Polycythemia	489
	<i>Venkataseshan Sundaram, Bikramjit Das</i>	
14.7	The Bleeding Neonate	498
	<i>Arun Kumar</i>	
14.8	Hemorrhagic Disease of the Newborn	503
	<i>JN Sharma</i>	
14.9	Thrombocytopenia in the Newborn	506
	<i>Pradeep Sharma</i>	
14.10	Cyanosis in the Newborn	508
	<i>K Anil Kuruvilla, Vijay Gupta</i>	
14.11	Necrotizing Enterocolitis	515
	<i>Krishna Kumar Diwakar</i>	
14.12	Retinopathy of Prematurity	521
	<i>Ashish Jain, Veeraraja B Sathenahalli, Karobi Lahiri Coutinho</i>	
14.13	Neonatal Transport	527
	<i>Neelam Kler, Anup Thakur</i>	
14.14	Follow-Up of the High-Risk Neonate	532
	<i>Shuchita Gupta</i>	

### Section 15: NEONATAL INFECTIONS

**Section Editor** Siddarth Ramji

15.1	Neonatal Sepsis	540
	<i>Suman Chaurasia, Ramesh Agarwal</i>	
15.2	Superficial Infections	547
	<i>Sriparna Basu, Ashok Kumar</i>	
15.3	Meningitis in the Newborn	552
	<i>Kumutha Jayaraman, Manigandan Chandrasekaran</i>	
15.4	Deep-seated Infections	559
	<i>Kumutha Jayaraman, Manigandan Chandrasekaran</i>	
15.5	Neonatal Tetanus	563
	<i>Mala Kumar, Shalini Tripathi</i>	
15.6	Intrauterine Infections	565
	<i>Sriparna Basu, Ashok Kumar</i>	



## Section 16: NEUROLOGICAL PROBLEMS OF THE NEWBORN INFANT

**Section Editor** Siddarth Ramji

16.1	Seizures in the Neonates	572
	<i>Amit Upadhyay, Pranjali Saxena</i>	
16.2	Hypoxic Ischemic Encephalopathy	578
	<i>B Vishnu Bhat, B Adhisivam</i>	
16.3	Intraventricular Hemorrhage and White Matter Injury	585
	<i>Shamik Trivedi, Amit M Mathur</i>	

## Section 17: RESPIRATORY PROBLEMS OF THE NEWBORN INFANT

**Section Editor** Siddarth Ramji

17.1	Approach to a Neonate with Respiratory Distress	592
	<i>Swarna Rekha Bhat</i>	
17.2	Neonatal Apnea	596
	<i>Manoj Modi</i>	
17.3	Neonatal Ventilation	600
	<i>Sourabh Dutta</i>	
17.4	Hyaline Membrane Disease	605
	<i>Praveen Kumar, Anuj Bhatti</i>	
17.5	Transient Tachypnea of the Newborn	612
	<i>Srinivas Murki</i>	
17.6	Meconium Aspiration Syndrome	614
	<i>Naveen Jain</i>	
17.7	Pulmonary Air Leaks in the Newborn	617
	<i>Manish Balde, Sanjay Wazir</i>	
17.8	Persistent Pulmonary Hypertension (PPHN)	622
	<i>Neeraj Gupta</i>	
17.9	Pulmonary Hemorrhage	629
	<i>Emily F Fishman, Rakesh Rao</i>	
17.10	Bronchopulmonary Dysplasia in Newborn	635
	<i>Samir Gupta, Sunil K Sinha</i>	

## Section 18: NEONATAL MALFORMATIONS

**Section Editor** Siddarth Ramji

18.1	Esophageal Atresia and Tracheoesophageal Fistula	640
	<i>Yogesh Kumar Sarin, Shalini Sinha</i>	
18.2	Diaphragmatic Hernia and Eventration	645
	<i>Shalini Sinha, Yogesh Kumar Sarin</i>	
18.3	Gastrointestinal and Abdominal Malformations	650
	<i>Satish Kumar Aggarwal</i>	
18.4	Genitourinary Malformations	661
	<i>Satish Kumar Aggarwal</i>	
18.5	CNS Malformations	670
	<i>Nidhi Sugandhi, Veereshwar Bhatnagar</i>	

## PART V: The Childhood Years

### Section 19: GROWTH: NORMAL AND ABNORMAL

**Section Editor** Anju Seth

19.1	Normal Growth	680
	<i>Ruchi Mishra, Vandana Jain</i>	
19.2	Factors Affecting Growth	684
	<i>Devi Dayal, Anil Kumar Bhalla</i>	
19.3	Assessment of Physical Growth	688
	<i>Anju Seth, Rajni Sharma</i>	
19.4	Dental Development and Anomalies	713
	<i>Sunanda Roychoudhury, Shakil Ahmed Nagori, Ajoy Roychoudhury</i>	
19.5	Bone Age and Predicted Final Height	723
	<i>M Vijayakumar, Anju Seth</i>	
19.6	Failure to Thrive	726
	<i>Sudha Rao Chandrashekhar</i>	
19.7	Overweight and Obesity	733
	<i>Rajesh Khadgawat, Aashima Dabas</i>	
19.8	Abnormalities of Stature	739
	<i>Senthil Senniappan, Leena Patel</i>	

### Section 20: DEVELOPMENT AND DEVELOPMENTAL DELAY

**Section Editors** Anand Pandit, Sudha Chaudhari

20.1	Introduction to Development, Laws of Development, and Factors Affecting Development	749
	<i>Satnam Kaur</i>	
20.2	Normal Development	753
	<i>Ujjwal Nene</i>	
20.3	Approach to Diagnosis of Developmental Delay: Developmental Screening and Surveillance	759
	<i>Sudha Chaudhari</i>	
20.4	Global Developmental Delay	766
	<i>Madhuri Kulkarni, Mona P Gajre</i>	
20.5	Intellectual Disability	770
	<i>Suja Koshy</i>	
20.6	Visual Impairment	780
	<i>Nikhil Rishikeshi, Sucheta Kulkarni</i>	
20.7	Hearing Impairment	782
	<i>Neelam Vaid</i>	
20.8	Cerebral Palsy	787
	<i>Sharmila Banerjee Mukherjee</i>	

## Section 21: BEHAVIOR AND LEARNING

**Section Editors** Monica Juneja, Devendra Mishra

21.1	Moral Development	800
	<i>Prahbjot Malhi, Rajalakshmi Iyer</i>	
21.2	Sleep Hygiene and Disorders of Sleep	803
	<i>Suresh Kotagal</i>	
21.3	Common Behavioral Problems	809
	<i>Praveen Suman</i>	
21.4	Enuresis and Encopresis	813
	<i>Piyush Gupta, Ruchi Mishra</i>	
21.5	Breath-Holding Spells	818
	<i>Sumaira Khalil, Devendra Mishra</i>	
21.6	Common Speech, Language and Communication Disorders	821
	<i>Prathibha Karanth</i>	
21.7	Autism Spectrum Disorder	827
	<i>Monica Juneja, Rahul Jain</i>	
21.8	Rett Syndrome	833
	<i>Monica Juneja, Rajni Khajuria</i>	
21.9	Attention Deficit Hyperactivity Disorder	836
	<i>Rajesh Sagar, Rohit Verma</i>	
21.10	Oppositional Defiant and Conduct Disorders	843
	<i>Rajesh Sagar, Rajevee Ranjan</i>	
21.11	Learning Disabilities	847
	<i>Nandini Mundkur, Chitra Sankar</i>	
21.12	Anorexia Nervosa and Bulimia	851
	<i>Koushik Sinha Deb, Rajesh Sagar</i>	
21.13	Anxiety Disorders	854
	<i>Shoba Srinath, Preeti Kandasamy</i>	
21.14	Evaluation of Mental Well-Being	856
	<i>Manju Mehta, Sneha Kapoor</i>	
21.15	Management of Psychological Illness	858
	<i>Paul Russell</i>	

## Section 22: NUTRITION AND NUTRITIONAL DISORDERS

**Section Editors** KE Elizabeth, Piyush Gupta

22.1	Nutrient Groups and Nutritional Requirements	863
	<i>KE Elizabeth, S Bindusha</i>	
22.2	Nutritive Values of Foods	868
	<i>Neetu Sharma, Piyush Gupta</i>	
22.3	Infant and Young Child Feeding	877
	<i>JP Dadhich</i>	
22.4	Feeding During Childhood and Food Allergy	881
	<i>KE Elizabeth, S Bindusha</i>	
22.5	Undernutrition: Prevalence and Etiology	884
	<i>Piyush Gupta, Neetu Sharma</i>	

22.6	Pathophysiology of Undernutrition	891
	<i>OP Mishra</i>	
22.7	Protein Energy Malnutrition	894
	<i>KE Elizabeth</i>	
22.8	Severe Acute Malnutrition	899
	<i>Praveen Kumar, Preeti Singh</i>	
22.9	Vitamin A	907
	<i>Neetu Sharma, Piyush Gupta</i>	
22.10	Vitamin B Complex Deficiency	913
	<i>Vineeta Gupta</i>	
22.11	Vitamin C and Scurvy	917
	<i>Tejinder Singh, Shaveta Kundra</i>	
22.12	Vitamin D, Nutritional Rickets and Hypervitaminosis D	920
	<i>S Balasubramanian</i>	
22.13	Iodine Deficiency Disorders	925
	<i>Umesh Kapil, Neha Sareen</i>	
22.14	Zinc in Child Health	928
	<i>Shashi Ajit Chiplonkar</i>	
22.15	Trace Elements in Nutrition and Health	932
	<i>P Leelakumari, KE Elizabeth</i>	
22.16	Fluorosis	935
	<i>Sunil Kumar Gupta</i>	
22.17	Enteral and Parenteral Nutrition	941
	<i>Ashish Bavdekar</i>	
22.18	Nutrition in the 21st Century	946
	<i>Gouri Rao Passi, Piyush Gupta</i>	
22.19	National Nutrition Programs	950
	<i>Dipty Jain, Veena Kamat, Vinit Warthe</i>	

## Section 23: IMMUNIZATION

**Section Editors** Vipin M Vashishtha, Ajay Kalra

23.1	Basic Concepts of Vaccination	953
	<i>Chandrakant Lahariya</i>	
23.2	Vaccine Administration Practices	962
	<i>Satish V Pandya</i>	
23.3	Scheduling of Vaccines	966
	<i>Vipin M Vashishtha</i>	
23.4	Vaccine Storage and Cold Chain	972
	<i>Karan Singh Sagar, Manish Jain</i>	
23.5	Adverse Events Following Immunization	978
	<i>Ajay Kalra</i>	
23.6	BCG Vaccine	982
	<i>Sangeeta Sharma</i>	
23.7	Poliovirus Vaccines	986
	<i>Puneet Kumar, Vipin M Vashishtha</i>	
23.8	Diphtheria, Tetanus and Pertussis Vaccines	991
	<i>Puneet Kumar, Vipin M Vashishtha</i>	

23.9	Hepatitis B Vaccine <i>Ajay Kalra</i>	995
23.10	<i>Haemophilus Influenzae</i> Type B (HIB) Vaccines <i>AK Patwari</i>	998
23.11	Measles Vaccine <i>Sumit Mehndiratta, AP Dubey</i>	1000
23.12	Rubella and Mumps Vaccines <i>Aashima Dabas, Piyush Gupta</i>	1002
23.13	Typhoid Fever Vaccines <i>Sushant Sahastrabudhe, Mohammad Imran Khan</i>	1005
23.14	Japanese Encephalitis Vaccine <i>VG Ramachandran</i>	1009
23.15	Rabies Vaccines <i>Anuradha Bose</i>	1011
23.16	Pneumococcal Vaccines <i>Puneet Kumar, Vipin M Vashishtha</i>	1014
23.17	Rotavirus Vaccines <i>Gagandeep Kang</i>	1018
23.18	Cholera Vaccines <i>Monjori Mitra</i>	1020
23.19	Varicella Vaccine <i>Rakesh Kumar</i>	1022
23.20	Hepatitis A Vaccine <i>Vikram Gagneja, AJ Chitkara</i>	1024
23.21	Meningococcal Vaccine <i>Jaydeep Choudhury</i>	1027
23.22	Seasonal and Pandemic Influenza Vaccines <i>Shobha Broor</i>	1029
23.23	Human Papillomavirus Vaccines <i>Srinivas G Kasi</i>	1034
23.24	Yellow Fever Vaccine <i>Parang N Mehta</i>	1038
23.25	Combination Vaccines <i>Niranjan Shendurnikar, Sheila Aiyer</i>	1040
23.26	Immunization in Special Situations <i>Panna Choudhury</i>	1043

## PART VI: The Adolescent

### Section 24: ADOLESCENT DEVELOPMENT

**Section Editor** MKC Nair

24.1	Adolescence and Adolescent <i>MKC Nair, Paul Russell</i>	1047
24.2	Sexual Development and Sexuality <i>Chandrika Rao</i>	1051
24.3	Psychosocial Development <i>Yamuna S</i>	1055

### Section 25: HEALTH ISSUES IN ADOLESCENCE

**Section Editor** MKC Nair

25.1	Factors Influencing Adolescent Health <i>Sukanta Chatterjee</i>	1061
25.2	Adolescent Nutrition <i>Preeti M Galagali</i>	1067
25.3	Mental Health <i>Priya Mary Mammen</i>	1074
25.4	Injuries, Violence and Suicide <i>Srikanta Basu</i>	1080
25.5	Menstrual Disorders and Polycystic Ovary Syndrome <i>Amita Suneja, Richa Aggarwal</i>	1087
25.6	Sexually Transmitted Infections <i>Newton Luiz</i>	1095
25.7	Teenage Pregnancy <i>Amita Suneja, Richa Aggarwal</i>	1100

### Section 26: CARE OF ADOLESCENTS

**Section Editor** MKC Nair

26.1	Promoting Health of Adolescents <i>Harish K Pemde, Kamlesh Harish</i>	1102
26.2	Adolescent Counseling <i>Atul M Kanikar</i>	1107
26.3	Adolescent Friendly Health Services <i>Rajesh Mehta, Neena Raina, Patanjali Dev Nayar</i>	1115

## Volume 2: Infections and Systemic Disorders

### PART VII: Infectious Diseases

#### Section 27: BASIC CONCEPTS

**Section Editors** Jaydeep Choudhury, Piyush Gupta

27.1	Epidemiology of Infectious Diseases <i>VG Ramachandran, Piyush Gupta</i>	1119	27.2	Laboratory Diagnosis of Infection <i>Sankar Sengupta</i>	1125
			27.3	Antimicrobial Resistance <i>Anuradha De</i>	1129
			27.4	Infection Control and Prevention <i>Jaydeep Choudhury</i>	1136

## Section 28: FEVER

**Section Editor** Piyush Gupta

28.1	Approach to a Child with Fever <i>Bhavna Dhingra, Piyush Gupta</i>	1140
28.2	Fever: General Principles of Management <i>Piyush Gupta, Bhavna Dhingra</i>	1143
28.3	Fever without Focus <i>Piyush Gupta, Bhavna Dhingra</i>	1146
28.4	Fever of Unknown Origin <i>Bhavna Dhingra, Piyush Gupta</i>	1149

## Section 29: BACTERIAL INFECTIONS

**Section Editors** Jaydeep Choudhury, Piyush Gupta

29.1	Natural History of Bacterial Infection <i>VG Ramachandran, Piyush Gupta</i>	1152
29.2	Principles of Antibiotic Therapy <i>Anita Shet</i>	1155
29.3	Diphtheria <i>Prerna Batra, Piyush Gupta</i>	1162
29.4	Pertussis <i>Piyush Gupta, Prerna Batra</i>	1166
29.5	Tetanus <i>Jaydeep Choudhury</i>	1169
29.6	Typhoid Fever <i>Apurba Ghosh, Monjori Mitra</i>	1171
29.7	Nontyphoidal Salmonellosis <i>Thangavelu Sangaralingam, Janani Ravi</i>	1176
29.8	<i>Haemophilus influenzae</i> B Infections <i>Somu Sivabalan</i>	1179
29.9	Pneumococcal Infections <i>Meenu Singh, Nishant Jaiswal</i>	1182
29.10	Streptococcal Infections <i>Pramod Sharma</i>	1185
29.11	Staphylococcal Infections <i>Zaki Syed</i>	1188
29.12	<i>Neisseria</i> Infections <i>Vidushi Mahajan</i>	1193
29.13	<i>Pseudomonas</i> Infections <i>Nupur Ganguly</i>	1196
29.14	Leptospirosis <i>Janani Sankar</i>	1198
29.15	Plague <i>Baldev S Prajapati, Rajal B Prajapati, Piyush Gupta</i>	1201
29.16	Brucellosis <i>Sriram Krishnamurthy</i>	1204

29.17	Relapsing Fever <i>P Ramachandran</i>	1207
29.18	Lyme Disease <i>P Ramachandran</i>	1210
29.19	Nocardiosis <i>Subhasish Bhattacharyya</i>	1212
29.20	Actinomycosis <i>Subhasish Bhattacharyya</i>	1214
29.21	<i>Helicobacter pylori</i> <i>John Matthai, Sarah Paul</i>	1215
29.22	Anaerobic Infections <i>Rekha Harish, Anuj Bhatti</i>	1217

## Section 30: MYCOBACTERIAL INFECTIONS

**Section Editor** Soumya Swaminathan

30.1	Antitubercular Drugs <i>Geetha Ramachandran</i>	1220
30.2	Tuberculosis <i>Soumya Swaminathan, N Pooranagangadevi, Ben J Marais</i>	1225
30.3	Atypical Mycobacterial Infections <i>C Padmapriyadarsini, Soumya Swaminathan</i>	1235
30.4	Leprosy <i>Rajeshwar Dayal, Manoj Kumar Singh</i>	1239

## Section 31: VIRAL DISEASES

**Section Editors** Ashok Kumar Dutta, Piyush Gupta

31.1	Epidemiology of Viral Infections <i>VG Ramachandran, Piyush Gupta</i>	1243
31.2	Poliomyelitis <i>Ashok Kumar Dutta</i>	1245
31.3	Measles <i>Shilpa Khanna Arora, Piyush Gupta</i>	1248
31.4	Mumps <i>Shilpa Khanna Arora, Piyush Gupta</i>	1252
31.5	Rubella <i>Pooja Dewan, Piyush Gupta</i>	1255
31.6	Varicella <i>Piyush Gupta, Aashima Dabas</i>	1259
31.7	Parvovirus Infections <i>Jagdish Chandra, Anu Maheshwari</i>	1263
31.8	Roseola Infections <i>Swati Singhal</i>	1268
31.9	Viral Hepatitis <i>Amit Goel, Chhavi Nanda</i>	1270
31.10	Rabies <i>Jaydeep Choudhury</i>	1275

31.11	Japanese Encephalitis <i>Rashmi Kumar, Piyush Tripathi</i>	1278	32.13	Filariasis <i>Ajay Gaur</i>	1368
31.12	Infectious Mononucleosis <i>Rashmi Ranjan Das</i>	1282	32.14	Intestinal, Liver and Lung Flukes <i>Vikas Jain</i>	1372
31.13	Enteroviral Infections <i>Annapurna Sudarsanam</i>	1287	32.15	Tapeworm Diseases <i>Ruchi Rai</i>	1376
31.14	Herpes Simplex Infections <i>Niranjan Mohanty, Pradeep S</i>	1292	32.16	Hydatid Disease: Echinococcosis <i>SK Gupta</i>	1380
31.15	Influenza <i>Sonal Kansra, Alison Scott</i>	1296	32.17	Schistosomiasis <i>Ritabrata Kundu, Devdeep Mukherjee</i>	1384
31.16	Dengue <i>Piyush Gupta, Aashima Dabas</i>	1299	<b>Section 33: FUNGAL INFECTIONS</b>		
31.17	Chikungunya Fever <i>Rajniti Prasad</i>	1307	<b>Section Editor</b> <i>Piyush Gupta</i>		
31.18	Viral Hemorrhagic Fevers <i>Nigam Prakash Narain, Priya Verma</i>	1310	33.1	Fungi <i>VG Ramachandran, Piyush Gupta</i>	1386
31.19	HIV and Acquired Immunodeficiency Syndrome <i>Milind S Tullu, Chhaya Divecha</i>	1313	33.2	Antifungal Therapy <i>Arunaloke Chakrabarti, Prashant Sood</i>	1387
<b>Section 32: PARASITIC INFECTIONS AND INFESTATIONS</b>			33.3	Candidiasis <i>Khaya Ghosh Uttam</i>	1392
<b>Section Editors</b> <i>Ritabrata Kundu, Piyush Gupta</i>			33.4	Aspergillosis <i>Kana Ram Jat</i>	1396
32.1	Epidemiology of Parasitic Infections <i>Piyush Gupta, VG Ramachandran</i>	1328	33.5	Cryptococcosis <i>Ankit Parakh</i>	1399
32.2	Malaria <i>Ritabrata Kundu</i>	1331	33.6	Coccidioidomycosis <i>James Homans, Yee Aye</i>	1402
32.3	Leishmaniasis <i>Shyam Sundar, Jaya Chakravarty</i>	1337	33.7	Blastomycosis <i>G Raghurama Rao</i>	1407
32.4	Amebiasis <i>Piyush Gupta, Aashima Dabas</i>	1343	33.8	Histoplasmosis <i>S Nivedhana, S Balasubramanian</i>	1409
32.5	Giardiasis <i>Aashima Dabas, Piyush Gupta</i>	1347	33.9	<i>Pneumocystis jirovecii</i> (previously classified as <i>P. carinii</i> ) <i>Ira Shah, Khushnuma Mullanfiroze</i>	1412
32.6	Cryptosporidiosis <i>Aashima Dabas, Piyush Gupta</i>	1350	<b>Section 34: RICKETTSIAL AND OTHER INFECTIONS</b>		
32.7	Ascariasis <i>Sutapa Ganguly</i>	1352	<b>Section Editors</b> <i>S Balasubramanian, Piyush Gupta</i>		
32.8	Hookworm Infestation <i>Maitreyi Basu, Sutapa Ganguly</i>	1355	34.1	Epidemiology, Classification, and Approach to Diagnosis of Rickettsial Infections <i>Narendra Rathi</i>	1415
32.9	Trichuriasis <i>Sutapa Ganguly</i>	1358	34.2	Spotted Fevers <i>Atul A Kulkarni</i>	1418
32.10	Enterobiasis <i>Dhrubojyoti Mridha, Sutapa Ganguly</i>	1360	34.3	Scrub Typhus <i>Veena R Parmar</i>	1422
32.11	Strongyloidiasis <i>Ravi Ambey, Tripty Naik</i>	1362	34.4	Epidemic Typhus <i>Sunil Vaidya, Atul A Kulkarni</i>	1424
32.12	Trichinosis <i>Akash Bang, Puja Hingorani</i>	1365	34.5	Murine Typhus (Endemic Typhus) <i>Govind Benakatti, LH Bidari</i>	1426



<b>34.6</b>	<i>Mycoplasma</i> Infections <i>Tanu Singhal</i>	1428	<b>35.19</b>	Abdominal Tuberculosis <i>Yogesh Waikar</i>	1496
<b>34.7</b>	Chlamydial Infections <i>Sulochana Putali Bai</i>	1430	<b>35.20</b>	Ascites <i>Malathi Sathiyasekeran, R Ganesh</i>	1498

## PART VIII: Systemic Disorders

### Section 35: GASTROINTESTINAL DISORDERS

**Section Editors** *A Riyaz, John Matthai*

<b>35.1</b>	Anatomy and Physiology <i>S Arivu Selvan</i>	1432	<b>35.23</b>	Appendicitis <i>Prakash Agarwal</i>	1506
<b>35.2</b>	Common Symptoms of Gastrointestinal Diseases <i>Sarah Paul, John Matthai</i>	1437	<b>35.24</b>	Testicular Torsion <i>Prakash Agarwal</i>	1508
<b>35.3</b>	Cleft Lip and Cleft Palate <i>VS Akbar Sherif, Sayed Mohammed Akbar</i>	1439	<b>35.25</b>	Inguinal Hernia <i>Prakash Agarwal</i>	1510
<b>35.4</b>	Dental Caries <i>Madhu S</i>	1442	<b>Section 36: DIARRHEAL ILLNESSES</b>		
<b>35.5</b>	Recurrent Parotitis <i>Prakash Agarwal</i>	1445	<b>Section Editor</b> <i>AK Patwari</i>		
<b>35.6</b>	Vomiting <i>Sumathi Bavanandam</i>	1447	<b>36.1</b>	Acute Watery Diarrhea <i>AK Patwari</i>	1511
<b>35.7</b>	Infantile Hypertrophic Pyloric Stenosis <i>Ketan Parikh</i>	1451	<b>36.2</b>	Dysentery <i>AKM Iqbal Kabir, Lazina Sharmin</i>	1519
<b>35.8</b>	Gastroesophageal Reflux <i>Elsie Jazmin Foglio, Dinesh S Pashankar</i>	1453	<b>36.3</b>	Cholera <i>Piyush Gupta, Rashi Singhal</i>	1523
<b>35.9</b>	Umbilical Hernia <i>Prakash Agarwal</i>	1457	<b>36.4</b>	Persistent Diarrhea <i>Shinjini Bhatnagar, Aashima Dabas, Dheeraj Shah</i>	1527
<b>35.10</b>	Constipation <i>Praveen Kumar, Preeti Singh</i>	1459	<b>36.5</b>	Chronic Diarrhea <i>BR Thapa, Srikanth KP, Babu Lal Meena</i>	1533
<b>35.11</b>	Hirschsprung Disease <i>Ketan Parikh</i>	1464	<b>36.6</b>	Antibiotic Associated Diarrhea <i>Seema Alam, Vikrant Sood</i>	1551
<b>35.12</b>	Chronic Abdominal Pain <i>B Bhaskar Raju, Sumathi Bavanandam</i>	1466	<b>Section 37: HEPATOBILIARY DISEASES</b>		
<b>35.13</b>	Acid Peptic Disease <i>R Bhanu Vikraman Pillai</i>	1470	<b>Section Editor</b> <i>Surender Kumar Yachha</i>		
<b>35.14</b>	Pancreatitis <i>A Riyaz, Geeta M Govindaraj</i>	1473	<b>37.1</b>	Applied Anatomy and Physiology of Liver and Biliary Tract <i>Vishnu Biradar</i>	1555
<b>35.15</b>	Practical Approach to Malabsorption <i>VS Sankaranarayanan</i>	1478	<b>37.2</b>	Liver Function Tests <i>Neelam Mohan, Sakshi Karkra</i>	1558
<b>35.16</b>	Specific Malabsorption Syndromes <i>Srinivas S</i>	1481	<b>37.3</b>	Neonatal Cholestasis <i>Surender Kumar Yachha, Moinak Sen Sarma</i>	1563
<b>35.17</b>	Inflammatory Bowel Disease <i>Rishi Bolia, Anshu Srivastava</i>	1484	<b>37.4</b>	Portal Hypertension <i>Surender Kumar Yachha, Moinak Sen Sarma</i>	1571
<b>35.18</b>	Celiac Disease <i>Lalit Bharadia</i>	1491	<b>37.5</b>	Gastrointestinal Bleeding <i>Nishant Wadhwa</i>	1586
			<b>37.6</b>	Liver Abscess <i>Upender Shava, Anshu Srivastava</i>	1593
			<b>37.7</b>	Acute Hepatitis <i>Barath Jagadisan</i>	1598

<b>37.8</b>	Chronic Liver Disease <i>Seema Alam, Rajeev Khanna</i>	1602	<b>38.18</b>	Other Clotting Factor Deficiencies <i>Sunil Gomber, Archana Kashyap</i>	1731
<b>37.9</b>	Hepatic Encephalopathy <i>Moinak Sen Sarma, Surender Kumar Yachha</i>	1616	<b>38.19</b>	Thrombocytopenia <i>Amita Trehan</i>	1735
<b>37.10</b>	Acute Liver Failure <i>Anupam Sibal, Vidyut Bhatia, Akshay Kapoor</i>	1624	<b>38.20</b>	Immune Thrombocytopenic Purpura <i>Jagdish Chandra, Dinesh Yadav</i>	1741
<b>37.11</b>	Liver Tumors <i>Karthick Sundaram, Naresh P Shanmugam</i>	1627	<b>38.21</b>	Platelet Function Defects <i>Neelam Varma</i>	1749
			<b>38.22</b>	Thrombotic Disorders <i>Sidharth Totadri, Deepak Bansal, RK Marwaha</i>	1753
<b>Section 38: DISORDERS OF HEMATOPOIETIC SYSTEM</b>			<b>38.23</b>	Disseminated Intravascular Coagulation <i>VK Khanna, Tarangini D, Anupam Sachdeva</i>	1762
<b>Section Editor</b> <i>VP Choudhry</i>			<b>38.24</b>	Blood Component Therapy <i>Anupam Verma, Hemlata, Nabajyoti Choudhury</i>	1767
<b>38.1</b>	The Hematopoietic System <i>Praveen C Sobti, Shruti Kakkar</i>	1632	<b>38.25</b>	Stem Cell Transplantation <i>Mammen Chandu</i>	1771
<b>38.2</b>	Approach to Diagnosis of Anemia <i>MR Lokeshwar, Swati Gupta, Swati Kanakia</i>	1641	<b>38.26</b>	Myelodysplastic Syndromes <i>Tathagata Chatterjee, VP Choudhry</i>	1776
<b>38.3</b>	Anemia: Etiology and Classification <i>Nitin Shah, Sunil Udgire</i>	1649	<b>Section 39: RESPIRATORY DISEASES</b>		
<b>38.4</b>	Congenital Bone Marrow Failure <i>Maitryee Bhattacharya, Meet Kumar</i>	1653	<b>Section Editors</b> <i>Varinder Singh, GR Sethi</i>		
<b>38.5</b>	Aplastic Anemia <i>Amita Mahajan</i>	1659	<b>39.1</b>	Anatomy and Physiology of Respiration <i>Pankaj C Vaidya</i>	1780
<b>38.6</b>	Iron Deficiency Anemia <i>Mamta Manglani</i>	1663	<b>39.2</b>	Approach to Diagnosis of a Respiratory Disorder <i>Soumya Tiwari, Varinder Singh</i>	1788
<b>38.7</b>	Megaloblastic Anemia <i>Sangeeta Mudaliar, Bharat Agarwal</i>	1669	<b>39.3</b>	Congenital Malformations of the Upper Respiratory Tract <i>D Vijayasekaran</i>	1792
<b>38.8</b>	Approach to Hemolytic Anemia <i>VP Choudhry</i>	1675	<b>39.4</b>	Epistaxis <i>Jagdish Chinnappa</i>	1795
<b>38.9</b>	Hemoglobinopathies <i>HP Pati, Deepti Mutreja</i>	1681	<b>39.5</b>	Allergic Rhinitis <i>Ankit Parakh, Varinder Singh</i>	1797
<b>38.10</b>	Thalassemia <i>VP Choudhry, JS Arora</i>	1685	<b>39.6</b>	Otitis Media <i>Jagdish Chinnappa</i>	1800
<b>38.11</b>	Sickle Cell Disease <i>Vibhawari S Dani, Dipty Jain</i>	1694	<b>39.7</b>	Approach to a Child with Cough <i>NK Subramanya, Vidya K</i>	1806
<b>38.12</b>	RBC Membrane Defects <i>Nitin Shah, Khushnuma Mullanfiroze</i>	1700	<b>39.8</b>	Common Cold and Acute Pharyngitis <i>Satnam Kaur, GR Sethi</i>	1809
<b>38.13</b>	Red Blood Cell Enzyme Defects <i>Manoranjan Mahapatra</i>	1704	<b>39.9</b>	Sinusitis <i>SD Subba Rao</i>	1813
<b>38.14</b>	Immune Hemolytic Anemia <i>Nita Radhakrishnan, Anupam Sachdeva</i>	1708	<b>39.10</b>	Tonsils and Adenoids <i>Pallab Chatterjee</i>	1816
<b>38.15</b>	Physiology of Hemostasis <i>Renu Saxena, Neha Singh</i>	1714	<b>39.11</b>	Obstructive Sleep Apnea <i>Zeynep Seda Uyan, Refika Ersu</i>	1820
<b>38.16</b>	Bleeding and Coagulation Disorders <i>Tulika Seth</i>	1719	<b>39.12</b>	Congenital Malformations of the Lower Respiratory Tract <i>D Vijayasekaran</i>	1825
<b>38.17</b>	Hemophilia <i>Pravas Mishra</i>	1724			

39.13	Stridor and Croup <i>Shalu Gupta</i>	1830	40.3	The Heart and Circulation <i>Munesh Tomar, Savitri Shrivastava</i>	1913
39.14	Approach to a Child with Fast Breathing <i>Soumya Tiwari, Varinder Singh</i>	1834	40.4	Genetic Basis of Heart Diseases <i>Sumaira Khalil, Seema Kapoor</i>	1916
39.15	Approach to a Child with Wheeze <i>Soumya Tiwari, Varinder Singh</i>	1836	40.5	Systemic Disorders with Heart Disease <i>Anita Khalil</i>	1921
39.16	Bronchiolitis <i>Ilin Kinimi</i>	1838	40.6	Cardiovascular Examination <i>M Zulfikar Ahamed</i>	1924
39.17	Alpha-1 Antitrypsin Deficiency <i>Kana Ram Jat, Rakesh Lodha, SK Kabra</i>	1844	40.7	Electrocardiogram <i>BRJ Kannan</i>	1929
39.18	Aspiration Syndromes <i>Mahesh Babu Ramamurthy, Michael Lim Teik Chung</i>	1846	40.8	Chest Skiagram in Heart Disease <i>BRJ Kannan</i>	1937
39.19	Preschool Wheeze and Bronchial Asthma <i>KR Bharath Kumar Reddy, Samatha Sonnappa</i>	1850	40.9	Echocardiography <i>Balu Vaidyanathan</i>	1943
39.20	Aerosol Therapy <i>Bruce K Rubin, Ronald W Williams</i>	1859	40.10	Cardiac Catheterization <i>Duraisamy Balaguru</i>	1949
39.21	Pneumonia <i>Swati Dublish, Varinder Singh</i>	1861	40.11	Cardiac Malpositions <i>P Syamasundar Rao</i>	1955
39.22	Parapneumonic Effusion and Empyema <i>Kamal Kumar Singhal, GR Sethi</i>	1870	40.12	Ventricular Septal Defects <i>IB Vijayalakshmi</i>	1965
39.23	Pneumothorax and Air Leaks <i>Mandeep Walia, Abhishek Somasekhara Aradhya</i>	1873	40.13	Atrial Septal Defects <i>K Sivakumar</i>	1971
39.24	Persistent and Recurrent Pneumonia <i>Ankit Parakh, Varinder Singh</i>	1876	40.14	Atrioventricular Septal Defects <i>Snehal Kulkarni, Tanuja Karande</i>	1976
39.25	Interstitial Lung Disease <i>A Bush</i>	1880	40.15	Patent Ductus Arteriosus <i>K Sivakumar</i>	1979
39.26	Hemoptysis and Alveolar Bleeds <i>Meenu Singh, Nandini Paul</i>	1884	40.16	Anomalous Left Coronary Artery from Pulmonary Artery, Coronary Arterial Fistula and Ruptured Sinus of Valsalva <i>MS Ranjith</i>	1984
39.27	Primary Ciliary Dyskinesia <i>Ada Y Yip, Daniel K Ng</i>	1886	40.17	Pulmonary Stenosis <i>Shreepal Jain, Bharat Dalvi</i>	1986
39.28	Cystic Fibrosis <i>SK Kabra, Kana Ram Jat, Rakesh Lodha</i>	1890	40.18	Coarctation of Aorta <i>Kshitij Sheth, Bharat Dalvi</i>	1991
39.29	Bronchiectasis <i>Lokesh Guglani</i>	1895	40.19	Aortic Stenosis <i>Smita Mishra</i>	1996
39.30	Lung Abscess <i>Kana Ram Jat, Meghna Sharma</i>	1899	40.20	Clinical Approach to Infants and Children with Cyanotic Congenital Heart Disease <i>M Zulfikar Ahamed</i>	2002
39.31	Tracheobronchial Foreign Body Aspiration <i>Varinder Singh, Ankit Parakh</i>	1901	40.21	Tetralogy of Fallot and Variants <i>Anita Saxena</i>	2006
39.32	Central Hypoventilation <i>Mahesh Babu Ramamurthy, Daniel YT Goh</i>	1903	40.22	Tricuspid Atresia <i>P Syamasundar Rao</i>	2014
Section 40: CARDIOVASCULAR DISORDERS			40.23	Transposition of Great Arteries <i>R Suresh Kumar, Navaneetha Sasikumar</i>	2023
Section Editors S Srinivasan, M Zulfikar Ahamed			40.24	Truncus Arteriosus <i>Duraisamy Balaguru</i>	2027
40.1	Historical Aspects and Advances in Pediatric Cardiology <i>S Srinivasan</i>	1906			
40.2	Development of the Heart <i>S Srinivasan</i>	1908			

<b>40.25</b>	Ebstein Anomaly, Pulmonary Arteriovenous Fistula, Corrected Transposition of Great Arteries <i>Sunita Maheshwari</i>	2030	<b>40.33</b>	Congestive Heart Failure <i>Parvathi U Iyer, Harsheen Kaur, Neeraj Awasthy</i>	2067
<b>40.26</b>	Admixture Lesions <i>Neeraj Awasthy, S Radhakrishnan</i>	2033	<b>40.34</b>	Infective Endocarditis <i>Shakuntala Prabhu, Sumitra Venkatesh</i>	2077
<b>40.27</b>	Hypoplastic Left Heart Syndrome <i>Joseph John Vettukattil</i>	2039	<b>40.35</b>	Myocardial Diseases: Myocarditis and Cardiomyopathies <i>Ronak Naik, Nishant Shah</i>	2084
<b>40.28</b>	Pulmonary Arterial Hypertension <i>Nageswara Rao Koneti</i>	2042	<b>40.36</b>	Diseases of the Pericardium <i>Manoj Kumar Rohit, Ankur Gupta</i>	2096
<b>40.29</b>	Acute Rheumatic Fever <i>B Anjaiah</i>	2048	<b>40.37</b>	Cardiac Dysrhythmias <i>Ramandeep S Ahuja, Rajnish Juneja</i>	2100
<b>40.30</b>	Rheumatic Heart Disease and Lesions of the Mitral Valve <i>R Krishna Kumar</i>	2053	<b>40.38</b>	Cardiac Emergencies <i>Umesh Dyamenahalli</i>	2117
<b>40.31</b>	Rheumatic Aortic Valve Disease <i>Savitri Shrivastava</i>	2060	<b>40.39</b>	Surgical Considerations in Congenital Heart Diseases <i>R Benedict Raj, S Srinivasan</i>	2122
<b>40.32</b>	Takayasu Arteritis <i>Biswajit Bandyopadhyay</i>	2064	<b>40.40</b>	Preventive Cardiology in the Young <i>S Sivasankaran</i>	2126

## Volume 3: Systemic Disorders and Social Pediatrics

### Section 41: DISORDERS OF THE KIDNEY AND URINARY TRACT

**Section Editors** Arvind Bagga, Aditi Sinha

<b>41.1</b>	Anatomy and Physiology <i>M Vijayakumar, Arvind Bagga</i>	2131	<b>41.9</b>	Proteinuria <i>Sushmita Banerjee</i>	2162
<b>41.2</b>	Investigations for Kidneys and Urinary Tract <i>Susan Uthup, Jyoti Sharma</i>	2135	<b>41.10</b>	Nephrotic Syndrome <i>Arvind Bagga, Aditi Sinha</i>	2164
<b>41.3</b>	Congenital Anomalies of Kidneys and Urinary Tract <i>Shilpa Sharma, Aditi Sinha</i>	2139	<b>41.11</b>	Acute Kidney Injury <i>Anil Vasudevan</i>	2173
<b>41.4</b>	Cystic Kidney Diseases <i>Shina Menon</i>	2145	<b>41.12</b>	Renal Replacement Therapy for Acute Kidney Injury <i>Sidharth Kumar Sethi, Rupesh Raina</i>	2178
<b>41.5</b>	Hematuria <i>Rajiv Sinha</i>	2148	<b>41.13</b>	Hemolytic Uremic Syndrome <i>Aditi Sinha, Arvind Bagga</i>	2180
<b>41.6</b>	Glomerulonephritis • Acute Nephritic Syndrome <i>Amarjeet Mehta</i> • Rapidly Progressive Glomerulonephritis <i>Arvind Bagga, Shina Menon</i> • Immunoglobulin A Nephropathy <i>Manisha Sahay</i>	2151	<b>41.14</b>	Renal Tubular Acidosis <i>Arvind Bagga, Aditi Sinha</i>	2184
<b>41.7</b>	Systemic Vasculitis and Lupus Nephritis <i>Ashima Gulati, Arvind Bagga</i>	2156	<b>41.15</b>	Tubular Disorders <i>Kamran Afzal</i>	2189
<b>41.8</b>	Alport Syndrome and Related Disorders <i>Mukta Mantan</i>	2160	<b>41.16</b>	Renal Calculi <i>Indira Agarwal</i>	2195
			<b>41.17</b>	Refractory Rickets <i>Abhijeet Saha</i>	2198
			<b>41.18</b>	Hypertension <i>Swasti Chaturvedi</i>	2202
			<b>41.19</b>	Urinary Tract Infection and Vesicoureteric Reflux <i>Pankaj Hari</i>	2207
			<b>41.20</b>	Dysfunctional Voiding <i>Madhuri Kanitkar, Suprita Kalra</i>	2213

41.21	Chronic Kidney Disease <i>Erica Winnicki, Lavjay Butani, Stephanie Nguyen</i>	2216	42.20	Inflammatory Demyelinating Disorders <i>Bindu PS</i>	2341
41.22	End-Stage Renal Disease <i>Kirtida Mistry, Asha Moudgil</i>	2219	42.21	Autoimmune and Paraneoplastic Encephalitis and Encephalopathies <i>Lokesh Lingappa, Sirisharani Siddaiahgari</i>	2348
Section 42: NEUROLOGICAL DISORDERS			42.22	Headache <i>Devendra Mishra</i>	2352
<b>Section Editors</b> <i>Satinder Aneja, Suvasini Sharma</i>			42.23	Movement Disorders <i>Debabrata Ghosh</i>	2359
42.1	Approach to Neurological Disorders <i>Suvasini Sharma, Satinder Aneja</i>	2222	42.24	Childhood Ataxia <i>Asuri N Prasad</i>	2366
42.2	Cerebrospinal Fluid and Neurophysiology <i>Anita Choudhary</i>	2228	42.25	Neurometabolic Disorders <i>Mahesh Kamate</i>	2372
42.3	Neuroimaging <i>Atin Kumar, Jyoti Kumar</i>	2233	42.26	Neurodegenerative Disorders <i>Naveen Sankhyan</i>	2377
42.4	Neural Tube Defects and Spinal Cord Malformations <i>Sujata Kanhere</i>	2243	42.27	Spinal Cord Disorders <i>Vykunta Raju KN</i>	2387
42.5	Brain Malformations <i>Jatinder S Goraya</i>	2249	42.28	Pseudotumor Cerebri <i>Anaita Udwadia-Hegde, Omkar P Hajirnis</i>	2393
42.6	Neurocutaneous Disorders <i>Maya Thomas, Renu George, Karthik Muthusamy</i>	2255	Section 43: NEUROMUSCULAR DISORDERS		
42.7	Hydrocephalus <i>Daljit Singh, Hukum Singh</i>	2264	<b>Section Editors</b> <i>Sheffali Gulati, J Andoni Urtizberea</i>		
42.8	Seizures and Epilepsy <i>Puneet Jain, Lakshminarayanan Kannan</i>	2269	43.1	Approach to Diagnosis of Neuromuscular Disorders <i>Sheffali Gulati, Jaya Shankar Kaushik, J Andoni Urtizberea, MC Sharma</i>	2395
42.9	Treatment of Seizures and Epilepsy <i>Gopinath Musuwadi Subramanian</i>	2276	43.2	Floppy Infant <i>Anaita Udwadia-Hegde, Shilpa Kulkarni</i>	2409
42.10	Febrile Seizures <i>Sangeetha Yoganathan</i>	2281	43.3	Acute Flaccid Paralysis <i>Biswaroop Chakrabarty, Sheffali Gulati</i>	2416
42.11	Status Epilepticus <i>Ravindra Arya, Katrina Peariso</i>	2284	43.4	Guillain-Barré Syndrome <i>Vrajesh Udani</i>	2421
42.12	Nonepileptic Paroxysmal Disorders <i>Hema Patel, David W Dunn</i>	2291	43.5	Spinal Muscular Atrophy <i>Soumya Sundaram, Muralidharan Nair</i>	2425
42.13	Coma, Raised Intracranial Pressure and Brain Death <i>Gurpreet Singh Kochar, Suvasini Sharma</i>	2296	43.6	Muscular Dystrophies <i>Satish V Khadilkar, Rakhil S Yadav</i>	2431
42.14	Stroke <i>Ramesh Konanki</i>	2304	43.7	Congenital Muscular Dystrophy <i>Sunil Pradhan, AK Meena</i>	2441
42.15	Pyogenic Meningitis <i>B Talukdar</i>	2314	43.8	Congenital Myopathies <i>Kimberly Amburgey, Michael W Lawlor, James J Dowling</i>	2453
42.16	Tuberculosis of the Central Nervous System <i>Chandrakanta, Rashmi Kumar</i>	2318	43.9	Neuromuscular Transmission Disorders <i>Venkateswaran Ramesh</i>	2458
42.17	Viral Encephalitis <i>Mary Iype</i>	2325	43.10	Hereditary Motor and Sensory Neuropathies <i>V Viswanathan</i>	2463
42.18	Neurocysticercosis <i>Pratibha Singh</i>	2329	43.11	Autonomic Neuropathies <i>Rachana Dubey, Ashok Jaryal, Sheffali Gulati</i>	2466
42.19	Brain Abscess <i>Prashant Jauhari, Jitendra Kumar Sahu</i>	2335			



## Section 44: DISORDERS OF THE ENDOCRINE GLANDS

**Section Editors** PSN Menon, Vijayalakshmi Bhatia

<b>44.1</b>	Principles of Endocrinology and Hormone Action	2474	<b>44.21</b>	Cryptorchidism and Micropenis	2559
	<i>Khalid Hussain</i>			<i>Aparna Limaye</i>	
<b>44.2</b>	Physiology of Neuroendocrinology	2479	<b>44.22</b>	Classification of Diabetes Mellitus	2562
	<i>Priyanka Gupta, Vijayalakshmi Bhatia</i>			<i>Aspi Irani</i>	
<b>44.3</b>	Growth Hormone Deficiency and Resistance	2483	<b>44.23</b>	Type 1 Diabetes Mellitus	2566
	<i>Arpita K Vyas, Ram K Menon</i>			<i>Aspi Irani</i>	
<b>44.4</b>	Polyuria, Diabetes Insipidus and Syndrome of Inappropriate Secretion of ADH	2490	<b>44.24</b>	Acute and Chronic Complications of Diabetes Mellitus	2573
	<i>Tushar Godbole, PSN Menon</i>			<i>KG Ravikumar</i>	
<b>44.5</b>	Thyroid Hormone Physiology	2494	<b>44.25</b>	Bone Mineral and Hormone Physiology	2578
	<i>Anna Simon</i>			<i>Philip G Murray, M Zulf Mughal</i>	
<b>44.6</b>	Hypothyroidism and Thyroiditis	2496	<b>44.26</b>	Calcium Disorders	2581
	<i>Palany Raghupathy</i>			<i>Shaila Sukthankar, Raja Padidela</i>	
<b>44.7</b>	Newborn Screening for Congenital Hypothyroidism	2501	<b>44.27</b>	Metabolic Rickets	2585
	<i>Anna Simon</i>			<i>Shaila Sukthankar, Raja Padidela</i>	
<b>44.8</b>	Hyperthyroidism	2502	<b>44.28</b>	Disorders with Bone Fragility	2589
	<i>Sobha Kumar</i>			<i>M Zulf Mughal</i>	
<b>44.9</b>	Goiter and Nodules	2504	<b>44.29</b>	Monogenic Obesity	2592
	<i>Lalitha Kailas, Riaz I</i>			<i>Leena Priyambada</i>	
<b>44.10</b>	Normal Puberty	2507	<b>44.30</b>	Hyperlipidemia	2596
	<i>Ruchi Parikh, Meena Desai</i>			<i>Nisha Bhavani</i>	
<b>44.11</b>	Delayed Puberty	2512	<b>44.31</b>	Endocrine Consequences of Thalassaemia Major	2599
	<i>Vijaya Sarathi, Nalini S Shah</i>			<i>Archana Dayal Arya</i>	
<b>44.12</b>	Precocious Puberty	2516	<b>44.32</b>	Endocrine Effects of Radiation and Cancer Chemotherapy	2602
	<i>Prisca Colaco</i>			<i>Margaret Zacharin</i>	
<b>44.13</b>	Gynecomastia	2521	<b>44.33</b>	Adult Consequences of IUGR and Prematurity	2605
	<i>Anju Virmani</i>			<i>Sarah Mathai, Paul Hofman</i>	
<b>44.14</b>	Normal Development and Physiology of the Adrenal Gland	2524	<b>Section 45: MALIGNANCIES IN CHILDREN</b>		
	<i>Rajesh Joshi</i>		<b>Section Editors</b> Brijesh Arora, Shripad Banavali		
<b>44.15</b>	Congenital Adrenal Hyperplasia	2527	<b>45.1</b>	Epidemiology of Cancers in Children	2607
	<i>Anurag Bajpai, PSN Menon</i>			<i>Ramandeep Singh</i>	
<b>44.16</b>	Adrenal Insufficiency and Polyglandular Failure	2531	<b>45.2</b>	Acute Lymphoblastic Leukemia	2612
	<i>M Vijayakumar</i>			<i>Revathi Raj, Deenadayalan M</i>	
<b>44.17</b>	Cushing Syndrome	2537	<b>45.3</b>	Acute Myeloid Leukemia	2619
	<i>Maha Elhassan, Michael A Wood</i>			<i>Akash Nahar, Yaddanapudi Ravindranath</i>	
<b>44.18</b>	Endocrine Hypertension	2543	<b>45.4</b>	Chronic Myelogenous Leukemia	2625
	<i>Praveen VP</i>			<i>Arathi Srinivasan, Julius Xavier Scott</i>	
<b>44.19</b>	Glucocorticoid Use and Withdrawal	2547	<b>45.5</b>	Myelodysplastic Syndrome and Juvenile Myelomonocytic Leukemia	2630
	<i>VK Bhardwaj</i>			<i>Sangeeta Mudaliar, Archana Swami</i>	
<b>44.20</b>	Disorders of Sexual Development	2549	<b>45.6</b>	Hodgkin Lymphoma	2635
	<i>Ganesh S Jevalikar, Preeti Dabaghao</i>			<i>Vishal Sondhi, Brijesh Arora</i>	
			<b>45.7</b>	Non-Hodgkin Lymphoma	2640
				<i>Nirav Thacker, Vikramjit S Kanwar, Tipu Nazeer</i>	

45.8	Neuroblastoma <i>Maya Prasad, PA Kurkure</i>	2648
45.9	Wilms Tumor <i>Sajid Qureshi, Monica Bhagat</i>	2654
45.10	Brain Tumors <i>Anaita Udwadia-Hegde, Omkar P Hajirnis, Girish Chinnaswamy</i>	2661
45.11	Retinoblastoma <i>Anirban Das, Deepak Bansal</i>	2677
45.12	Soft Tissue Tumors <i>Sandeep Jain, Gauri Kapoor</i>	2685
45.13	Histiocytic Disorders <i>Gaurav Narula, Nirmalya D Pradhan</i>	2689
45.14	Bone Tumors <i>Ashish Gulia, Tushar Vora</i>	2695
45.15	Oncological Emergencies and Supportive Care <i>Anand Prakash, ATK Rau</i>	2701
45.16	Hematopoietic Stem Cell Transplant <i>Satyendra Katewa, Satya Prakash Yadav</i>	2710

## Section 46: RHEUMATOLOGICAL DISORDERS

**Section Editors** *Surjit Singh, Anju Gupta*

46.1	Approach to a Child with Rheumatological Disorder <i>Anand Prahalad Rao</i>	2718
46.2	Laboratory Investigations for Rheumatological Disorders <i>Anju Gupta, Tapas Kumar Sabui</i>	2723
46.3	Juvenile Idiopathic Arthritis <i>Sujata Sawhney</i>	2727
46.4	Large Vessel Vasculitis: Takayasu Arteritis <i>Anju Gupta</i>	2733
46.5	Medium Vessel Vasculitis: Kawasaki Disease and Polyarteritis Nodosa <i>Sikha Agarwal, Surjit Singh</i>	2737
46.6	Small Vessel Vasculitis: ANCA Associated Vasculitis and Henoch-Schönlein Purpura <i>Nutan Kamath, Rakesh Mondal</i>	2741
46.7	Juvenile Dermatomyositis <i>Priyanka Pal</i>	2747
46.8	Systemic Lupus Erythematosus: Clinical Manifestations <i>Sathish Kumar</i>	2751
46.9	Management of Systemic Lupus Erythematosus <i>Aruna Bhat</i>	2756
46.10	Juvenile Scleroderma <i>Suma Balan</i>	2759
46.11	Antiphospholipid Syndrome <i>Jasmina Ahluwalia, Anju Gupta</i>	2763

## Section 47: COMMON EYE ABNORMALITIES

**Section Editor** *Kirti Singh*

47.1	Common Visual Problems <i>Kirti Singh</i>	2766
47.2	Congenital Anomalies <i>Karobi Lahiri Coutinho</i>	2771
47.3	Refractive Errors <i>Kirti Singh, Divya Jain</i>	2774
47.4	Cornea and Conjunctiva <i>Ritu Arora, Aditi Manudhane</i>	2781
47.5	Uveitis <i>SR Rathinam, Prachi Agashe</i>	2786
47.6	Cataract and Lens-related Issues <i>Abhay R Vasavada, Sajani K Shah</i>	2792
47.7	Glaucoma <i>Kirti Singh, Savleen Kaur</i>	2799
47.8	Optic Nerve and Pupil <i>Digvijay Singh, Pradeep Sharma</i>	2805
47.9	Strabismus and Motility Disorders <i>AK Amitava, Shivani Grover</i>	2810
47.10	Eyelid, Orbit and Lacrimal Sac <i>Apjit Kaur</i>	2821
47.11	Ocular Injuries <i>Kalpna Narendran, Sandra C Ganesh</i>	2828
47.12	Ocular Manifestations of Systemic Disorders <i>Koushik Tripathy, Pradeep Venkatesh</i>	2833
47.13	Visually Impaired Child <i>Kirti Singh, Ankush Mutreja</i>	2843

## Section 48: COMMON SKIN PROBLEMS

**Section Editors** *Sandipan Dhar, Raghubir Banerjee,  
Rajib Malakar, Apurba Ghosh*

48.1	Skin of the Newborn: Physiological and Pathological Changes <i>Keshavmurthy A Adya, Arun C Inamadar</i>	2850
48.2	Care of Skin in the Newborn <i>S Sacchidanand, Preeti Sheth</i>	2858
48.3	Infections and Infestations <i>S Criton</i>	2861
48.4	Congenital Vascular and Melanocytic Malformations <i>Manish K Shah</i>	2869
48.5	Vitiligo and Other Hypopigmentary Diseases <i>Tarun Narang, Amrinder Jit Kanwar</i>	2872
48.6	Atopic Dermatitis <i>Deepak A Parikh, Abhijit Saha</i>	2879
48.7	Contact Dermatitis <i>Raghubir Banerjee, Sandipan Dhar</i>	2881
48.8	Urticaria and Mastocytosis <i>Deepika Pandhi, Rahul Arora</i>	2883

48.9	Cutaneous Drug Reactions <i>Rajib Malakar, Sandipan Dhar</i>	2890
48.10	Cutaneous Manifestations of Nutritional Deficiency Diseases <i>Vibhu Mendiratta</i>	2893
48.11	Cutaneous Manifestations of Collagen Vascular Diseases <i>Yogesh S Marfatia</i>	2896
48.12	Neurocutaneous Syndromes <i>Resham J Vasani</i>	2900
48.13	Vesiculobullous Disorders <i>Bhawna Wadhwa, Rashmi Sarkar</i>	2905
48.14	Papulosquamous Diseases <i>Ravi Hiremagalore, Subhash Lokre, Priya Bishnoi</i>	2908
48.15	Ichthyosis <i>Deepika Pandhi, Deepashree Daulatabad</i>	2915
48.16	Genetic Cutaneous Disorders <i>Manjyot Manish Gautam</i>	2921
48.17	Hair Disorders <i>Tarang Goyal</i>	2924

## Section 49: DISORDERS OF BONES AND JOINTS

**Section Editor** Harish S Hosalkar

49.1	Assessment of the Locomotor System <i>Jayanth Sundar Sampath, Harish S Hosalkar</i>	2928
49.2	Osteomyelitis <i>Mandar V Agashe, Harish S Hosalkar</i>	2935
49.3	Septic Arthritis <i>Mandar V Agashe, Harish S Hosalkar</i>	2939
49.4	Neck Problems <i>Vijay HD Kamath, Harish S Hosalkar</i>	2942
49.5	Scoliosis and Kyphosis <i>Vijay HD Kamath, Harish S Hosalkar</i>	2949
49.6	Developmental Dysplasia of the Hip (DDH) <i>Venkatadass K, Harish S Hosalkar</i>	2959
49.7	Legg-Calvé-Perthes Disease <i>Venkatadass K, Harish S Hosalkar</i>	2963
49.8	Osgood-Schlatter Disease <i>Joana Manuel Ferreira Freitas, Harish S Hosalkar</i>	2966
49.9	Congenital Talipes Equinovarus <i>Mandar V Agashe, Harish S Hosalkar</i>	2968
49.10	Skeletal Dysplasias <i>Kuldeep Singh, Abhay Elhence</i>	2971
49.11	Arthrogryposis <i>Jayanth Sundar Sampath, Harish S Hosalkar</i>	2985

## PART IX: Child in the Social Milieu

### Section 50: VULNERABLE CHILDREN

**Section Editor** Sanjay Chaturvedi

50.1	Vulnerability <i>Dheeraj Shah, Piyush Gupta</i>	2988
50.2	Street Children <i>Pranab Chatterjee, Sanjay Chaturvedi</i>	2990
50.3	Child Labor <i>SR Banerjee</i>	2994
50.4	Child Abuse and Neglect <i>Kiran Aggarwal</i>	2997
50.5	Adoption: Medical and Legal Issues <i>Samir H Dalwai</i>	3004
50.6	Rights of the Child <i>Swati Y Bhawe, Piyush Gupta</i>	3007

### Section 51: COMMUNITY PEDIATRICS

**Section Editor** Piyush Gupta

51.1	Indicators of Child Health <i>Piyush Gupta, Dhulika Dhingra</i>	3010
51.2	Environment and Child Health <i>Dhulika Dhingra, Piyush Gupta</i>	3017
51.3	Lead Poisoning <i>Dhulika Dhingra, Piyush Gupta</i>	3022
51.4	Programs for Child Health <i>Amir Maroof Khan, Piyush Gupta</i>	3024
51.5	Integrated Management of Neonatal and Childhood Illness (IMNCI) <i>AK Patwari</i>	3027

## PART X: Annexures

### LABORATORY VALUES AND DRUG DOSES

**Section Editor** Pooja Dewan

<b>Annexure A:</b>	Laboratory Reference Values <i>Nidhi Bedi, Pooja Dewan</i>	3041
<b>Annexure B:</b>	Drug Doses <i>Pooja Dewan, Nidhi Bedi</i>	3050

# PART I Pediatrics—Yesterday, Today, Tomorrow

## Section 1 INTRODUCTION TO PEDIATRICS

**Section Editors** Piyush Gupta, PSN Menon

### Chapter 1.1

### Evolution of Pediatrics

KN Agarwal

Pediatrics is the medical science for children, who are in a phase of active growth and progressive development. The word *pediatrics* and its cognates mean *healer of children*; derived from two Greek words: *pais* (child) and *iatros* (doctor or healer).

Newborns, toddlers, children and adolescents have physical and emotional needs and health concerns different from adults. They are growing at varying rates in different phases of life—somatic growth, growth and development of brain, lymphoid tissue enlargement, and sexual development; thus energy needs and body metabolism remain active. In contrast adults are in a static maintenance phase, thus their macro- and micro-nutrient needs are more or less regulated and unchanging. Pediatricians take care of all these needs from birth up to age 18. Present estimates are that brain growth completes around 25 years of age. The science of pediatrics has intimate relationship with mother from conception and birth, making obstetrics, gynecology and pediatrics almost inseparable. In addition it is hard to recognize diseases in young children with inherent difficulty in oral communication, and in whom eliciting clinical information is problematic.

### DISEASES OF CHILDREN AND THEIR MANAGEMENT IN ANCIENT TIMES

#### India

The “*Atharva Veda*” (1000 BC), a medical textbook explaining how to treat diseases, described *breastmilk* as nectar. “*Charaka Samhita*” (400–200 BC) and “*Kashyap Samhita*” (written by a pediatrician around 6th century BC to 2nd century AD) described importance of breastmilk and advised breastfeeding from the first day of birth. “*Sushruta Samhita*” (dealing with surgical procedures; 500 BC) stated breastmilk as beverage of immortality. Unfortunately it advised discarding of colostrum for the first three days and advocated feeding of honey and butter to facilitate discharge of meconium. Infant bath with lukewarm water and feeding of cereal and/or lentil (*annapraasan*) was recommended after 6 months of age.

Charaka knew that blood vessels brought food to various parts of the body and carried wastes away. He also made the earliest Indian reference to smallpox. Madhava (700 AD) practiced inoculation to keep people from catching smallpox, by scraping pus or scabs from the patient and administering as an inoculation, either by sticking it into the skin on a needle, or by blowing the powder up the nose.

#### Egypt

*Ebers Papyrus* (1550 BC) is a summary of the medical and surgical therapeutics practiced in ancient Egypt. In a tiny pediatric section which is mainly prognostic it reads as follows:

- To get a supply of milk in a woman's breast for suckling a child, warm the bones of swordfish in oil and rub her back with it.
- Prognosis for a child on the day its birth: if it cries nicely, it will live; if it cries badly, it will die. If it wails loudly, it will die; if it drops its face downwards, it will die immediately.

*Ebers Papyrus* also describes a few other topics including breastfeeding, a cure for worms, and treatment of eye diseases.

#### Islamic Empire

##### (Iraq, Iran, Israel, Lebanon and Syria)

Islamic physicians studied in depth all the medical observations and logic of Hippocrates, his followers and Galen, combined with the work of the Indian physicians Sushruta and Charaka, whose books were translated into Arabic around 750 AD. Their observations helped to develop useful cures for some diseases. Another achievement of these practitioners was that they started the world's first hospitals, where the contagious patients of smallpox and measles were isolated and treated.

Al Razi (870–900 AD), Persian physician wrote in a book the first description of how to differentiate measles and smallpox. However he did not mention inoculation though it was already being done in India. Ibn Sina, the great Arabian physician (known as Avicenna in Europe, 990 AD) discussed tetanus, worm infestations, convulsions, meningitis and umbilical abscess. He was the first to observe that tuberculosis and smallpox are contagious.

#### China

Pediatrics was one of the oldest specialties within Chinese medicine and dates from the early first millennium. This form of Asian medicine is the oldest and second largest medical system in the world today and is used by one quarter of the world's population. Children according to Chinese belief are weak and susceptible to diseases that affect the lungs (such as colds, coughs, allergies and asthma) and the spleen (or digestive complaints such as colic, vomiting, diarrhea, indigestion, and stomach aches). In traditional Chinese medicine, there are four primary methods of treating children—dietary therapy, Chinese herbal medicine, Chinese pediatric massage and acupuncture.

#### Greece

Around 300 BC and afterwards Greek physicians established a logical system for understanding disease. “*Hippocratic Writings*”, named after the first and most famous of these physicians, (460 BC) give descriptions for cephalhematoma, hydrocephalus, clubfoot, worm infestations, diarrhea, scrofula, asthma, and mumps. Significant advances were made in childbearing with the



introduction of the “*Hippocratic Corpus*” in the 3rd century BC, though this document advised the practice of many superstitions.

Galen (200 AD) suggested advancement in medicine for women, though he focused mostly on specific diseases with some aspects of labor. He also wrote of ear discharge, pneumonia, intestinal prolapse and possibly rickets.

Soranus of Ephesus (98–138 AD) wrote in the 2nd century on childbirth and obstetrics. For birth, the mother was made to sit on a birthing stool with a midwife in front of her and female aids standing at her sides. In a normal head-first delivery, the cervical opening was stretched slightly, and the rest of the body was pulled out. He instructed the midwife to wrap her hands in pieces of cloth or thin paper so that the slippery newborn did not slide out of her grasp. On the care of the newborn, his teachings as described in “*On Diseases of Women*” were followed to a large extent. He was the first to advise the salting and saddling of the newborn infant, a practice dating back to 600 BC. He also described a testing of the breastmilk by the behavior of a drop of milk placed on fingernail. This continued for over 1600 years.

Weakness at birth was attributed to prematurity, with heavy mortality. But Isaac Newton (1643–1727), Christopher Wren (1632–1723), and Jonathan Swift (1667–1745) were all premature infants, yet all lived a long vigorous life.

## HISTORY OF MODERN PEDIATRICS

Major events related to child health are listed in a chronological order in **Table 1**.

### Europe (United Kingdom, Belgium, Denmark, Italy, France, Germany and Sweden)

In 15th century four pediatric books were published in succession describing general pediatric ailments such as cough, ear infection, measles, smallpox, rheumatism and diarrhea. These were written by Paulus Bagellardus (Italy, 1472, *De Infantium Aegritudinibus et Remediis*), Bartholomaeus Metlinger (Germany, 1473, *Ein Regiment der Jungerkinder*), Cornelius Roelans (Belgium, 1483, no title) and Heinrich von Louffenburg (Germany, 1491, *Versehung des Leibs*).

This was followed by detailed description of diseases in children. Eucharius Roesslin (Germany, early 16th century) wrote a book on *Midwifery and Pediatrics*, which reviewed 35 common ailments including many infections. Faventinus de Victorious (Italy, 1544) published a book with chapter on aphthous ulcers, measles and smallpox. Thomas Phaer (England, 1544) published the first English language pediatric book, “*The Boke of Chyldren*” with chapters on meningitis, diseases of the ear, quinsy, diarrheal disorders, worm infestations, smallpox, measles, fever and a disease description similar to Kawasaki disease.

Many infectious disorders were described subsequently. Giovanne P Ingrassia (Italy, 1553) differentiated scarlet fever from measles. Hieronymus Mercurialis (Italy, 1583) wrote about *King’s evil* (scrofulous glands). Guillaume de Baillou (France, 1640) was the first to describe whooping cough as distinct entity covering the 1578 epidemic, as well as rubeola and scarlet fever. Johannes Sgambatus (Italy, 1620) made important descriptions of diphtheria while Thomas Bartholin (Denmark, 1646) described its contagious nature and mode of death by throttling.

The second English language book by Robert Pemell (1653) covered extensively many common infestations, otitis, oral ulcers, fevers, smallpox, measles and erysipelas. The third English book in 1664 by J Starsmare covered the same topics including *scrofula*. Thomas Sydenham (England) described chorea in 1686, measles in 1670 and scarlet fever in 1675. Willis (England, famous for *circle of Willis*) described pertussis in 1675. Walter Harris (England,

1689) wrote a book on *diseases of infants* covering plague, venereal diseases and strongly advocated inoculation against smallpox. This popular book had 18 editions and continued for another 53 years. John Fothergill (England, 1748) described ulcerative pharyngitis, diphtheria and scarlet fever.

Chickenpox was described in 1760 by François Boissier de Sauvages (France). In 1765 Nils Rosén von Rosenstein (Sweden) described scarlet fever of 1744 epidemic in detail including the post-streptococcal nephritis. The credit of describing tubercular meningitis in three clinical stages with autopsy findings goes to Robert Whytt (Scotland, 1768).

Michael Underwood’s (UK) book on *diseases of children* in 1784 was probably the best early published treatise on pediatric diseases. It had 17 editions and provided first descriptions of poliomyelitis and sclerema. Neonatal tetanus was first described by Joseph Clarke (Ireland) 1789. In the same year Edward Jenner published his report of 23 years of vaccination to prevent variola (smallpox).

By late 1700s and early 1800s, the need to attend specifically to the care, development, and diseases of children became more apparent and specialization in pediatrics evolved, particularly in Germany and France. *The Society for Infant Therapeutics* was formed in Germany in 1883. The British Pediatric Association was established in 1928 with George Frederic Still as the first president. The Royal College of Paediatrics and Child Health status was granted to British Paediatric Association in 1996. Its official journal “*Archives of Diseases in Childhood*” started its publication in 1926.

The first generally accepted pediatric hospital in Europe, the *Hôpital des Enfants Malades* (Hospital for Sick Children), opened in Paris in June 1802. The famous Great Ormond Street Children’s Hospital of London was established by Charles West in 1848 followed by Hospital for Children at Edinburgh in 1856.

### Pediatrics in the USA

The Father of American Pediatrics is considered to be Abraham Jacobi (1830–1919), a German pediatrician, who arrived in New York in 1853 and established the pediatrics chair at the New York Medical College in 1861. He is credited with the organization of the first pediatric society, publication of pediatric journal and development of pediatric departments in New York hospitals. He was a prolific writer and taught extensively about the feeding and hygiene of children. He, in association with pioneers such as Luther Emmett Holt in New York, J Forsyth Meigs in Philadelphia, and William McKim Marriott in St. Louis rapidly expanded the specialty through their writings and teachings. The first independent pediatrics hospital was founded in Philadelphia in 1855 followed by Boston (Massachusetts) in 1869. The American Academy of Pediatrics was established in 1930 and the American Board of Pediatrics in 1933.

Luther E Holt Sr., who succeeded Jacobi, wrote the book, “*The Care and Feeding of Children*” in 1894, which was later developed into the “*Holt’s Pediatrics*”. J P Crozier published “*The Diseases of Infants and Children*”, which in turn became Griffith and Mitchell’s “*Pediatrics*”, then Mitchell and Nelson’s “*Pediatrics*”; Waldo E. Nelson’s “*Pediatrics*” in 1954, and in 1984 “*Nelson’s Pediatrics*”, edited by Richard Behrman. It has been the world’s most trusted pediatrics resource for over 80 years. Pediatrics specialties have developed in diagnosis and management with approach of intrauterine diagnosis and treatment, identifying genetic disorders and study of genomics. The advances continue to provide the medical community with new diagnostic tools and therapies. Today in addition to general pediatrics, pediatricians can choose to specialize in a number of fields, including:

- Adolescent medicine
- Child abuse



**Table 1** History of major events related to pediatrics

<i>Year</i>	<i>Pioneer</i>	<i>Event</i>
1789	Edward Jenner, England	Cowpox vaccination for smallpox, first vaccine for any disease
1789	Benjamin Rush, USA	Description of cholera infantum, summer diarrhea
1818	James Blundell, England	First successful human blood transfusion for postpartum hemorrhage
1857	Louis Pasteur, France	Identification of microbes as a cause of disease
1865	Gregor Mendel, Austria	Principles of heredity
1882	Robert Koch, Germany	Discovery of the tubercular bacillus; Koch's postulates
1885	Louis Pasteur, France	Rabies vaccine; pasteurization of milk
1890	Emil von Behring, Germany	Discovery of diphtheria toxin and antitoxins
1895	Wilhelm C Roentgen, Germany	Discovery of radiograph (X-ray)
1900	Karl Landsteiner, Austria	Discovery of blood groups
1908	Archibald Garrod, England	Inborn errors of metabolism
1910	James Herrick, USA	Sickle cell anemia
1913	Bela Schick, USA	Schick test for immunity to diphtheria
1921	Edward Mellanby, England	Vitamin D deficiency causes rickets
1921	Thomas B Cooley, USA	Thalassemia major
1922	Frederick G Banting and Charles H Best, Canada	Discovery of insulin to treat diabetes mellitus
1923	Alexander Thomas Glenny, England and Gaston Ramon, France	Diphtheria toxoid for active immunization
1926	Louis W Sauer, USA	Vaccine against whooping cough (pertussis)
1927	Albert Calmette and Camille Guérin, France	Vaccine against tuberculosis
1928	Alexander Fleming, England	Discovery of penicillin
1931	Alvin C Coburn, USA	Hemolytic streptococcal infection and rheumatic fever
1943	Selman A Waksman, USA	Discovery of streptomycin
1948	United Nations	The formation of WHO
1952	Virginia Apgar, USA	Development of the Apgar score
1952	James Watson and Francis Crick, England	Double-helix structure of DNA
1954	Jonas Salk, USA	Inactivated polio vaccine
1956	La Leche League, USA	Promotion of breastfeeding
1957	Albert Sabin, Poland/USA	Oral polio vaccine
1959	The United Nations	Declaration of the rights of child
1959	Mary Ellen Avery and John Mead, USA	Surfactant
1963	Robert Guthrie, USA	Screening test for phenylketonuria—newborn screening
1964	John Enders, USA	Vaccine against measles
1965	Louis Gluck, USA	First newborn intensive care unit
1966	Dilip Mahalanabis, India	Development of modified ORS in Kolkata
1967	Maurice Hilleman, USA	Vaccine against mumps
1970	Maurice Hilleman, USA	Vaccine against rubella
1974	Michiaki Takahashi, Japan	Vaccine against chickenpox (varicella)
1977	Robert Austrian, USA	Vaccine against pneumococcal pneumonia
1977	WHO	Eradication of smallpox from the world
1978	Robert Edwards and Patrick Steptoe, UK	First test tube baby—Louise Joy Brown
1981	Baruch Blumberg and Irving Millman, USA	Vaccine against hepatitis B
1981	Robert Gallo, USA	HIV (AIDS) virus identified
1986	Alec Jeffreys, England	DNA typing or genetic fingerprinting
1992	Maurice Hilleman, USA	Vaccine against hepatitis A
2000	Francis S Collins and J Craig Venter, USA	Mapping of human genome

- Developmental and behavioral pediatrics
- Neonatology
- Pediatric allergy and immunology
- Pediatric cardiology
- Pediatric critical care
- Pediatric dermatology
- Pediatric emergency medicine
- Pediatric endocrinology
- Pediatric gastroenterology-hepatology
- Pediatric hematology
- Pediatric infectious diseases
- Pediatric nephrology
- Pediatric neurology
- Pediatric oncology
- Pediatric ophthalmology
- Pediatric pulmonology
- Pediatric psychiatry
- Pediatric rheumatology

Other pediatric specialists especially those in pediatric surgery, pediatric urology or pediatric radiodiagnosis are not necessarily pediatricians; however they undergo training in their own fields, and then receive additional specialty pediatric training.

## HISTORY OF PEDIATRICS IN INDIA

Pediatrics made a formal beginning in Mumbai (erstwhile Bombay) in 1928, under the leadership of George Coelho, called the Father of Pediatrics in India. He was the head of the department of pediatrics at the Bai Jerbai Wadia Hospital for Children, the first independent children's hospital in India. In 1929, Dr Coelho started the *Association of Pediatrics of India* in Bombay in 1950. Pediatric departments soon came into existence at other centers, Nair Hospital, Mumbai (Shantilal Sheth), Patna (LSN Prasad), Delhi (Pran N Taneja) and Indore (JN Pohowalla).

In 1933, Dr K C Chaudhry founded the first independent pediatric journal namely, the "*Indian Journal of Pediatrics*"; in Kolkata (Calcutta). In 1948 he started the *Indian Pediatric Society*. By 1958, the Indian Pediatric Society organized nine national pediatric conferences in different cities and in 1961 the first Asian Pediatric Conference was held at New Delhi. His efforts to make pediatrics an independent subject are worth mentioning.

The state of Tamil Nadu has the honor and pride of having created the first chair of professor of pediatrics in India at the Madras Medical College (Chennai) in 1948 with the appointment of Professor ST Achar.

The Indian Pediatric Society and the Association of Pediatricians of India combined to form the *Indian Academy of Pediatrics (IAP)* as the single representative body of pediatricians of India and the first national conference of the IAP was held in Pune in 1964. The official journal of the IAP "*Indian Pediatrics*", incorporated the "*Indian Journal of Child Health*" and the "*Journal of the Indian Pediatric Society*" and commenced publication in January 1964 from Kolkata.

The academy has promoted different specialties in the field of pediatrics through its various chapters. One of the major activities undertaken by the IAP since its inception is to organize continuing medical education programs all over the country. IAP has its office in Mumbai while Delhi is the seat of its official publication, "*Indian Pediatrics*".

## Pediatric Education in India

Nagpur (University of Bombay) was the first to start pediatrics examination in MBBS. Medical Council of India decided in 1997 that pediatrics will be a separate subject for examination of undergraduate (MBBS) training. The first postgraduate course for

diploma in child health was started at Bai Jerbai Wadia Hospital for Children in 1944 under University of Bombay (Mumbai) in 1946. First MD pediatrics course was also started at Nagpur.

Doctorate of Medicine (DM) courses were started late with gastroenterology in Postgraduate Institute of Medical Education and Research (PGIMER) at Chandigarh in 1989, followed Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow in 2009. DM in neonatology also began at PGIMER, Chandigarh in 1989. Subsequently DM neonatology courses have begun in other centres including All-India Institute of Medical Sciences (AIIMS), New Delhi. In 1991 SGPGIMS, Lucknow started DM in clinical genetics and reserved one seat each for pediatric postgraduates for DM courses in neurology, cardiology, gastroenterology and immunology. AIIMS, New Delhi now offers DM courses in pediatric neurology (2009), nephrology (2013) and pulmonology (2013). PGIMER, Chandigarh offers DM courses in pediatric critical care, pediatric hemato-oncology, child and adolescent psychiatry, and pediatric rheumatology (2013). The first MCh course in pediatric surgery was started at AIIMS, New Delhi in 1972.

## Major Achievements in Child Health and Care in India

By 1938, when American Academy of Pediatrics celebrated its 50th anniversary, US achievements related to child care were demonstrated by the following indices—life expectancy of more than 60 years, infant mortality rate (IMR) of 55/1000, and neonatal mortality rate (NMR) of 30/1000. It is heartening to note that the 50th year (2013) of IAP was celebrated with a life expectancy for men 62.4 and women 64.2 years; IMR of 50/1000 (in the year 2009) and NMR of 31/1000 (in the year 2011). In January 2014, WHO declared India *polio free* as the last case of paralytic polio was seen on 13th January 2011 in Kolkata.

Launched on 2nd October 1975, Integrated Child Development Scheme (ICDS) today represents one of the world's largest and most unique programs for early childhood development. ICDS is the foremost symbol of India's commitment to her children, India's response to the challenge of providing preschool education on one hand and breaking the vicious cycle of malnutrition, morbidity, reduced learning capacity and mortality, on the other.

## MORE ON THIS TOPIC

- Abt AF. Abt-Garrison History of Pediatrics. Philadelphia: WB Saunders; 1965.
- Bansal CP, Gupta S. The past half century of Indian Academy of Pediatrics (IAP). *Indian Pediatr*. 2013;50(1):39-48.
- Chaudhuri KC. Medical education with particular reference to pediatric teaching in Indian universities. *Indian J Pediatr*. 1958;25(123):288-94.
- Colón AR, Colón PA. *Nurturing Children: A History of Pediatrics*. Westport, Conn: Greenwood Press; 1999.
- Holmes B, Kitterman PG. *Medicine in ancient Egypt*. Cincinnati, OH: Lancet-Clinic Press; 1914.
- Medical Council of India. Salient features of regulations on graduate medical education. 1997. From: [www.mciindia.org/RulesandRegulations/GraduateMedicalEducationRegulations1997.aspx](http://www.mciindia.org/RulesandRegulations/GraduateMedicalEducationRegulations1997.aspx). Accessed August 22, 2014.
- Pearson HA, Anunziato D, Baker JP, et al. Committee report: American Pediatrics: milestones at the millennium. *Pediatrics*. 2001;107(6):1482-91.
- Pearson HA. The history of pediatrics in the United States. In: McMillan JA, DeAngelis CD, Feigin RD, Warshaw JB. *Oski's Pediatrics*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. pp. 2-7.
- Phaer T. *The Boke of Chyldren*. Edinburgh & London: E & S Livingstone; 1955.
- Radbill SX. *Pediatrics*. In: Debus AG, (Ed). *Medicine in 7th Century England*. Berkley: University of California Press; 1974. pp. 237-40.
- Shulman ST. The history of Pediatric Infectious Diseases. *Pediatr Res*. 2004;55(1): 163-76.
- Still GF. *The History of Paediatrics*. London: Oxford University Press; 1931.

## Chapter 1.2

# 20 Milestones in the History of Pediatrics

Santosh K Bhargava

In the history of world medicine there have been numerous remarkable milestones which have changed the course of disease. The present chapter describes milestones which are especially relevant or exclusive to pediatrics from ancient times to contemporary period and their current relevance in our time.

## EMERGENCE OF THE FIELD OF PEDIATRICS

The first description of pediatrics in our ancient scriptures is in the "*Sushruta Samhita*" in 800–1000 BC. Later descriptions of the medical care of children appear in 2nd century AD by Soraneus in Greece; and in the string of Rhazes in Persia in 865–925 AD. The first printed published book on diseases of children by Bagellardus (please see Chapter 1) entitled "*Little book on Diseases of Children*" appeared in 1472. The first children's hospital *Hôpital des Enfants Malades* (French = Hospital for Sick Children), was established in Paris in 1802. Dr Abraham Jacobi's sustained publications in New York Medical Journal helped further establish the field of pediatrics. As pediatrics extended its scope in clinical practice, it was recognized as an independent discipline in last century.

## SURVIVAL OF THE CHILD

It is believed that child survival has been the prime concern of the society. In ancient times surprisingly many societies and cultures aimed to destroy rather than save majority of newborns for varied reasons for being girls or for sacrificial and economic reasons. It is ironical that attention to child survival occurred through the needs of French armies to compensate for losses of fighting men rather than as a social measure. In 18th century half the human race died in infancy and this varied from 100 to 250 per 1000 births through late 19th century. As the appalling situation on infant mortality dawned on leaders, health and welfare measures were introduced. It continued to decline in some countries to single digit, but it remains a challenge to many countries including India where several intervention programs, such as Integrated Management of Neonatal and Childhood Illness, were introduced but the results were not as expected. Globally under five, infant and neonatal mortality rates are an important parameter of human development index and hence child survival is now universally a national child health priority in the world.

## THE ORIGIN OF DISEASE: THE GERM THEORY

The germ theory was proposed in the 16th century but it was only from the 17th century onwards that it began to be accepted. In brief, it states that some diseases are caused by microorganisms which are too small to be visible to naked eye. It remained unproven until Robert Koch in 1877 identified tubercle bacilli as the causative organism for tuberculosis. Thereafter, Louis Pasteur, in 1882 propounded the *germ theory of disease* by demonstrating that specific bacteria cause specific diseases such as anthrax. Classically, he discovered the pathology of the puerperal fever and the pyogenic vibrio in the blood, and suggested using boric acid to kill these microorganisms before and after confinement. In modern times we use this knowledge acquired through centuries of research and observations to successfully treat and prevent numerous infectious diseases of childhood.

## THE DEVELOPMENT OF VACCINES

One of the most famous milestones in the history of medicine is the inoculation of children and adults with dried scab material recovered from smallpox patients by variolation technique in 17th and 18th centuries. It was Edward Jenner in 1796 who first vaccinated with smallpox vaccine. Initially the development of vaccines was slow. But in last several decades new scientific discoveries and technologies led to rapid advances in virology, molecular biology, and vaccinology. Currently, vaccination is available against numerous infectious diseases which led to their sharp decline. Through vaccination, scientists and physicians were not only able to offer protection but eradicated diseases like smallpox globally and poliomyelitis in many countries, including India.

## THE DEVELOPMENT OF ANTIMICROBIAL THERAPY

In the 18th century, physicians used carminatives and blue pigments for treating infections and disease. The German physician Domas successfully used a synthetic red dye prontosil for surgically acquired streptococcal infection. Later in 1932, he discovered sulfonamides which saved many lives from acute infections including rheumatic fever. The miracle drug *penicillin* was discovered by Alexander Fleming in 1928 but was not fully used for treatment until 1940s when Florey and Chain produced it commercially. Since then, scientists across the world have discovered numerous antibiotics, antifungal, antiviral, and antiparasitic drugs. Antibacterial group of drugs such as penicillin, tetracycline, aminoglycosides, cephalosporin, macrolides, and antitubercular drugs have dramatically reduced morbidity and mortality. On the other hand, bacteria and microbes continue to develop drug resistance which is now presenting a major challenge to researchers and clinicians.

## THE DEVELOPMENT OF PEDIATRICS FOR PRIMARY AND SPECIALTY CARE

In ancient times children died or suffered largely because of diseases caused by environment, sanitation, hunger or unrecognized causes. In the 17th to 19th century infections such as diarrhea, typhoid, tuberculosis and pneumonia caused many deaths. These diseases are still prevalent in the 21st century. The patterns of diseases changed from infectious to noninfectious diseases, and diseases not amenable to antimicrobial therapy. Over time, increasingly morbidity and mortality was observed from multifactorial systemic diseases related to system dysfunction and grouped as cardiovascular, respiratory, neurological, and gastrointestinal diseases. Pediatrics which initially developed as primary care medicine has now many specialty and super specialties under its umbrella. This has led to unprecedented advances in the care of children with heart disease, lung disease, childhood cancer, prematurity, etc.

## THE DEVELOPMENT OF NEONATOLOGY

In the later half of 20th century, the newborn infant was increasingly recognized as a distinct challenge needing special attention and special newborn care units were developed. Gradually, the newborn care developed into the triage system of primary, secondary, tertiary and regionalization care. In 1952, Virginia Apgar developed the *Apgar score* helping in identification of severity of birth asphyxia. Newborn care made rapid progress with double volume exchange transfusion for hemolytic disease, treatment of patent ductus arteriosus, advent of phototherapy, care of low birthweight and preterms, and recognition of oxygen toxicity. Fetal growth curves were published by Lubchenco from USA in 1967 and by Ghosh and Bhargava in 1969 from India.

These classified newborns as being small, appropriate, or large for gestational age. Surfactant deficiency was recognized as a cause of hyaline membrane disease and treated with surfactant replacement therapy. Respiratory failure outcome improved with availability of blood gas analysis, assisted pulmonary ventilation and ventilator support. The focus currently is on noninvasive ventilation for minimizing lung injury. Finding that room air is as good as enriched oxygen air for resuscitation of newborn, was another remarkable research application.

The developed world continued to make rapid progress with advanced technology but these remained beyond the reach of most in many parts of world including India and resulted in slow decline in neonatal mortality. It was the development of *Essential Newborn Care (ENC)* program conceptualized in 1994 by Bhargava and colleagues and pioneered by the Government of India and National Neonatology Forum India which made the real breakthrough in newborn care for this part of the world. ENC is now a cornerstone for delivery of newborn care in India and several developing countries. The rapid advances in newborn care resulted in dramatic improvement in survival of newborns including the very premature and low birthweight infants.

### EXCLUSIVE BREASTFEEDING

The fact that breastmilk is best for an infant is known from antiquity. The practice to breastfeed all newborns declined in 20th and 21st century in many countries. The emergence of social groups such as *La Leche League*, established in 1956, vigorously promoted and advocated breastfeeding and fought the battles of feeding bottles. In 1960s, commercial baby formula was marketed and competed with breastmilk. The publicity, convenience, social culture and beliefs severely affected breastfeeding practices. This prompted professionals, government and non-government agencies to act. Their efforts resulted in World Health Organization (WHO) and United Nations Children's Fund (UNICEF) bringing in the *International Code of Marketing of Breastmilk Substitutes* in 1981. This was adopted with modifications by many countries including India. The current recommendation is for *exclusive breastfeeding for the first 6 months* of life. It has shown immediate and long-term advantages in prevention of infections, adult diseases, and food allergy.

### THE WELL BABY CLINICS, ROAD TO HEALTH CARD, AND UNDER-5 CLINICS

The concept that mother and child should be seen as a pair was responsible for special infant clinics known as *Well Baby Clinics*. In 1892, Pierre Robin encouraged mothers to bring their healthy infants for weighing, which spread rapidly in Europe. In US the clinics focused on clean milk to prevent infections. In 1974 David Morley introduced the *Road to Health Card* to monitor the growth of infants and children serial weighing. This identified faltering growth in children at the earliest. These were further modified to suit *under-5 clinics*. Today, under-5 clinics and well baby clinics are norms offering inclusive preventive advice on infant care, feeding, immunization, growth, and development.

### GROWTH MONITORING

Weighing the child to monitor his/her well-being began to be practiced in late 19th century. Serial measurement at different ages led to the construction of Harvard growth curves, USA and Tanner's growth curves, UK which became standard reference for children. These were followed by the National Center for Health Statistics (NCHS) growth curves developed for US children. Subsequently these were adapted for international use by Centers for Disease

Control (CDC) and WHO. In 2007, WHO released its own growth curves for 0–5 year olds after a multicountry study in which six countries, including India, participated.

An interesting analysis by the Cohort group of pooled data of similar cohorts from five countries Institute of Nutrition of Central America and Panama (Guatemala); Cebu (Philippines); Pelotas (Brazil); B2 Twenty (South Africa); and The New Delhi Birth Cohort (India) showed adverse effect of maternal and child undernutrition on adult diseases, human capital development including income, education and height and birthweight of the next offspring. They also showed that accelerated growth in first 2 years benefits adult life but rapid weight gain after 2 years of age leads to increased fat mass, adiposity and overweight. Growth monitoring is thus a simple effective tool to assess child's nutrition and well-being.

### EVOLUTION OF DEVELOPMENTAL PEDIATRICS

Child development studies began in late 19th century. Several standard developmental scales are now available for assessment of development, behavior, and intelligence from newborn to adolescence periods. These tools have been modified or adapted by individual countries for their use because development is highly culture depended. In India, adaptations have been worked out at Baroda and Trivandrum.

The sharp increase in survival of low birthweight, extremely premature infants has necessitated prompt recognition of developmental and other deficits. Friedman coined the term *Behavioral Pediatrics* and defined it as "*an area within pediatrics which focuses in psychological, social and learning problem of children and adolescence*". This has now developed into the science of developmental pediatrics and behavioral sciences. The focus here is on multi-disciplinary team approach with pediatrician, developmental pediatrician, therapists, speech therapist and others. Specialists in this area investigate and manage communication delays, autism, attention deficit disorders, and other learning disabilities that require early diagnosis and intervention.

### ORAL REHYDRATION SALT (ORS) SOLUTION

Oral rehydration salt solution is one of the most acclaimed advances in modern science for treatment of dehydration and diarrhea. The use of oral solutions for fluid loss is described from ancient times. Bengali and US research scientists in 1960s discovered a simple electrolyte solution which was formulated to treat cholera epidemic patients in Bangladesh at the International Centre for Diarrhoeal Disease Research, Bangladesh. The development occurred as a dire need as logistically it was impossible to provide intravenous fluid therapy in villages. Cash and David Nalin first and later Mahalanabis and colleagues demonstrated its successful use by scientific studies on large scale. The WHO recommends a standard formulation, which is now universally used and can be modified for different uses. This *simple solution* has resolved a monumental problem and saved millions of lives till date.

### SOCIAL IMPLICATIONS OF CHILD HEALTH

Despite all campaigns and awareness the plight of child in social milieu continues. He/she is neglected and exploited in every possible way in health, education; nutrition, violence, sexual abuse and as child labor. Jacobi in 19th century said that "*it is not enough for physicians to work by the bedside in a hospital but it is equally important for him to influence hospital boards, health department legislator, judge and the seat of council*". Pediatricians and socially conscious people have to be proactive to protect and plead for the child. It is the sustained social activism which got results.



*Battered child syndrome* description by Kempke in 1962 made it a medicolegal and social issue. Sustained focus on abortions, killing of the girl child, child marriage, child abuse, violence and labor all led to enactments of laws benefiting children.

## THE RIGHTS OF CHILD

The continuous assault on children's physical, mental, and emotional health, exploitation, employment in hazardous professions, absent or limited rights as human being has been building a guilty conscience in society. It took almost 6 decades for government and non-government organizations to convene UN convention on *Rights of the Child*. It was passed as an international declaration in 1990. The Rights of the Child Declaration confers rights for a life with dignity, protection from exploitation, and rights to education, love, play, be the first to get help, and have a name and family. In 1991, India and several countries ratified this declaration.

## GENETICS IN PEDIATRICS

Genetics emerged as a specialty about half a century ago. Many pediatrics departments took lead in this field because of the recognition of genetic disorders, syndromes and malformations in children. Today genetics has developed into a specialized subject and has expanded to prenatal screening of diseases, cytogenetic, molecular genetics and in diagnosis of several disorders including asthma, growth failure, hypertension, and diabetes mellitus type 2. The gene therapy is beginning to be used for some diseases and has enormous potential.

## GENOMICS, PROTEOMICS AND METABOLOMICS

The development of *genomics* was the natural progression of research in genetics. From single gene identification it progressed to the formation of *Human Genome Project* and finally to mapping of the *human genome* in 2003. Genome sequence data now provides an opportunity for clinical application of genetic information. Its application to pediatrics is similar to genetics and for population studies. The term *proteomics* coined in 1994, seeks to investigate protein functions as it relates to its environment and biological setting. It was believed that identification of specific proteins will lead to development of new drugs and biomarkers. These are studied in body fluids, cells and tissues and have vast potential in research and clinical application in oncology, cardiology, neonatology, vaccine research and others. *Metabolomics* derives its name from *metabolome* a term described for a collection of metabolites in body fluids, tissues, organs and biological cells. The application includes analysis of body biological fluid through noninvasive or minimal invasive procedures in the fields of nutrition, prenatal disease, and neonatology. It is likely to help detection of diseases, classify patients based on biochemical profiles, and monitor disease progress.

## BIOINFORMATICS IN PEDIATRICS

Development in *bioinformatics* is transforming medical research by playing a critical role in understanding the molecular basis of diseases, identifying markers for disease predisposition, diagnosis

and prognosis of disease, and developing better vaccines and therapeutics. Considering critical role in rapid diagnosis, better therapeutic and efficient vaccines, bioinformatics is going to play a major role in reducing neonatal and child morbidity and mortality.

## FETAL MEDICINE AND SURGERY

Fetal medicine is one of the recent rapidly emerging specialties. It intends to save fetal life and help reach a normal outcome. The fetal well-being needs careful assessment by obtaining maternal and pregnancy history, and conducting physical examination. Currently the most important assessment is by ultrasonography for fetal growth; malformations, placental blood flow, etc. Laboratory tests and amniocentesis are performed for high risk pregnancies. Fetal surgery is possible either by minimal or major surgical intervention. Minimal surgery is by fetoscopy used for fetal transfusion, bladder neck obstruction and certain congenital heart ailments. The major fetal surgery is now available for neural tube defect and diaphragmatic hernia, through a cesarean section.

## DEVELOPMENTAL ORIGIN OF ADULT DISEASE: BARKER'S HYPOTHESIS

It was the Barker's hypothesis of *fetal origins of adult disease* that caused interest in the fetomaternal metabolism, nutrition, environment, and fetal growth. His studies and others who confirmed later showed that size at birth is related to the risk of developing disease in later life. Significant relationship was found between reduced birthweight and increased risk of coronary heart disease, diabetes, hypertension and stroke in adulthood. Most believers in his hypothesis believe that these relationships are those of fetal programming by nutritional stimuli or excess fetal glucocorticoid exposure. The New Delhi Birth Cohort has also confirmed the findings and observations made by David Barker. It has concluded that it is possible to track these diseases with serial body growth measurement from early childhood to adulthood.

## ETHICS IN PEDIATRICS

Ethics in pediatric practice is being viewed with an increasing interest since pediatrician is the custodian of the child who may not be able to express verbally. The pediatrician has to put the interest of the child as foremost. Pediatrician should follow general code of ethics in patient care, surgical intervention, investigations or research. The general principles include respecting individual autonomy, competence, beneficence with the honest truth, assure and maintain confidentiality and avoidance of personal bias. One should be extremely cautious about conflict of interest and be frank to admit that all medical care has limitation. It is always helpful to obtain written consent of parents or wherever applicable from the child.

## MORE ON THIS TOPIC

Chowdhury AMR, Cash RA. Third Impression: A Simple Solution. Dhaka, Bangladesh: The University Press Limited; 1996.

Consortium of health oriented research in transitioning societies (COHORTS). From [www.cohortsgroup.org](http://www.cohortsgroup.org). Accessed August 25, 2014.

## Chapter 1.3

# Status of Child Health

RN Srivastava

Every child is born with a development potential that is determined by genetic and environmental factors. It is the duty and responsibility of everyone (parents, community, civil society and the governments) to ensure that he/she achieves that. Whereas pediatricians are chiefly involved with care of the sick child and health related issues, they must also be cognizant of various other factors that affect child health and development and make efforts to tackle adverse elements.

Globally, the child has been defined as one below the age of 18 years. That characterization widens the scope of child health. Traditionally, pediatricians have been mostly concerned with problems of the younger child and the neonate. Various issues during the adolescent period and the transition to adulthood also need to be addressed by pediatricians.

## GLOBAL PERSPECTIVES OF CHILD HEALTH

The WHO defines health as “*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*”. However, most low- and middle-income countries would be satisfied with *abolition or at least control of common diseases and provision of adequate nutrition*. Early development, education, care and protection are crucial for children. Various aspects of child health are vastly different between affluent countries and economically poor countries, which account for the majority of the world’s population. Understandably, there is a small proportion of underprivileged children in rich countries as well, and affluent population in the developing nations. Availability of proper health care, economic status and education greatly impact child health and development. It is estimated that 75 countries having low- and middle-income account for more than 95% of maternal and child deaths (UNICEF, 2010). A lack of financial protection for the costs of health care and failure to avail of the facilities wherever available are chiefly responsible for these and need to be identified and appropriately addressed by different countries (Lancet, 2013).

## Child Health in Affluent Nations

The economically developed, educated countries have almost eliminated common infections and preventable diseases and nutritional deficiency. Improved sanitation and hygiene, provision of safe water, universal application of immunizations, and availability of health care have resulted in a vastly improved health status of the child population. However, various socioeconomic factors have led to emergence of fresh challenges. Besides, there is a risk of importing diseases, such as malaria, dengue fever and viral infections, from travelers from other countries.

Several problems are particularly important in rich countries, but are of increasing concern in low- and middle-income countries. The latter are facing the double burden of infections and communicable diseases as well as noncommunicable diseases and lifestyle related disorders.

## Obesity and Metabolic Syndrome

Obesity has assumed epidemic proportions in affluent countries. The number of overweight children in the USA has reportedly doubled in children and quadrupled in adolescents over the past 30 years. In 2012 more than one-third of children and adolescents

were obese. Obesity is also a problem in developing countries in Africa, China and India. About 5% of school children are reportedly obese. Severe obesity is associated with the metabolic syndrome, type 2 diabetes mellitus and nonalcoholic fatty liver disease. Obesity also leads to hypertension and renal disease and joint problems. Sedentary habits, and excessive consumption of food containing carbohydrate, fats and salt have become the norm and very difficult to modify. Childhood obesity is an important contributor to adult obesity and diabetes.

## Substance Abuse and Sexually Transmitted Diseases

There is a high incidence of substance abuse in adolescents, which is reflective of the family and societal mores. There is a high rate of mortality from drug abuse related automobile accidents and overdosage. The USA has some of the highest rates of sexually transmitted diseases (STDs) in the industrialized nations. In a study by Center for Disease Control, one in four girls between the ages of 14 and 19 was found to have at least one STD caused by human papillomavirus, chlamydia, herpes simplex virus, or trichomonas. Substance abuse (alcohol, tobacco, cannabis, opiates, glue sniffing) is common in children in India and appears to be increasing, especially in street children and adolescents.

## Child Health Status in Developing Countries

Child health in developing countries is greatly influenced by poverty, illiteracy, misinformation and traditional adverse beliefs. A lack of availability of safe water, poor sanitation and hygiene, environmental pollution and overcrowded living conditions play important roles in the prevalence of diseases and disability. Large family size, denial of proper health care and education adversely affect child development. Among the small, affluent proportion of the population, lifestyle diseases and other problems seen in developed countries are also being increasingly encountered in economically poor countries. There are large differences in child health status in urban and rural communities, the latter comprising 70% of more of the population. Modern medical care facilities are mostly confined to big and small cities. Various health parameters, such as maternal and infant mortality rate (IMR), under-5 mortality in regions within a country, where literacy rates are high and health care provided, are closer to those seen in affluent countries. Thus national statistical information or even regional data within a country need to be carefully evaluated and stratified according to demographic and socioeconomic profile.

## Maternal and Perinatal Care and Infant Mortality

Maternal undernutrition and small stature are closely related to low birthweight babies. The mortality rates are high in such babies since expert perinatal management is often not available.

## Infant Mortality

Infant mortality rate (IMR) is regarded as an indicator of the level of health in a country. There has been a consistent decline in IMR in India from around 80 per 1,000 livebirths in 1981 to 40 in 2014; the current IMR remains high as compared to developed countries. The national figure is high chiefly due to poor performance in large northern states (>50 in MP, Odisha, UP). More than two-thirds of infant deaths occur before 1 month of age, in the neonatal period. The decline in IMR is sharper in urban areas and is influenced by maternal factors such as nutrition, anemia, age below 18 years, birth spacing, level of education and overall socioeconomic conditions. There has been a small or no decline in early neonatal mortality rate, an indicator of the quality of perinatal care, which remains at 30. **Table 1** shows the IMR in certain developed countries and those with low- or middle-income population.



**Table 1** Infant mortality rates (IMR; per 1,000 livebirths per year) in some developed and developing countries in 2014

Afghanistan	70	Nepal	32
Australia	3	Pakistan	69
Bangladesh	33	Sierra Leone	117
Bhutan	30	Singapore	2
Brazil	12	Sri Lanka	8
China	11	Sweden	2
Congo	100	United Kingdom	4
India	40	United States of America	6
Mali	78	Zambia	56

Source: State of the World Children, UNICEF 2015.

### Immunizations

In most countries, vaccinations against common diseases are freely available. However, adequate *routine* vaccination coverage varies widely. Ignorance, suspicions and misinformation of the benefits of protection from such procedures among illiterate communities hinder universal application of vaccinations and continued morbidity and often serious complications from preventable diseases.

### Common Early Childhood Illnesses

In underprivileged communities, rural and urban, common illnesses, such as diarrhea, upper respiratory infections, skin infections, are often accepted as parts of *growing up* and proper medical attention is not provided. Such recurrent episodes adversely impact nutrition and growth.

### Undernutrition

Information about the importance of breastfeeding and oral rehydration management of diarrhea is widely known, and the incidence of severe forms of undernutrition has markedly decreased. However, milder forms remain very common. Although the prevalence of stunting of linear growth of children younger than 5 years has decreased during the past two decades, it is high in South Asia and Sub-Saharan Africa. Globally, it affected at least 165 million children in 2011 whereas wasting affected at least 52 million. Specific nutrient deficiency of iron, iodine, vitamin A and D are frequent and together with stunting adversely affect attainment of full developmental potential. It is estimated that various morbidities of undernutrition combined with suboptimal breastfeeding may cause 3.1 million deaths annually (45% of all child deaths in 2011).

### Common Diseases, Still Widely Prevalent

A large number of diseases can be controlled with provision of safe water, application of basic hygienic and sanitation measures, vector control and immunizations. Unfortunately, these facilities are inadequate in developing countries resulting in a very high morbidity that adversely impacts child health.

### Diarrheal Diseases and Other Waterborne Infections

Lack of safe water is responsible for a heavy burden of diarrhea (cholera in several countries), dysentery, typhoid and hepatitis A. Ensuring safe water and proper sanitation is very difficult in overcrowded urban localities. Increasing migration to cities and huge construction activities put heavy demands on water. In rural areas access to water is often difficult. The costs and technological

limitations in providing safe water present formidable challenges. However, information and functional education about the dangers from *unsafe* drinking water and poor sanitation and harmful traditional practices can be provided to the underprivileged population, which would lead to changes in behavior and habits and thus help toward control of several common diseases. Infant and under-5 mortality rates are lower in communities with access to safe water and improved toilets.

### Tuberculosis

Tuberculosis continues to remain a very difficult public health problem in India and many developing countries. Overcrowded living conditions, delay in diagnosis, inadequate treatment (despite provision of medications free of cost) and multidrug resistance contribute to the high prevalence and considerable mortality from tuberculosis (2 million every year, mostly in developing countries). In India 3–4 million children have tuberculosis and about 94 million are at risk of developing the disease. The annual infection rate is between 3% and 5%, which may be higher because of lack of early diagnosis.

### Malaria

Malaria is an important cause of illness and death in many parts of the world, especially Sub-Saharan Africa. About 600,000 children in Africa die of malaria each year. Falciparum malaria is common in several states in India and presents a particularly challenging problem with difficulties in diagnosis and drug resistance. Mosquito control measures including the use of medicated mosquito curtains and larvicide agents have been employed. Global efforts are being made to develop an effective malaria vaccine.

### HIV Infection, Viral Hepatitis

A lack of institution of proper preventive measures continues to be responsible for high incidence of HIV infections in many developing countries particularly in Africa. Hepatitis B is also very common as vaccinations are not widely available.

### Early Development and Education

A stimulatory environment and opportunities for preschool learning experiences are severely restricted for the majority of children in developing countries. In India, the Right to Education ensuring free of cost primary education was enacted in 2009. School enrolments have increased but the proportion of school dropouts remains very high. School infrastructure facilities are very often inadequate and educational achievements remain limited. A large proportion of poorly literate and physically underdeveloped population cannot fully contribute to national development.

### Child Abuse and Neglect, Child Labor, Natural and Man-made Disasters

Over the past three decades, global concern has been raised over the very complex problems of child abuse and neglect. Inadequate care and lack of education hinder the child health status and achievement of his/her developmental potential. The dimensions of the various issues vary greatly in rich and poor countries. Physical abuse, exploitation, child labor, child sexual abuse and trafficking are particularly common in developing countries. Millions of children in poor countries, who ought to be in schools, are working in organized or nonformal work, often in hazardous conditions. Child physical and sexual abuses are also of major concern in Northern America and Europe. Children are highly vulnerable during natural (floods, earthquakes) or man-made conflicts (wars, internal conflicts). Besides the problems of diseases and nutrition, their education and learning suffer and adversely impact their long-term development.

One hundred and eighty-nine United Nations member States have pledged to achieve by 2015 several Millennium Development Goals (MDG) that include, among others, eradication of extreme poverty and hunger, universal primary education, and reduction by half the proportion of people without sustainable access to safe drinking water. However, in many countries these goals are not likely to be met with in near future. MDG related to child health will be discussed in the subsequent Chapter.

## CONCLUSION

Health status of children is greatly influenced by multiple factors that include availability of health care, socioeconomic status, literacy and traditional beliefs, family size, sanitation and hygiene and lifestyle habits. Within a country there are variations in health parameters between rich and poor, and rural and urban. High prevalence of many diseases, which have largely been eliminated in affluent countries, contributes to ill-health and mortality

in children in middle- and low-income countries. A wider, comprehensive approach is needed to identify the problems and institute appropriate remedial measures.

## MORE ON THIS TOPIC

Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet*. 2013; 382:427-51.

Frenk J, Moon S. Governance challenges in global health. *N Engl J Med*. 2013;368:936-42.

Mills A. Health care systems in low- and middle-income countries. *N Engl J Med*. 2014;370:552-7.

Srivastava RN, Seth R, Van Niekerk J. Child abuse and neglect: challenges and opportunities. New Delhi: Jaypee Brothers; 2013.

UNICEF. The State of the World's Children in Numbers: Every Child Counts—Revealing Disparities, Advancing Children's Right. New York: UNICEF; 2014.

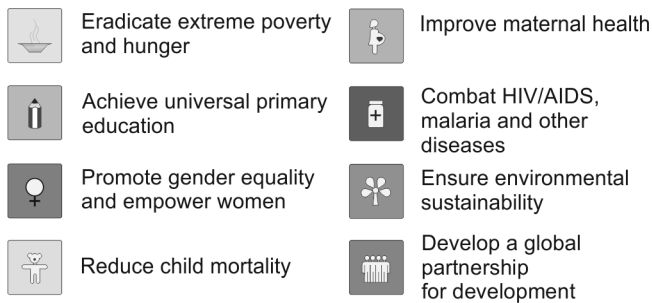
United Nations General Assembly. A world fit for children. Resolution Adopted by the General Assembly. New York: UNICEF; 2010. p. S-27/2.

## Chapter 1.4

# Millennium Development Goals for Child Health

Raju C Shah, Pratima Shah, Kunal Ahya

In the last two decades of the last millennium, many international conferences were held to discuss issues related to poverty and childhood mortality without success. In the September 2000, a largest ever summit of 147 heads and representatives of 189 countries was organized to discuss the health and development issues. Participants of this summit agreed to the need of commitment to develop third world countries. In this Summit, a declaration of eight Millennium Development Goals (MDGs) was signed by all the participants. MDGs (**Fig. 1**) are aimed to get rid of poverty and improve humanity on a global level. The targets and indicators of MDGs form the guidelines for planning policy interventions and to monitor progress in human development and poverty reduction in the third world countries.



**Figure 1** The 8 Millennium Development Goals

Millennium Development Goals are a set of 8 goals, 18 targets, and 48 indicators adopted by United Nations (**Table 1**). The indicators are categorized according to the targets, for measuring the progress toward the individual targets. The MDGs in India are based on the framework provided by United Nations Development Group in 2003. Out of the 18 targets, 12 targets (targets 1–11 and target 18) are relevant to India. There are 35 indicators which correspond to the 12 targets. Even though the goals are depicted in general terms, the targets under them are more focused and further the indicators under each target are specifically outlined to define the expected level of achievements in well-defined areas and in a given time frame.

Millennium Development Goals have helped the government to do better planning at national and subnational levels and implement more intensive policies and programs. Various development schemes and programs are formulated and implemented under the Five Year Plans (FYP) in India. The goal of the 12th FYP (2012–2017) was to achieve *faster, more inclusive and sustainable growth*, which is in tune with the MDGs. **Table 2** shows the various plans implemented in India under the 12th FYP to achieve the MDGs. Of all these goals, the MDG 4 is related to child mortality, which can give us better indicator of overall improvement in health system. Millennium Development Goals for Health for India are listed below:

- Marshaling the required resources
- Strengthening health systems and institutions
- Scaling up effective priority interventions

- Empowering women and girls
- Mitigating food insecurity and reducing hunger and malnutrition
- Ensuring good governance and effective leadership in the stewardship of resources for development and health
- Improving water and sanitation services
- Ensuring a motivated workforce.

## MILLENNIUM DEVELOPMENT GOAL 4: REDUCE CHILD MORTALITY

The global under-5 mortality (U5MR) trend between 1970 and 2013 is shown in **Table 3**. The U5MR was around 143 per 1,000 livebirths in 1970 and decreased by slightly more than two-third to 44 per 1,000 livebirths in 2013.

The U5MR rate in India (**Fig. 2**) has declined from 125 per 1,000 livebirths in 1990 to 52 in 2012. As per the trend, India will achieve U5MR of 49 by 2015, missing the target by 7%. The infant mortality rate (IMR) in India has decreased by nearly 50% from 1990 to 2012 (**Fig. 3**). In 2012, the IMR has reached 42 per 1,000 livebirths. The IMR has reached to 40 in 2014, missing the target of 27 by 2015 as per the MDG goal.

The coverage at national level of the proportion of 12–23 months children immunized with measles vaccine has increased from 42.2% in 1992 to 74.1% in 2009. According to the trend, India is likely to cover about 89% children by 2015, falling short by around 11% for the target of 100%.

## ADDRESSING ISSUES OF CHILD MORTALITY

National Policy for Children was adopted by the Government of India on 26th April 2013. Guidelines outlined in the policy must be honored by the Government at the national, state and local level. The policy mentions the undeniable rights of every child like survival, health, nutrition, education, development, protection and participation. The policy states that the state shall take necessary measures to:

- Improve maternal health care, including antenatal care, safe delivery by skilled health personnel, postnatal care and nutritional support
- Address key causes and determinants of child mortality through interventions based on continuum of care, with emphasis on nutrition, safe drinking water, sanitation and health education
- Provide universal and affordable access to services for prevention, treatment, care and management of neonatal and childhood illnesses and protect children from all waterborne, vector borne, communicable and other childhood diseases.

The health of the mother has an important impact on the health of the child. Thus measures for improvement of mother's health are important for improving the survival of the newborn. Higher resources are allocated under National Rural Health Mission (NRHM) to states and districts with weak health indicators. The major programs addressing the needs of mother and children (at child care and child survival) are discussed below, in brief.

## Institutional Delivery through Janani Suraksha Yojana and Janani Shishu Suraksha Karyakram

To ensure skilled birth attendance by promoting institutional delivery will help reduce both maternal and neonatal mortality. *Janani Suraksha Yojana* provides cash assistance and encourages pregnant women to opt for institutional delivery. In *Janani Shishu Suraksha Karyakram*, the pregnant woman gets complete zero expense delivery including cesarean section operation, as well as transport, food, drugs and diagnostics.

**Table 1** Millennium Development Goals: Targets and indicators**Goal 1: Eradicate Extreme Poverty and Hunger**

**Target 1:** Between 1990 and 2015, halve the proportion of people whose income is less than one dollar a day

**Indicator 1A:** Poverty headcount ratio (percentage of population below the national poverty line)

**Indicator 2:** Poverty gap ratio

**Indicator 3:** Share of poorest quintile in national consumption

**Target 2:** Halve, between 1990 and 2015, the proportion of people who suffer from hunger

**Indicator 4:** Prevalence of underweight children under 3 years of age

**Goal 2: Achieve Universal Primary Education**

**Target 3:** Ensure that by 2015, children everywhere, boys and girls alike, will be able to complete a full course of primary education

**Indicator 6:** Net enrolment ratio in primary education

**Indicator 7:** Proportion of pupils starting Grade 1 who reach Grade 5

**Indicator 8:** Literacy rate of 15–24 years old

**Goal 3: Promote Gender Equality and Empower Women**

**Target 4:** Eliminate gender disparity in primary and secondary education, preferably by 2005, and in all levels of education, no later than 2015

**Indicator 9:** Ratio of girls to boys in primary, secondary and tertiary education

**Indicator 10:** Ratio of literate women to men, 15–24 years old

**Indicator 11:** Share of women in wage employment in the nonagricultural sector

**Indicator 12:** Proportion of seats held by women in National Parliament

**Goal 4: Reduce Child Mortality**

**Target 5:** Reduce by two third, between 1990 and 2015, the under-5 mortality rate

**Indicator 13:** Under-5 mortality rate

**Indicator 14:** Infant mortality rate

**Indicator 15:** Proportion of 1-year-old children immunized against measles

**Goal 5: Improve Maternal Health**

**Target 6:** Reduce by three quarters, between 1990 and 2015, the maternal mortality rate

**Indicator 16:** Maternal mortality ratio

**Indicator 17:** Proportion of births attended by skilled health personnel

**Goal 6: Combat HIV/AIDS, Malaria and Other Diseases**

**Target 7:** Have halted by 2015 and begun to reverse the spread of HIV/AIDS

**Indicator 18:** HIV prevalence among pregnant women aged 15–24 years

**Indicator 19:** Condom use rate of the contraceptive prevalence rate (condom use to overall contraceptive use among currently married women, 15–49 years percent)

**Indicator 19A:** Condom use at last high-risk sex (condom use rate among nonregular sex partners 15–24 years)

**Indicator 19B:** Percentage of population aged 15–24 years with comprehensive correct knowledge of HIV/AIDS

**Target 8:** Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases

**Indicator 21:** Prevalence and death rates associated with malaria

**Indicator 22:** Proportion of population in malaria risk areas using effective malaria prevention and treatment measures (percentage of population covered under use of residuary spray in high-risk areas)

**Indicator 23:** Prevalence and death rates associated with tuberculosis

**Indicator 24:** Proportion of tuberculosis cases detected and cured under DOTS

**Goal 7: Ensure Environmental Sustainability**

**Target 9:** Integrate the principles of sustainable development into country policies and programs and reverse the loss of environmental resources

**Indicator 25:** Proportion of land area covered by forest

**Indicator 26:** Ratio of area protected (to maintain biological diversity) to surface area

**Indicator 27:** Energy use per unit of GDP (rupee)

**Indicator 28:** Carbon dioxide emissions per capita and consumption of ozone-depleting chlorofluorocarbons (ODP tons)

**Indicator 29:** Proportion of the households using solid fuels

**Target 10:** Halve, by 2015, the proportion of people without sustainable access to safe drinking water and basic sanitation

**Indicator 30:** Proportion of population with sustainable access to an improved water source, urban and rural

**Indicator 31:** Proportion of population with access to improved sanitation, urban and rural

**Target 11:** By 2020, to have achieved a significant improvement in the lives of at least 100 million slum dwellers

**Indicator 32:** Slum population as percentage of urban population

**Goal 8: Develop a Global Partnership for Development**

**Target 18:** In cooperation with the private sector, make available the benefits of new technologies, especially information and communication

**Indicator 47:** Telephone lines and cellular subscribers per 100 population

**Indicator 48A:** Internet subscribers per 100 population

**Indicator 48B:** Personal computers per 100 population

*Abbreviations:* DOTS, directly observed treatment, short-course; GDP, gross domestic product; ODP, ozone-depleting potential.

**Table 2** Important 12th Plan programs addressing MDGs in India

Department of Agriculture and Cooperation	
National Food Security Mission	MDG 1
Rashtriya Krishi Vikas Yojana	MDG 1
Department of Rural Development	
National Rural Employment Scheme (MGNREGA)	MDG 1
Indira Awas Yojana	MDG 1
National Rural Livelihood Mission	MDG 1
Ministry of Housing and Urban Poverty Alleviation	
National Urban Livelihood Mission	MDG 1
Rajiv Awas Yojana	MDG 1
Department of School Education and Literacy	
Sarva Shiksha Abhiyan	MDG 2, MDG 3
National Program Nutritional Support to Primary Education (Mid Day Meal)	MDG 2, MDG 3
Rashtriya Madhyamic Shiksha Abhiyan	MDG 3
Department of Higher Education	
Rashtriya Uchhtar Shiksha Abhiyan	MDG 3
Department of Health and Family Welfare	
National Health Mission including NRHM	MDG 4, MDG 5
Ministry of Women and Child Development	
Integrated Child Development Schemes (ICDS)	MDG 4, MDG 5
National Mission for Empowerment of Women including Indira Gandhi Matritav Sahyog Yojana	MDG 3, MDG 5
Ministry of Health and Family Welfare	
National Vector Borne Diseases Control Program	MDG 6
Revised National TB Control Program	MDG 6
Department of AIDS Control	
National AIDS and STD Control Program	MDG 6
Ministry of Environment and Forests	
National Afforestation Program (National Mission for Green India)	MDG 7
Ministry of Drinking Water Supply and Sanitation	
National Rural Drinking Water Program	MDG 7
Nirmal Bharat Abhiyan	MDG 7
Ministry of Urban Development	
Jawaharlal Nehru National Urban Renewal Mission	MDG 7
Ministry of Information Technology/Ministry of Finance	
National E Governance and Action Plan	MDG 8

Abbreviations: NRHM, National Rural Health Mission; TB, tuberculosis; STD, sexually transmitted disease; MGNREGA, Mahatma Gandhi National Rural Employment Guarantee Act.

## Facility-based Newborn Care

*Special newborn care units* (SNCUs) are setup at district hospitals and medical colleges. These care for the sick newborn and are equipped with radiant warmer, phototherapy unit, oxygen hoods, infusion pumps, laryngoscope and endotracheal tubes, bag and mask, nasal cannulas and weighing scale. SNCU is a 12–20 bedded unit and requires four trained doctors and 10–12 nurses for round the clock services. Almost 400 SNCUs are now functional in the country.

*Newborn stabilization units* are setup at community health center/first referral units. These units provide services like resuscitation, provision of warmth, early initiation of breastfeeding, prevention of infection and cord care, supporting care including oxygen, IV fluids, provision for monitoring of vital signs including blood pressure and referral services. These are four-bedded units with trained doctors and nurses for stabilization of sick newborns.

*Newborn baby care corners* are setup in all facilities where deliveries are taking place. This is one-bedded facility attached to the labor room and operation theater for provision of essential newborn care. The services include resuscitation, provision of warmth, and prevention of infection and cord care and early initiation of breastfeeding. The equipment at newborn care corners include weighing scale, radiant warmer, suction machine and mucus sucker.

## Home-based Newborn Care

Home-based newborn care through Accredited Social Health Activist (ASHA) workers has been initiated to improve newborn care practices at the community level and for early detection and referral of sick newborn babies. All newborns will be visited by ASHA workers as per the specified schedule, up to 42 days of life. They have to ensure recording of weight of the newborn; BCG vaccination, first dose of oral polio vaccine and diphtheria, pertussis, and tetanus vaccination; both the mother and the newborn are safe till 42 days of the delivery; and that registration of birth has been done.

## Capacity Building of Health-care Providers

Trainings are conducted under NRHM to train doctors, nurses and auxiliary nurse midwife (ANM) for early diagnosis and case management of common ailments of children, as per the *Integrated Management of Neonatal and Child Illness* (IMNCI) strategy and *Navjat Shishu Suraksha Karyakram*.

Integrated Management of Neonatal and Child Illness includes interventions to prevent and manage the commonest major childhood illnesses which cause death, i.e., neonatal illnesses, acute respiratory infections, diarrhea, measles, malaria, and malnutrition. The objective is to implement IMNCI package at the household

**Table 3** Global morality rate (per 1,000 livebirths) for early neonatal, late neonatal, postneonatal, child and under-5 age from 1970–2013

Mortality rate	1970	1980	1990	2000	2013
Early neonatal (0–6 days)	31.4 (30.0–32.8)	26.7 (25.7–27.7)	22.6 (21.8–23.3)	19.8 (19.2–20.4)	14.0 (13.5–14.6)
Late neonatal (7–28 days)	16.8 (16.3–17.4)	12.8 (12.6–13.1)	9.3 (9.1–9.5)	7.2 (7.1–7.4)	4.4 (4.1–4.6)
Postneonatal (29–364 days)	48.1 (45.1–51.4)	36.5 (34.9–38.2)	27.6 (26.4–28.8)	22.2 (21.3–23.0)	13.2 (12.4–14.1)
Child (1–4 years)	54.1 (49.8–58.7)	38.7 (36.2–41.3)	27.9 (26.1–29.6)	22.1 (20.9–23.3)	13.1 (12.0–14.3)
Under-5 (0–4 years)	142.6 (138.5–146.9)	110.0 (108.1–111.7)	84.6 (83.3–85.9)	69.4 (68.5–70.4)	44.0 (41.9–46.3)

Source: Wang, et al. Global Burden Study. Lancet. 2014.



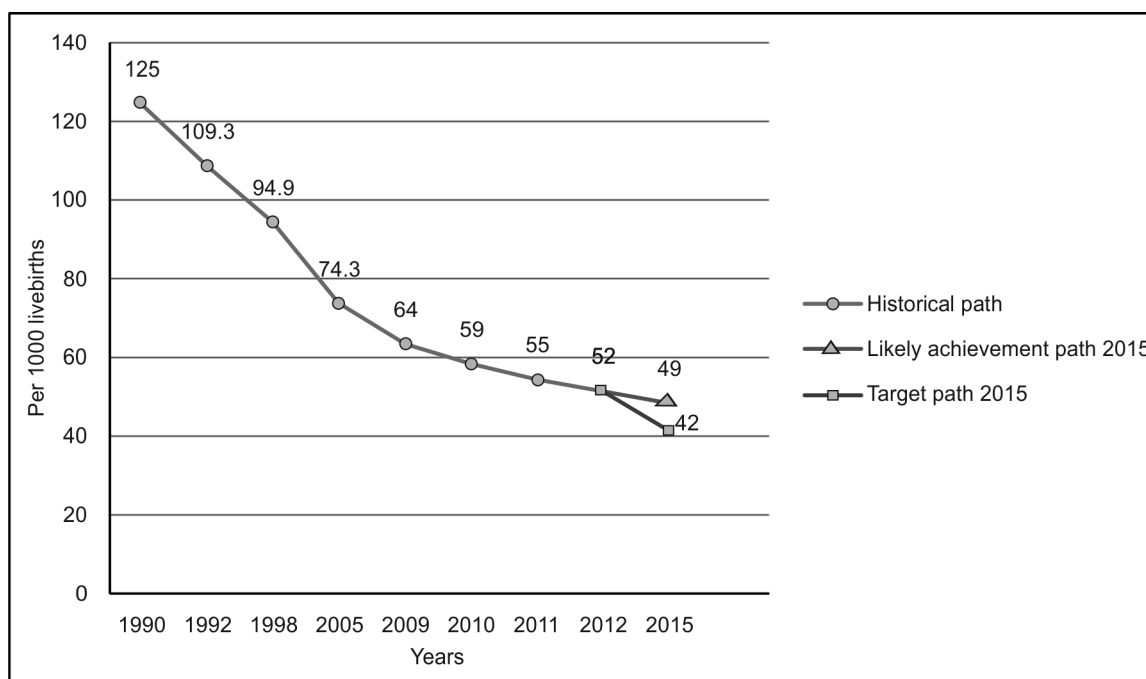


Figure 2 Trend in under-5 mortality rate (India)

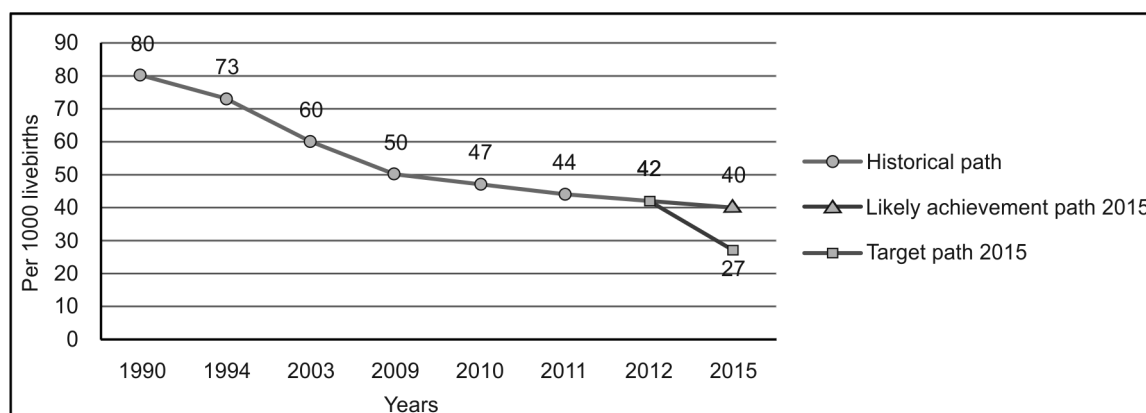


Figure 3 Trend in infant mortality rate (India)

level and subcenter, primary health center level, to provide a comprehensive newborn and child health services to address major neonatal and childhood illnesses. More than 500 districts and 5 lakh health-care providers have been trained in IMNCI.

*Navjat Shishu Suraksha Karyakram* program is launched to address basic newborn care and resuscitation, and issues at birth, i.e., prevention of hypothermia, prevention of infection, and early initiation of breastfeeding. The objective of this program is to have one person trained in basic newborn care and resuscitation available at every delivery.

### Management of Malnutrition and Other Morbidities

Malnutrition reduces immunity of children to infections and hence increasing mortality and morbidity among children. Exclusive breastfeeding is promoted for first 6 months of life as it reduces neonatal mortality. Appropriate infant and young child feeding practices are also promoted. For prevention of anemia, iron and

folic acid are provided to the children. Almost 600 nutritional rehabilitation centers have been established for management of severe acute malnutrition, across the country. Reduction in morbidity and mortality due to acute respiratory infections and diarrheal diseases is encouraged by early identification of cases and managing them properly. Promotion of zinc and oral rehydration salts supplies is ensured. Micronutrient malnutrition is addressed by supplementation with micronutrients through supplies of vitamin A and iron folic acid tablets.

### Universal Immunization Program

Immunization program of India is one of the largest immunization programs in the world. Under this program, Government of India is providing vaccination to prevent seven vaccine preventable diseases, i.e., diphtheria, pertussis, tetanus, polio, measles, BCG, and hepatitis B. *Haemophilus Influenza B* vaccine as part of a liquid pentavalent vaccine is also introduced in many states recently. Some newer initiatives have been introduced to strengthen routine



immunization, e.g., provision of auto disable syringe to ensure injection safety.

### Mother and Child Tracking System

A web based mother and child tracking system has been introduced to enable tracking of all pregnant women and newborns so as to monitor and ensure that complete services are provided to them. States are encouraged to send beneficiary wise SMS alerts to ANMs on weekly basis and also reminders to beneficiaries reminding them of the dates on which services are due.

### Integrated Child Development Services Scheme

Integrated Child Development Services is a centrally sponsored scheme aimed at holistic development of children below 6 years of age and pregnant women and lactating mothers by providing a package of six services comprising of (a) supplementary nutrition; (b) preschool nonformal education; (c) nutrition and health education; (d) immunization; (e) health checkup; and (f) referral services through *Anganwadi* center at grassroots level.

In India, the achievements as per the MDGs vary for different indicators. For some of the indicators, India has achieved the targets ahead of the time line, like indicator 1A, i.e., halving the percentage of population below the poverty line. Targets 1, 3, 4, 7 and 18 are on track, while targets 5, 8 and 9 are moderately on track, targets 2 and 6 are off track. Target 10 is on track for drinking water and off track for sanitation. The trend reversal types of targets (targets 7 and 8) have been realized in India, as India have successfully halted and reversed the spread of HIV/AIDS and malaria and tuberculosis.

The ultimate responsibility to achieve the MDGs, to monitor and report on progress, lies with the Government of India.

Effective leadership and appropriate stewardship of national and international resources for development, in general, and health development, in particular, are the keys for achieving the MDGs. There is need for strengthening health systems and scaling up of all the programs at all levels at a priority level to achieve MDGs.

### MORE ON THIS TOPIC

- Boopathy GM, Maitra S, Bhaskar S, et al. Millennium Development Goals India Country Report. Social Statistics Division, Ministry of Statistics and Programme Implementation, New Delhi: Government of India; 2014.
- Das E, Panwar DS, Fischer EA, et al. Performance of accredited social health activists. *Indian Pediatr.* 2014;51:142-4.
- Jeyalakshmi S, Maitra S, Bhaskhar S, et al. Towards achieving Millennium Development Goals. Social Statistics Division, Ministry of Statistics and Programme Implementation, New Delhi: Government of India; 2013.
- Lim SS, Dandona L, Hoisington JA, et al. India's Janani Suraksha Yojana, a conditional cash transfer programme to increase births in health facilities: An impact evaluation. *Lancet.* 2010; 375:2009-23.
- Millennium Development Goals Indicators. From: <http://unstats.un.org/unsd/mdg/Host.aspx?Content=Indicators/OfficialList.%20htm>. Accessed June 5, 2014.
- Navjaat Shishu Suraksha Karyakram: Basic newborn care and resuscitation program: Ministry of Health and Family Welfare Government of India facilitator's guide. From: <http://nihfw.org/pdf/NCHRC-Publications/NavjaatShishuFacGui.pdf>. Accessed June 4, 2014.
- United Nations General Assembly. United Nations millennium declaration. Resolution Adopted by the General Assembly. New York; 2000. p. 55/2.
- Wang H, Liddell CA, Coates MM, et al. Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2014.

## Chapter 1.5

# Evidence-based Care in Pediatrics

Joseph L Mathew

The term *evidence-based medicine* (EBM) has become a buzz phrase in recent decades. It is heard in all scientific deliberations in health care. Although it is not universally accepted, resistance to this form of clinical practice is gradually diminishing. The scope of EBM has been broadened with terms like *evidence-based practice* and *evidence-based health care*. Some experts prefer to use the more neutral phrase *evidence-informed* rather than *evidence-based* as it signifies that evidence has been considered in the decision-making process, though not necessarily applied. Whatever term is used, broadly it refers to the scientific discipline of incorporating research and clinical evidence into health-care decisions and practice. In this sense, evidence-based pediatrics is not different from other forms of evidence-based health care.

### WHAT IS EVIDENCE-BASED HEALTH CARE?

Excerpts from some of the definitions for EBM proposed by various experts during the evolution of EBM, help to clarify the concept and (perhaps more important the) scope of EBM (**Table 1**). For want of a more specific definition, *evidence-based pediatric care* can be taken to include the principles, processes and practice of EBM (as highlighted in **Table 1**) for the health and well-being of children.

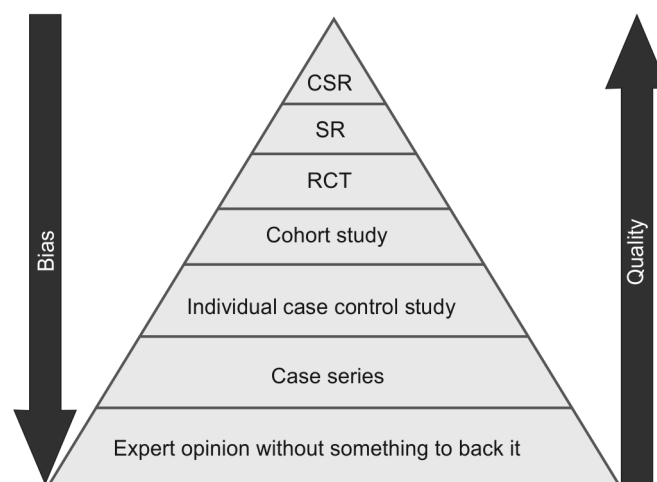
**Table 1** Excerpts from definitions of evidence-based medicine

1996	"conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patient" (Sackett, et al. BMJ. 1996; 312:71-2)
1998	"integration of good evidence with clinical expertise and patient values" (Straus and Sackett. BMJ. 1998;317:339-42)
2002	"to encourage practitioners and patients to pay due respect—no more, no less—to current best evidence in making decisions" (Haynes, et al. BMJ. 2002;324:1350)
2003	"Integrating clinical expertise with best available external evidence in the care of the individual patients keeping in mind the patient's circumstances" (Sehon and Stanley. BMC. 2003;3:14)
2005	"way of thinking arguing that health care decisions need to be focused on research-based evidence" (De Backer, Verh K. Acad Belg. 2005;67:205-17).

It is perhaps relevant at this point to also understand what is not *evidence-based care*. Applying the results or conclusion section of one or more research papers in clinical practice; or seeking or identifying research papers that support or justify whatever a professional is doing; do not constitute evidence-based care. Other misconceptions about EBM are that its purpose is to make practice of health care more *democratic*, in the sense that, professionals with and without vast experience are at the same level of subservience to research evidence. Some professionals mistakenly also believe that its main application is to judge whether interventions that work in developed country settings can be applied to local settings; while others feel that *evidence-based care* reduces the need for clinical judgment as all children with a given clinical condition could be treated with a uniform protocol.

Strictly speaking, the term *evidence-based* may be a misnomer because it implies that there is a scope for *non-evidence-based practice* as well. However, in fact almost all health-care professionals use some kind of evidence to base their clinical decisions and it is unlikely that anyone acts solely on personal whims. However, there is a wide latitude in what constitutes *evidence* and even more about what constitutes *best evidence*. All professionals would agree that *evidence* is based on observations in the clinical or research setting, and that greater the number of observations pointing in a given direction, the more likely (though not necessary) that it points toward the *truth*. However, *best evidence* creates controversy. Many professionals argue that their personal experience and observations constitute the best evidence for their patients (and practice setting). However, the traditional evidence hierarchy places *expert opinion* right at the bottom of the pyramid (**Fig. 1**), even below case reports of individual patients. But, the definition of EBM insists that clinical expertise is a significant component! This apparent paradox can be resolved if we understand that *best evidence* is based on efforts to remove or resolve systematic error or bias (defined in simple terms as anything which leads away from the truth) from the observations comprising evidence. In other words, any form of evidence that has a lower risk of bias would climb upwards on the evidence hierarchy and vice versa. This is why randomized controlled trials (RCTs) of interventions and systematic reviews of RCT are ranked highest in the evidence hierarchy.

*Patient values* include the unique circumstances (such as health-care setting, personal or social issues, economic status, etc.) of individual patients for and hopefully by whom health-care decisions are made. In a well-developed health-care system (unlike the provider-driven settings in most developing countries), patients, i.e., consumers of health care are provided the



**Figure 1** The evidence hierarchy

Abbreviations: CSR, Cochrane systematic reviews; SR, systematic reviews; RCT, randomized controlled trial

professional's judgment (based on clinical expertise) and the best evidence (based on relevant research and the experience in that health-care setting); and they are encouraged to make decisions factoring-in their perception, situation and expectations. The role of the professional is to facilitate this process and guide patients in the right direction. Ideally, this is how evidence-based care is to be practiced. Therefore, it may happen that while professional judgment and research evidence point to a certain direction, the patient chooses not to take that direction on account of his or

her values. When such a decision is a shared process between the patient and the professional then it too constitutes *evidence-informed practice*.

## EVIDENCE-BASED PRACTICE

A detailed description of how to practice evidence-based health care is outside the scope of this chapter. Readers are referred to access “More on this Topic” given at the end of this chapter for excellent summaries and freely available online resources. A brief outline of the steps involved in evidence-based practice is presented in **Table 2**.

It should be clearly recognized that evidence is a tool to facilitate appropriate decision-making and is not the decision itself. A parallel can be drawn from the various laboratory tests ordered by professionals. Good physicians use the results of laboratory tests to confirm what they suspect on the basis of their knowledge and clinical expertise. They also factor in the circumstances of an individual patient and the local health-care setting. They would not base their decision(s) solely on the basis of the test results no matter how impressive they appear to be. This is how evidence is expected to be used in the real world. In contrast, some physicians order a battery of laboratory tests without clinical justification; and then proceed to treat the abnormal results irrespective of their (ir)relevance. There are some who practice EBM in a similar inappropriate fashion.

## Quality of Evidence

Evidence used for decision-making needs to be critically appraised for quality which determines its internal and external validity. Quality usually refers to two different aspects, viz. *methodological quality* (related to the study design) and *process quality* (related to the process of generating the evidence). The former includes methodological refinements in research studies that are designed to reduce bias, for example, randomization and allocation concealment to minimize selection bias, intention-to-treat analysis to mitigate attrition bias, etc. The latter includes procedures to minimize errors in data collection, for example, averaging of multiple measurements, instrument calibration, using gold standard tests or methods, etc. There are various tools available for appraising primary and secondary research for *methodological quality*, whereas the judgment of *process quality* is often left to the discretion of researchers, or journal editors or the peer review process.

Recognizing the need to support health-care professionals in using evidence as a tool in pediatric practice, “*Indian Pediatrics*” initiated the EURECA [Evidence that is Understandable, Relevant, Extendible (to the local setting), Current and Appraised critically] section some years back. The idea was to provide high quality evidence in an easy to understand format, on various aspects of child health, facilitating pediatricians in the country and region, to make informed decisions (Mathew. *Indian Pediatr.* 2008;45:95-8).

However, evidence-informed pediatric practice involves much more than accessing, appraising and applying the relevant evidence. It involves a careful appraisal of additional issues such as financial costs, cost-effectiveness of interventions, social implications, feasibility, logistics, long-term impact, etc. These components together form the discipline of health technology assessment (HTA). Most developed health-care systems rely on information provided by HTA organizations to guide their decision-making system. In contrast, many developing health-care systems lack such facilities and experience challenges in making rational decisions at the individual, institutional, organizational, or national level.

## CHALLENGES TO EVIDENCE-BASED PEDIATRICS PRACTICE

Health-care professionals expect research evidence to provide answers to their decision-making questions, such as “Should I use this medicine or vaccine or test or procedure?” However, research evidence is designed to address specific clinical questions [in the famous PICO format (identify the patient problem or population (P), intervention (I), comparison (C) and outcome (s) (O))] from which individual stakeholders (professionals, patients and health-care systems at large) are expected to derive conclusions and then make their decisions. Thus evidence cannot dictate what a professional should do. It is designed to provide information on the basis of which, the professional and patient together have to make a shared decision, incorporating clinical experience and personal values, respectively. This requires knowledge and skills to understand, interpret and apply research evidence. This is the art of practicing the science of EBM.

Often, health-care professionals appreciate the value of incorporating evidence in their decision-making processes, but the evidence is either unavailable or inaccessible (at the time or place required). This is largely related to the health-care setting wherein crowded clinics or wards and limited technological facilities, pose challenges to the real time access and application of research evidence. This situation has undergone tremendous improvement with the availability of mobile phone based applications and better internet connectivity at the point of care.

Even when evidence is available, there are challenges to applying it. Some of these are related to the evidence itself. Of more than 140 Cochrane reviews related to the field of *pediatric pulmonology*, 30% were not applicable in India simply because the intervention is either not available, or not accessible, or not affordable, or not acceptable. About 35% reviews do not offer definite conclusions and hence cannot be applied. Only one-third (35%) reviews have conclusions that have the potential to be applied in the Indian context (Mathew, 2006). The other major limiting issue in evidence-based practice is the generalizability of evidence. As for many issues in health-care, evidence generated from a particular setting may not be directly applicable to other settings. This could be on account of biological characteristics of the patient (population) or disease, health-care system differences, locally relevant guidelines, or even cultural practices or traditions. Some of these limitations may operate even when evidence is generated from the same or similar setting. For example, evidence on milder forms of disease cannot be extrapolated to patients with severe disease, or those with comorbidities, etc. In such situations, professional judgment is required to determine applicability of evidence, i.e., can the evidence be implemented in my setting? If yes, would it result in similar effects?

Sometimes, all the available evidence does not point in the same direction. Recently an interesting situation arose with the clinically important question of whether daily treatment (compared to intermittent treatment) is appropriate for children with tuberculosis. A systematic review published in 2010 (Menon et al. *Indian Pediatr.* 47:67-73) suggested that daily treatment is superior, based on which the World Health Organization altered its recommendations to favor daily therapy against its previous leaning towards intermittent therapy. A recent Cochrane review (Bose et al., Cochrane 2014), analyzing the same trials and data, reported the absence of any difference between the two treatment regimens, supporting the view that intermittent therapy is as efficacious as daily treatment. The authors explained the difference on the basis of methodological errors in the older

**Table 2** Steps in evidence-based practice

No.	Steps	Remarks
1	Identify an area in your health-care practice where there is uncertainty about what should/could be done for a particular patient or problem.	In general, a common starting point for EBM or EBP is an encounter with a patient, and the need for answers for that particular patient.
2	Frame an answerable question by converting decision questions into clinical questions, using the PICOT format. P = Population/ Patient/ Problem I = Intervention or Exposure C = Comparison O = Outcome(s) of interest T = Time-frame over which outcomes are considered	<p>Exposure is a better term because it encompasses interventions, diagnostic tests, risk factors, prognostic factors, etc., and is applicable to any study design.</p> <p>Outcomes could be hard outcomes such as mortality, cure, etc.; or soft/surrogate outcomes which are indirect markers believed to reflect the hard outcome(s). These are more plentiful but less robust. When in doubt, opt for patient-centric outcomes, i.e., which are relevant to patients.</p> <p>Time-frame is often not included, but it could be important because certain outcomes develop over time, (and although important may not be captured adequately in a research study) while others occur in the short-term and are easier to record.</p> <p>Some experts add an additional component called Study design (S), which gives the option of focusing the clinical question to specific designs. For example, efficacy of interventions is best answered through randomized trials, but this may not be the ideal design to capture rare adverse events.</p>
3	Search and collate literature to access and identify best evidence addressing the clinical question.	<p>Literature search could be broad-based (sensitive) or focused (specific).</p> <p>Some of the tips and tricks to refine literature searches include: (i) choosing appropriate search terms with the aid of MeSH terms, (ii) starting with a highly sensitive search and narrowing down to a more specific search, (iii) using multiple databases that include the Cochrane Library (free access within India), Medline through PubMed, and subject specific databases, (iv) using Filters/Limits to increase specificity, and (v) recording the output carefully.</p> <p>It is important to target high quality evidence in literature search. Hence one could restrict the search to specific study designs associated with low(er) risk of bias, or look for systematic reviews of such studies.</p>
4	Critically appraise the literature	<p>There are numerous tools that facilitate a rapid and fairly easy appraisal of Methodological quality. Most of these are available online and reflect: (i) whether the study included methodological refinements limiting bias, thereby assessing validity, (ii) the main results and whether these are both statistically as well as clinically significant; and (iii) if yes, whether the results could be applied to the individual patient in the real-life setting.</p> <p>Process quality requires some understanding of the subject area, in order to judge whether the procedures described in the research evidence, are valid (or not).</p>
5	Synthesize the best evidence	<p>For <i>users</i>, i.e., those who would use the evidence, such a synthesis would be available through a systematic review. For <i>doers</i>, i.e., those who would generate the best evidence, the synthesis is under the umbrella of a systematic review (with or without meta-analysis).</p> <p>If systematic reviews are not available, synthesis involves carefully extracting data from individual pieces of evidence and putting it together.</p>
6	Interpret the evidence	Interpretation of evidence requires basic knowledge and skill in the subject area, research methodology, and biostatistics. Although an in-depth knowledge may not be required, broad understanding is required to interpret the evidence as opposed to blindly believing the authors' conclusions.
7	Consider applying the evidence based on your clinical expertise and a shared understanding of the patient's values	<p>Before attempting to apply the evidence, a free and frank discussion with the patient (and especially family where children are involved) is required to explain the information gained through your clinical expertise and the current best evidence.</p> <p>This has to be put together with the patient (family) preferences, beliefs, perceptions apprehensions, concerns, desires, financial status, logistic considerations, etc. The evidence should be applied only after a mutually acceptable shared decision is reached jointly by the health-care provider and recipient.</p>
8	Assess the results	<p>Evaluate the results whether or not the intervention was applied.</p> <p>Ensure that patients (families) are participant to the evaluation process.</p>



review. Clearly the WHO had failed to recognize this when it framed its guidance. Such situations can confuse potential users of evidence and drive them away to more traditional formats of decision-making.

### Efficacy versus Effectiveness

Research evidence usually presents information of the *efficacy* (and sometimes) safety of interventions from research settings, whereas in real-life, we require information on *effectiveness*. In simple terms, efficacy addresses the issue “Does this work in a highly controlled research setting?” whereas effectiveness reflects “Will this work in the real-world health-care setting?” Assessment of effectiveness requires a careful appraisal of issues beyond efficacy and safety, and encompasses aspects like the health-care setting, feasibility, logistics and cost considerations of the intervention (and its alternatives), social aspects and other issues.

It should also be recognized that *health-care interventions* (therapeutic/diagnostic) rather than *health problems* are the usual starting point for generating primary and secondary research evidence. Therefore, practice of EBM can become a process of applying interventions that are supported by evidence, at the cost of ignoring other options for which robust evidence on efficacy may not be readily available. For example, research evidence may suggest that a particular vaccine is efficacious in a given setting, but there may not be sufficient evidence on alternate measures to tackle the health-care problem (through better sanitation, hygiene, and nutrition). In such a situation, implementation of the efficacious intervention gives the impression of evidence-based practice.

### Tertiary Research

The complexity involved with understanding, interpreting and thereafter applying research evidence has spawned a new brand of analysis referred to as *tertiary research* (for want of a better term). This form of research has become critical for health-care stakeholders (professionals, patients, policy-makers, advocacy groups, lay press, etc.) to cut through the technical jargon in research, identify the relevant message and provide a summary that can serve as a tool for evidence-based decisions. In that sense, it demands a very high level of skill and integrity from the tertiary researcher. The former, because it is more complicated than generating primary or secondary evidence and leaving the stakeholder to interpret the same. The latter because the tertiary researcher can consciously or unconsciously mislead the stakeholder in the direction of his/her own bias(es). Unfortunately, although a lot of tertiary research products are in circulation (commentaries, evidence-based editorials, evidence summaries, non-systematically generated guidelines/recommendations, etc.) which are appealing to the end-user, the methodological process for validation of such research is still under development.

### Conflict of Interest

As with all aspects of life, conflicts of interest appear in health-care practice also. It was hoped that generation and application of high quality scientific evidence could reduce some of the biased decisions associated with various conflicts of interest. In this context, evidence has been a two-edged sword in the battle to minimize bias arising from industry pressure. On the one hand, robust evidence has been crucial in facilitating appropriate decisions. On the other hand, industry sponsored research has led to a plethora of high quality (primary and even secondary) evidence from which it is difficult to sift the relevant information. In the context of developing health-care systems, the influence of industry on professional decision-making without accessing the evidence, cannot be over-emphasized.

## WHAT IS THE WAY FORWARD?

Clearly, the way forward to develop a system of evidence-based practice of pediatrics revolves around empowerment. Empowerment is a broad term that encompasses multiple facets and multiple stakeholders. On the one hand, we need to empower health-care providers and health-care consumers to contribute together to generate high quality evidence. This includes research evidence (through well designed studies, systematic reviews and even tertiary research) as well as clinical evidence (through meticulous documentation of observations, peer review, external validation, etc.). This in turn requires developing a pool of people with the requisite knowledge and skills who in turn can become the nucleus for building up (and sustaining) the effort. Such efforts have been made in recent years through the activities of the South Asian Cochrane Network and Center which are bearing fruit. In addition, similar efforts at empowerment have been made through the SIGNET (Singapore Indian Group Networking for Empowerment Training) program and also the Advanced Center for Evidence-Based Child Health (both based at Chandigarh), the excellent paper writing workshops conducted under the aegis of “*Indian Pediatrics*” and various other institutional, organizational and national efforts. Nevertheless, currently these efforts are mostly provider driven rather than demand driven. It is believed that a demand-driven approach can be boosted through introduction of principles of EBM at the undergraduate training level (for all categories of health-care professionals associated with child health).

Further, while these efforts have been successful in enlarging the pool of *doers* who generate primary and secondary evidence, it is unclear whether there is a concomitant pool of empowered *users*. Ideally, empowerment efforts should focus on both users (who would demand appropriate evidence on locally relevant issues) and doers who could fulfill the demand. In the context of evidence-based health-care, the list of users extends far beyond health-care professionals and encompasses virtually everyone who participates in decisions affecting children. This includes policy-makers, organizational leaders, health-care institutions, lay press, and of course the general public. Evidence-based pediatrics practice would take off in the real sense only when all these stakeholders are empowered enough to demand evidence-based practice, interpret its tools, and judge its application.

## MORE ON THIS TOPIC

- Akobeng AK. Evidence-based child health (Series 1-5). Arch Dis Child. 2005;90: 837-52.
- Centre for evidence-based medicine Oxford. From: <http://www.cebm.net/?o=1014/>. Accessed 5 May, 2014.
- Mathew JL. Applicability of evidence as a health technology tool in developing countries. Invited presentation at the Plenary session of the 3<sup>rd</sup> Health Technology Assessment International (HTAI) meeting. Australia: Adelaide; 2006.
- Mathew JL. Beneath, behind, besides and beyond Evidence-Based Medicine. Indian Pediatr. 2010;47:225-7.
- Mathew JL. Know Essentials: A tool for informed decisions in the absence of formal HTA systems. Int J Tech Assess Health Care. 2011;27:139-50.
- Mathew JL, Singh M. Evidence based child health: fly but with feet on the ground! Indian Pediatr. 2008;45:95-8.
- Sehon SR, Stanley DE. A philosophical analysis of the evidence-based medicine debate. BMC Health Serv Res. 2003;3:14.
- Wang S, Moss JR, Hiller JE. Applicability and transferability of interventions in evidence-based public health. Health Promotion International. 2005;21: 76-83.
- White B. Making evidence-based medicine doable in everyday practice. From: [www.aafp.org/fpm](http://www.aafp.org/fpm). Accessed May 30, 2014.



# PART II Basic Sciences as Applied to Pediatrics

## Section 2 GENETICS AND GENETIC DISORDERS

Section Editor Shubha R Phadke

### Chapter 2.1

### Gene, Genome and Genetic Basis of Diseases

Girisha KM

Genetic constitution of an individual has direct bearing on health and disease. The genetic information is contained in the chromosomes inside the nucleus and a fraction in mitochondria, together referred to as the genome. Some use the words *nuclear genome* and *mitochondrial genome* to separate these entities. This information forms the basis of inheritance of *characters* or *phenotypes* from one generation to the other during reproduction (meiosis) and it is copied to the daughter cells during growth of an organism (mitosis). For the comprehension of human health and diseases, understanding of the structure, function, regulation and variations in deoxyribonucleic acid (DNA) is essential. This chapter discusses the molecular basis of inheritance, gives insight into genetic variations among individuals and their clinical implications.

#### DEOXYRIBONUCLEIC ACID

Deoxyribonucleic acid is the basic molecule that contains the genetic information. DNA is a long polymer of four different nucleotides. Each nucleotide has a nitrogenous base, a deoxyribose sugar and a phosphate group. Nitrogenous bases are purines: adenine (A) and guanine (G); and pyrimidines: cytosine (C) and thymine (T). Sugar and phosphate molecules form two sides of the ladder that are held by strong phosphodiester bonds. The two strands of the ladder run antiparallel to each other with one strand having the orientation of 5' to 3' direction and the other of 3' to 5' direction (**Fig. 1**). The nitrogenous bases facing inside are held by weak hydrogen bonds which facilitate the separation during replication and transcription. Nearly 2 meters of DNA is condensed about 10,000 times and packaged into 46 chromosomes in human nucleated cells. The DNA is first wound around a histone protein core to form a nucleosome, which in turn forms a helical solenoid. The solenoids are then arranged into chromatin loops, which are attached to a protein scaffold and further packaged into chromosomes. Ribonucleic acid (RNA) differs from DNA in having a ribose sugar in place of deoxyribose, and a pyrimidine uracil (U) in place of thymine and is single stranded.

#### DNA Replication

Transmission of genetic information from parent cell to its progeny occurs by replication of DNA. The DNA replication is a crucial

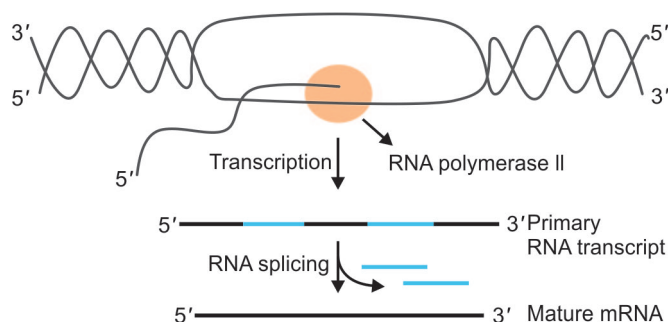


**Figure 1** Illustration of DNA double helix. The two strands of sugar-phosphate backbone run in opposite direction. Strands are held together by hydrogen bonds in between the nitrogenous bases; two hydrogen bonds are formed between adenine (A) and thymine (T) and three hydrogen bonds between guanine (G) and cytosine (C)

event which leads to the formation of two identical copies of the original DNA that get segregated into two daughter cells during cell division. The replication begins with uncoiling and separation of two strands of the DNA molecule by the enzyme helicase. Each strand of the DNA guides the synthesis of its complementary copy through complementary base pairing. Adenine pairs with thymine and cytosine pairs with guanine resulting in formation of two DNA molecules identical to the original parent molecule. This process conserves the genetic information, and transmits it unchanged to each daughter cell and hence called semiconservative synthesis. The vital enzyme in the course of DNA synthesis is DNA polymerase. The synthesis of new DNA strand proceeds in 5' to 3' direction during the S (synthetic) phase of the cell cycle. This process initiates at several sites concurrently. This leads to formation of one continuous strand named leading strand which is the copy of the 3' to 5' strand; and the other strand named lagging strand is synthesized in parts. These parts are called Okazaki fragments which are later joined together by the enzyme DNA ligase.

#### Transcription

Transcription leads to formation of RNA from DNA which then migrates to cytoplasm for synthesis of proteins (**Fig. 2**). The



**Figure 2** The process of transcription starts with the synthesis of single strand of RNA using double-stranded DNA as template by the enzyme RNA polymerase II. The two strands of the DNA molecule are separated from one another, exposing the nitrogenous bases and the antisense strand or template strand is actively transcribed. The RNA produced is known as primary RNA transcript which undergoes RNA splicing. During the splicing event, the introns (blue) are removed and the exons (black) are joined together to produce mature mRNA

product of transcription is called a transcript. The transcript of the coding DNA is known as messenger RNA (mRNA). The mRNA is synthesized by the enzyme RNA polymerase that adds complementary ribonucleotides to the RNA chain. Thymine is replaced by uracil in the mRNA. The particular strand of DNA that acts as a template for synthesis of mRNA is called *antisense strand* so that the new molecule of mRNA is the copy of the other *sense strand*.

The mRNA thus formed is further processed by removal of introns at specific splice sites, addition of a methylated guanine nucleotide to the 5' end of the molecule (5' capping) and addition of about 200 adenylate residues at the 3' end (polyadenylation). The mRNA leaves the nucleus to cytoplasm after several processing events and is then translated into a polypeptide chain or a protein.

### THE GENETIC CODE: HOW DO THE GENES CODE FOR PROTEINS?

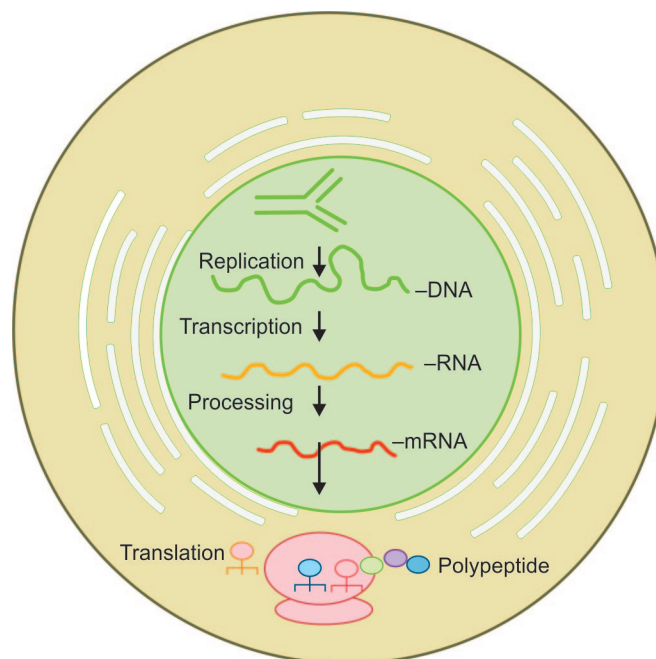
There are 20 different amino acids which are the basic units of protein. The sequence of triplet nucleotide bases in the DNA molecule that specifies the sequence of amino acids in the protein molecule is called the genetic code (**Fig. 3**). After transcription, the codons on mRNA are non-overlapping, and are read as per translational reading frame. Among 64 possible triplet codons from four nucleotides, more than one codon code for same amino acid (called degeneracy, since there are only 20 amino acids). Three codons terminate polypeptide chain synthesis (stop codons). The genetic code from DNA is transmitted to codons of the mRNA during transcription which is then decoded into specific amino acids during translation.

### Translation

The codons of mRNA direct the synthesis of a polypeptide chain by incorporating specific amino acids during the process of translation. In the ribosomes, the site of protein synthesis, the processed transcript molecules with the help of specific transfer RNAs (tRNA) carrying the *anticodons* for individual amino acids synthesize the polypeptide chain. The polypeptide chains undergo several post-translational modifications (hydroxylation, methylation, glycosylation, proteolytic cleavage, etc.) to become functional proteins that are transported to their specific cellular locations. The process of transfer of genetic information from DNA to RNA to protein is sometimes referred to as *central dogma* of molecular biology (**Fig. 4**).

	U	C	A	G	
U	Phe Phe Leu Leu	Ser Ser Ser Ser	Tyr Tyr STOP STOP	Cys Cys STOP Trp	U C A G
C	Leu Leu Leu Leu	Pro Pro Pro Pro	His His Gln Gln	Arg Arg Arg Arg	U C A G
A	Ile Ile Ile Met	Thr Thr Thr Thr	Asn Asn Lys Lys	Ser Ser Arg Arg	U C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U C A G

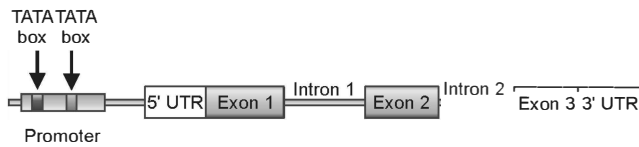
**Figure 3** The genetic codes from DNA are transcribed to codons in mRNA. Three nucleotides (triplet) code for an amino acid. The codes are degenerate (each amino acid is coded by more than one codon). Three stop codons terminate the polypeptide chain synthesis



**Figure 4** Central dogma of molecular biology: Flow of genetic information from DNA to RNA to protein. Replication: a double-stranded nucleic acid is duplicated to give identical copies which are equally distributed to both the daughter cells. Transcription: Gene, a DNA segment, is transcribed into a single-stranded sequence of RNA which then moves from nucleus to cytoplasm. Translation: In the cytoplasm, the RNA sequence is translated into a sequence of amino acids as the protein by ribosomes and tRNA

### Gene

A *gene* may be conceptualized as the stretch of DNA that contains the information required for a functional product. The product encoded may be a polypeptide or an RNA molecule. It was thought



**Figure 5** Simplified overview of structure of a gene: A typical protein-coding gene is made up of a promoter (facilitates the binding of RNA polymerase to the gene during transcription), a transcriptional start site (contains the initiation codon ATG), exons (encode the information for a functional protein), introns and the 5' and 3' untranslated sequences (play a role in gene regulation). Other regulatory elements may be near or far away from these sequences

that the coding sequence of a gene lies in continuity, which is now known to be a rarity. Now, the *gene* has been shown to consist of amino acid coding exons, intervening noncoding introns, promoter sequences at 5' region that initiate transcription, 3' sequences that give stability to mRNA molecule in the cytoplasm and other regulatory elements like enhancers, silencers, and locus control regions (**Fig. 5**). Genes may overlap, may be found within another gene, or even the same sequence may be transcribed in reverse direction to produce another product.

### Regulation of Gene Expression

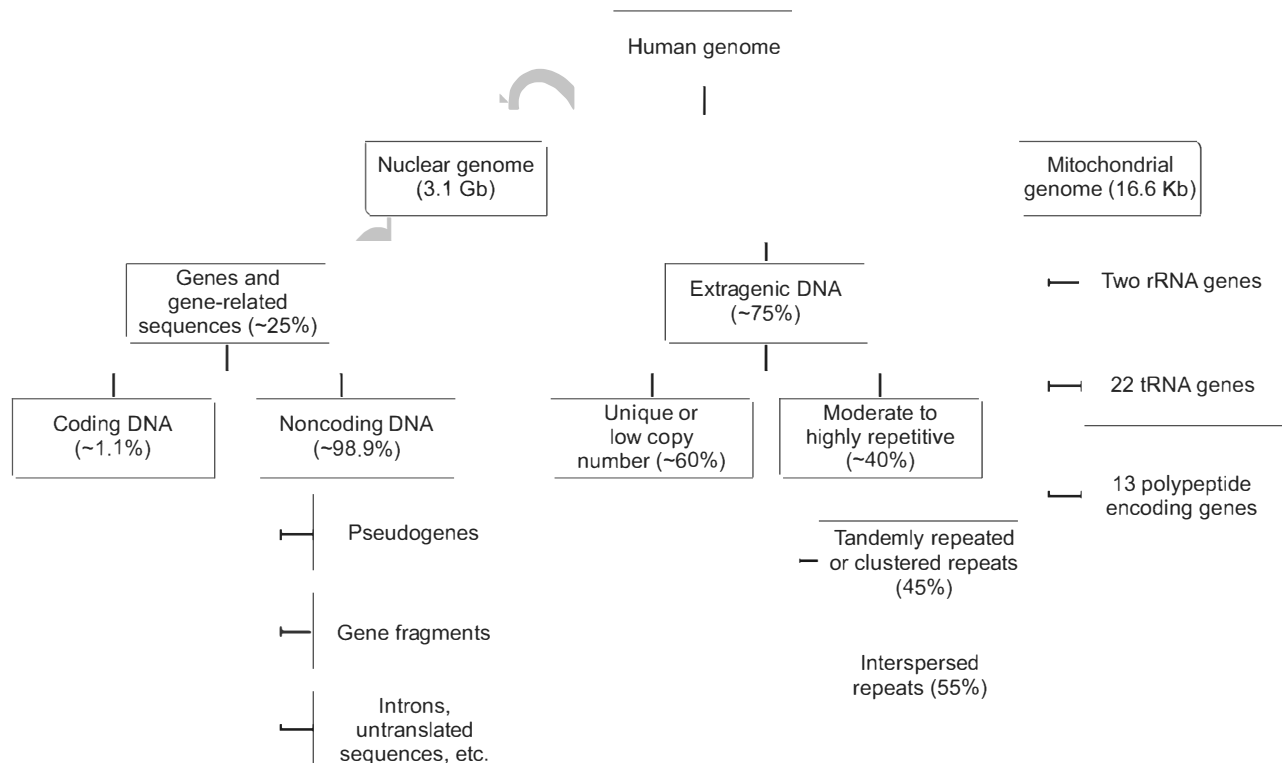
The genes in each human cell control all the cellular processes and maintain homeostasis. Their expression varies at different stages of development, and depends on the cell/tissue type. Several complex pathways are involved in controlling the temporal and spatial expressions of genes. Gene expression may be regulated via signaling molecules that bind to regulatory

sequences of DNA (transcription factors), nuclear receptors (hormones) or even specific ligands located at the cell surface for signal transduction. The transcription factors may bind to promoter elements (TATA, GC and CAAT boxes) of the specific genes located adjacent to the coding region (cis-acting) to regulate the pace of protein synthesis, or to enhancer or silencer elements located at a distance and act on both copies of the gene (trans-acting) to enhance or suppress the transcription. Transcription factors themselves are coded by genes and bind to DNA to regulate gene expression. Gene activity may also be related to patterns of chromatin condensation and methylation. Heterochromatin is the part of the DNA which is usually highly condensed and is characterized by histone modification that makes it inaccessible to transcription factors, whereas euchromatin is decondensed and transcriptionally more active. Though regulation of expression of most of the genes is mediated by transcription factors, regulation can also occur at various stages of protein synthesis. Alternative splicing is a mechanism where a gene can code for more than one protein or at varying rates. Some regulatory sequences are now known to harbor mutations, though exact mechanisms of gene regulations are not fully elucidated yet.

### ORGANIZATION OF THE GENOME

The *human genome* refers to the complete set of genetic information in human cells. In other words, genome refers to the entire DNA content of the cell. It comprises two parts: a large nuclear genome ( $3 \times 10^9$  bp) and a very small mitochondrial genome (16.6 kb; **Flow chart 1**). The nuclear genome provides a great bulk of genetic information, most of which specifies synthesis of proteins of the body. Mitochondria possess their own

**Flow chart 1** Organization of human genome



genome which encodes their own tRNA, ribosomal RNA and few of their own polypeptides.

## Nuclear Genes

It is estimated that there are about 22,000 protein coding genes in the entire nuclear genome. The size of the genes vary greatly, with small genes comprising of 1–3 exons (beta globin) and large genes with up to 79 exons (dystrophin gene, ~2.2 Mb).

Unique single-copy genes are present in single copy (in the haploid set of chromosomes and double in the diploid normal human cell). These encode the polypeptides that are involved in a wide variety of cellular functions: enzymes, receptors, regulators and structural proteins. Some others are members of multigene families. These arise through gene duplication events during evolution. These may be found in physically close clusters, like alpha and beta globin genes on chromosome 16 and 11, respectively or dispersed throughout the genome, like the *HOX* gene family, which are important developmental genes. The genes which encode the ribosomal RNAs are clustered as tandem arrays at the short arms of the acrocentric chromosomes and those encoding the tRNAs occur in numerous clusters throughout the genome. These constitute classic gene families. Genes encoding the human leukocyte antigens and the T-cell receptor genes belong to the immunoglobulin gene superfamily. Pseudogenes closely resemble known structural genes but do not have well-known functions. They are thought to have arisen either by duplication of genes that have lost function due to mutations or by insertion of complementary DNA sequences lacking promoter sequences.

## Extragenic DNA

The noncoding regions of human genome (98–99%) are made up of repetitive DNA sequences that are predominantly inactive. These have also been referred to as junk DNA, but have some uncertain regulatory role. Some are tandem repeats of varying lengths of DNA molecule and include satellites and minisatellites. Highly polymorphic short tandem repeats of core units made up of 10–100 base pairs are used in DNA fingerprinting. Microsatellites consist of tandem repeats of 2–4 base pairs sequences located throughout the genome. Some repetitive DNA is interspersed throughout the genome.

## Mitochondrial DNA

Mitochondria contain their own 16.6 kb circular DNA (mtDNA). It encodes for 37 genes including two for ribosomal RNA, 22 for tRNA and 13 for polypeptide sequences. It is important to recognize that most of the protein components of mitochondria are product of nuclear genes and mutations in them are responsible for the so called *mitochondrial diseases* and yet exhibit autosomal inheritance.

## Sequence Variations in Human Genome

Humans display a remarkable degree of genetic variation, mostly in the noncoding regions. The most obvious traits include height, blood pressure and skin color. Variation in disease traits, response to drugs and susceptibility to diseases are also attributable to the genetic variations. Even though the sequence of human nuclear DNA is 99.9% similar between any two individuals, only 0.1% difference is sufficient for no two individuals to be alike.

## MUTATIONS AND POLYMORPHISM

A change in DNA sequence that is heritable is known as mutation. DNA sequences and genes may vary from person-to-person as a

consequence of mutation. *Allele* refers to the different sequences on a particular location (locus) of the chromosome and each individual has two copies of gene and sequences of both the copies of the gene at a given locus may be similar or different (alleles). A homozygous individual has the same allele on both members of a chromosome pair and the alleles differ in a heterozygote. The genotype refers to the alleles present at a given locus. The locus is said to be polymorphic if it has two or more alleles where the frequency of the minor allele exceeds 1% in a population. Usually such alleles do not produce significant phenotypic effect (these are neutral in effect), but are presumed to be selected/maintained in the population. These can serve as useful genetic markers for mapping disease traits. These variations are also responsible for visible variations between two individuals and also for the variability in susceptibility to various common diseases including infectious diseases.

## Mutation Types

The variations in the human genome may occur at the genomic level as in aneuploidy, at chromosomal level as in translocations/inversions/duplications/deletions, or at the gene level as in point mutations or small deletions/duplications. A germline mutation affects cells that produce gametes and is transmitted from parent to offspring and results in inherited/familial genetic conditions, whereas a somatic mutation is confined to somatic cells and is responsible for cancers or somatic mosaicism.

Mutations in individual genes are classified on the basis of sequence change and its consequence on protein product and its function. Substitution refers to replacement of a single nucleotide by another and is the most common type of mutation. Transition refers to substitution of the same type of nucleotide (i.e., purine by purine, or pyrimidine by pyrimidine nucleotide). The reverse is transversion. Substitutions can result in a synonymous change (silent, with same amino acid retained in the protein product), or a nonsynonymous change of amino acid. Nonsynonymous mutations are missense when the altered amino acid affects protein function or stability, and nonsense when it leads to creation of a stop codon and terminates synthesis of polypeptide chain.

Deletions result from loss of one or more nucleotides. If it occurs in the coding sequence, it may disrupt the reading frame (frame shift mutation), unless the deletion affects nucleotides that are a multiple of three (in frame). Larger deletions involving a part or whole of the gene also occur.

Insertion refers to addition of one or more nucleotides into a gene. Depending on the number of nucleotides inserted, the mutation may cause a shift in the reading frame. Expansion of triplet repeats is a form of insertion.

Substitution, insertion and deletion may affect the splice site, either by activating a cryptic splice site or by abolition of a regular splice site. This may result in exon skipping, retention of intronic sequences and frame shift.

Functionally, a mutation can lead to loss of function of a protein (deletion of some exons of dystrophin gene in Duchenne muscular dystrophy), haploinsufficiency (50% of the protein product is insufficient for normal cellular function as in familial hypercholesterolemia) or gain of function (as in achondroplasia), or rarely a dominant-negative effect where product of mutant gene in heterozygous state results in loss of activity of normal gene product of the corresponding allele as well (osteogenesis imperfecta).

It is important to note that about 85% of the disease causing variations are located in the coding regions, rest are spread in the noncoding regions (introns or regulatory regions).



## GENETIC ALTERATIONS IN DISEASE

The above mutations are illustrated by several common genetic conditions. Down syndrome occurs due to an extra copy of chromosome 21 and Turner syndrome due to lack of second sex chromosome. Cri du chat syndrome occurs due to deletion of a small terminal segment of short arm of chromosome 5. DiGeorge syndrome and Williams syndrome are examples of large deletions that are however beyond the resolution of karyotyping. Beta thalassemia is characterized by several point mutations (missense) in beta globin gene whereas alpha thalassemia commonly occurs due to deletion of a large segment of alpha globin gene. Duchenne muscular dystrophy usually results from large deletions (in about 60% of cases) and rarely from large duplications (in about 10%). All cases of sickle cell disease occur due to a single missense mutation in beta globin gene (valine replacing glutamic acid at sixth position of beta globin chain in any population) and two missense mutations account for almost all cases of achondroplasia (G-to-A transition or G-to-C transversion at nucleotide 1,138 of the *FGFR3* gene resulting in glycine to arginine substitution at 380 amino acid). The most common mutation (accounting for a third of all cases) in cystic fibrosis is a deletion involving a codon [three nucleotides, in cystic fibrosis transmembrane conductance regulator (CFTR)]. Fragile X mental retardation has triplet repeat expansion (CGG) in the *FMR1* gene.

It is very pertinent to note the spectrum of genetic defects which are often unique to the disease and sometimes even to the population or ethnicity (delta F508 is common in Caucasians with cystic fibrosis). A genetic disease can be caused by different mutations in the same gene (beta globin in beta thalassemia) or by mutations in several genes (retinitis pigmentosa, hereditary ichthyosis and hereditary hearing loss). Different diseases or phenotypes can be caused by mutations in a single gene (mutations in *FGFR3* cause achondroplasia, hypochondroplasia, Muenke craniosynostosis, thanatophoric dysplasia; mutations in fibrillin 1 cause Marfan syndrome with tall stature and acromicric dysplasia with short stature). Hence, it is vital to understand the genetic basis of every disease to select a suitable diagnostic test. It is equally important to know the implications of a positive and a negative test result.

### Single Nucleotide Polymorphisms

Single nucleotide polymorphisms (SNPs, also pronounced as snips) refer to single base differences in the DNA sequence, found throughout the human genome with a frequency of about 1 per 1000 bp. Each SNP occurs at a frequency of more than 1% of the population. These are mostly biallelic and occur in both coding and noncoding regions of the genome. They can be easily typed and many sites can be assayed simultaneously by automated techniques. Combination of SNPs can be used to construct haplotypes, or SNP profiles which serve as powerful tools to study linkage, genetic predisposition to multifactorial diseases and pharmacogenetics. More recently, SNP microarrays have been extensively used for genome wide association studies and give information on genetic variations across the genome associated with a multifactorial disease.

### Copy Number Variants

Humans have two copies for any particular segment of DNA on two homologous chromosomes. In some areas, the number of copies of a particular segment varies between two human genomes

(of two individuals). This phenomenon is termed copy number variation (CNV) and more of such CNVs are being uncovered by the use of array comparative genomic hybridization which is being widely used for evaluation of children with intellectual disability. A CNV may vary in size from 1 kb to several mega bases and can occur anywhere in the genome. Usually they result from deletion-duplication events and are heritable. It is estimated that approximately 0.4% of the genome of unrelated people typically differs with respect to copy number. Like any other genetic variation, CNVs have been found to be associated with disease susceptibility and resistance. CNVs can result in having either too many or too few of the dosage sensitive genes, which may be responsible for substantial amount of human phenotypic variability, complex behavioral traits, and disease susceptibility. However, they are usually not fully penetrant.

## HUMAN GENOME PROJECT

Completion of the Human Genome Project is a landmark in medical genetics. It began in 1991 and produced the first draft sequence of the human genome by 2001, ahead of its scheduled date of completion. A completed sequence of human genome was unveiled in 2003. The entire data is now available in the public domain. In addition to sequencing of the entire human genome, the project had several other objectives and areas of work as well: human gene maps and mapping of human inherited diseases, maps of model organisms, development of new DNA technologies, and development of bioinformatics, comparative genomics and functional genomics. The project also had an important component to look into various ethical issues arising out of genome research. The project has provided a map of genetic markers using many thousands of polymorphisms (variations) distributed throughout the genome. The information is getting updated regularly and can be easily accessed through the dedicated websites. As a component of the project, several model organisms have been sequenced and their genes show significant homology to genes in humans and provide an opportunity to study candidate genes for human diseases. These model organisms are also invaluable tools to study expression of genes and function of their protein products in normal development as well as their dysfunction in inherited disorders. The newer techniques (next-generation sequencing) have drastically reduced the time to sequence the entire genome of an individual to few weeks and promise to be of great value in diagnosis of genetic diseases in the clinical laboratories. However, knowing the entire genome has significant ethical and social implications in both research and clinical practice as one is likely to receive information that was not sought in the first place.

## THE GENETIC BASIS OF INHERITANCE

The subsequent chapter will deal on modes of inheritance in greater detail. However, it is important to understand that some genes have a large influence on the phenotype and they exhibit monogenic or single gene or Mendelian inheritance. Their effects sometimes can be influenced by modifier genes or environment, which have a very minor effect. Digenic and oligogenic inheritance suggests a large influence of two or a few genes on the phenotype. Polygenic inheritance is said to occur when a finite number of genes contribute additively to the phenotype. When several genetic and environmental factors play a role to cause the disease, it is termed a multifactorial disease. This is exemplified by sickle cell disease



(monogenic), cleft palate and diabetes mellitus (multifactorial) and measles (environmental) where contribution of genes to the disease phenotype gradually declines and that of environmental factors increases. The phenotypes we actually see are a result of complex interplay between several genetic and environmental factors.

## ANALYSIS OF HUMAN GENOME

Analysis of human genome is vital for diagnosis and assessment of predisposition to genetic diseases. This can be done in several ways. The chromosomes can be counted and their large structural variations (more than 5–10 Mb) can be identified by a karyotype. A specific mutation that is known to cause the disease in question can be identified by either sequencing the region of interest or by targeted mutation analysis (using aptly modified polymerase chain reaction or by using the restriction fragment length polymorphism created by the nucleotide variation). Gene/s known to cause a specific disease can be analyzed by sequencing it/them entirely. If the variation involves a deletion or duplication of a larger area, fluorescence in situ hybridization or chromosomal microarray will be useful strategies. Extensive modification of polymerase chain reactions are widely used for laboratory diagnosis of several genetic diseases. Techniques like multiplex ligation dependent probe amplification can be used not only to detect CNVs, but also other changes at the DNA level.

Currently, next-generation sequencing has gained prominence both as a diagnostic tool in the clinic and research tool in identification of novel genes. The selected genes that are sequenced may be incorporated into a gene-panel (for diseases which have same or similar phenotype). The entire coding region (whole exome that is likely to harbor mutations for about 85% of monogenic diseases) or whole genome may also be sequenced by this technology. They will also be cost-efficient soon and are likely to be the first level of diagnostic test for many of the monogenic disorders.

## IN A NUTSHELL

1. DNA is located in the nucleus and is packaged into 46 chromosomes.
2. A very small amount of DNA is located in the mitochondria that the offspring receives from the mother.
3. Only 1.1% of the genome codes (approximately 22,000 genes) for proteins and rest of the genome is noncoding, but may have some unknown/regulatory role.
4. Deoxyribonucleic acid is transcribed to mRNA which is then translated to polypeptides. Polypeptides undergo several modifications to form structural and functional units of the cell.
5. Variations in the DNA sequence are likely to contribute normal variation between two individuals and are termed polymorphisms.
6. Mutations are rare sequence variations and are likely to alter the quantity or quality of the protein that the gene codes for.
7. Monogenic diseases are caused by genes of large effect on the phenotype whereas polygenic and multifactorial diseases have sequence variations in genes with small effect.
8. Phenotypes are influenced by genetic as well as nongenetic (environmental) factors.
9. Recent advances in understanding of human genome and sequencing technologies promise an exciting era of clinical genetics practice applicable to all fields of medicine.

## MORE ON THIS TOPIC

- Collins FS, McKusick VA. Implications of the Human Genome Project for medical science. *JAMA*. 2001;285:540-4.
- Ku CS, Cooper DN, Polychronakos C, et al. Exome sequencing: dual role as a discovery and diagnostic tool. *Ann Neurol*. 2012;71:5-14.
- McCarthy MI, Hirschhorn JN. Genome-wide association studies: potential next steps on a genetic journey. *Hum Mol Genet*. 2008;17:R156-65.
- Phadke SR. *Genetics for Clinicians*. Bangalore: Prism Books Pvt Ltd; 2007.
- Strachan T. *Genetics and Genomics in Medicine*. Oxford: Garland Science; 2014.

## Chapter 2.2

# Patterns of Inheritance

Prajnya Ranganath, Shubha R Phadke

The gene, the basic molecular and functional unit of heredity, is essentially a sequence of nucleotides within the chromosome. The position of a gene on a chromosome is called a locus and the alternate forms of a gene at a given locus are called *alleles*. Each human somatic cell has a diploid number of chromosomes, i.e., 22 pairs of autosomes and one pair of sex chromosomes. Therefore, every individual has two copies of a gene, one on each of a homologous pair of chromosomes. An individual may be *homozygous* (both copies identical) or *heterozygous* (different alleles on two chromosomes) at any given locus. Of the two alleles of a gene in an individual, the one which is expressed phenotypically is called the *dominant allele*. The *recessive allele* is expressed only when it is present in a homozygous state.

Genetic disorders are conditions that result from mutations in genes, a *mutation* being a random heritable change in the nucleotide sequence of a gene. A genetic disorder that results from mutation in one or both alleles of a single gene is called a *monogenic or single-gene disorder*, while one that results from a combination of multiple genetic and environmental influences is called a *multifactorial disorder*.

Patterns of inheritance were first elucidated by Gregor Mendel, the Austrian monk referred to as the Father of Genetics, through his hybridization experiments on garden peas. He formulated the Mendel's laws of heredity—the law of segregation and the law of independent assortment—based on his observations. Later, with improved understanding of human genetics, it was found that unifactorial inheritance of single-gene disorders follows the same principles outlined by Mendel and unifactorial or monogenic inheritance became synonymous with *Mendelian inheritance*. Mechanisms of inheritance which do not follow the Mendelian principles are referred to as *non-Mendelian types of inheritance*. Patterns of Mendelian inheritance and common non-Mendelian genetic mechanisms are listed in **Table 1**. A good and comprehensive pedigree provides a very good clue to the pattern of inheritance of a genetic disorder in a family.

**Table 1** Mendelian and non-Mendelian patterns of inheritance

Mendelian inheritance patterns	Non-Mendelian mechanisms
<ul style="list-style-type: none"> <li>Autosomal dominant inheritance</li> <li>Autosomal recessive inheritance</li> <li>X-linked inheritance               <ul style="list-style-type: none"> <li>X-linked recessive</li> <li>X-linked dominant</li> </ul> </li> <li>Y-linked inheritance</li> </ul>	<ul style="list-style-type: none"> <li>Trinucleotide repeat expansion</li> <li>Mitochondrial inheritance</li> <li>Genomic imprinting</li> <li>Uniparental disomy</li> <li>Mosaicism (somatic and gonadal)</li> <li>Oligogenic inheritance</li> <li>Multifactorial inheritance</li> </ul>

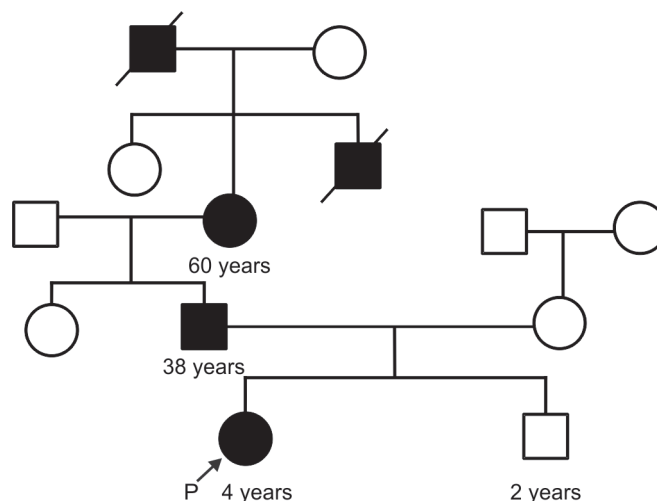
## MENDELIAN INHERITANCE

### Autosomal Dominant Inheritance

#### Case 1

P, a 4-year-old female child, was brought for evaluation of generalized tonic-clonic seizures. On examination, she was found to have around ten café-au-lait spots distributed over her trunk and

limbs and Lisch nodules in both eyes. Her father was also found to have multiple café-au-lait spots in addition to multiple cutaneous neurofibromas all over his body, optic gliomas and scoliosis. There was history of similar skin lesions and cutaneous swellings in the paternal grandmother and some more paternal relatives (**Fig. 1**). MRI brain revealed abnormal signal intensities in the basal ganglia and brain stem. A diagnosis of neurofibromatosis type 1 (von Recklinghausen disease) was made and the family was counseled accordingly.



**Figure 1** Pedigree of Case 1 showing affected members in each generation

Neurofibromatosis type 1 is a classic example of an autosomal dominant disorder. As can be seen from the given pedigree, multiple generations of the family are affected, there is a vertical transmission of the condition from one generation to the next and both male and female individuals are affected in the family. Phenotypic manifestations of the disorder are seen even in heterozygous individuals, i.e., with mutation in just one copy of the gene. The chance of an affected parent transmitting the disease-causing mutant allele to each of his/her offspring is 1 in 2 and therefore the risk of recurrence of the condition in each offspring of an affected individual (irrespective of the sex of the transmitting parent or of the offspring) is 50%. The principles of inheritance of autosomal dominant disorders are listed in **Box 1**. Other examples of disorders which show an autosomal dominant pattern of inheritance are achondroplasia, tuberous sclerosis, Marfan syndrome, hereditary spherocytosis and familial hypercholesterolemia.

#### BOX 1 Principles of inheritance of autosomal dominant disorders

- Only one copy of the abnormal gene is required to produce a phenotype
- Affected individual has an affected parent (usually)
- Passed from one generation to the next (vertical transmission)
- Both males and females are equally affected
- Disorder may be transmitted to offspring of either sex
- Risk of recurrence in offspring of an affected individual is 50%.

In the case mentioned here, the child had seizures in addition to café-au-lait spots and Lisch nodules, her father had café-au-lait spots, cutaneous neurofibromas, optic gliomas and scoliosis and her paternal grandmother had café-au-lait spots and cutaneous neurofibromas. Thus, the clinical manifestations of the condition

were variable with a different set of clinical features being seen in each of the affected family members. This variation in clinical features of the same disorder in different affected individuals (sometimes even within members of the same family) is called *variable expressivity*. Another classical example of an autosomal dominant condition which displays marked clinical variability is tuberous sclerosis, wherein manifestations in affected members of even the same family can range from just cutaneous pigmentary lesions (hypomelanotic macules, shagreen patches and facial angiofibromas) with normal intellect to infantile spasms/hypsarrhythmia syndrome and severe intellectual disability. For some autosomal dominant genetic disorders, phenotypic manifestations of the disease may not be seen in some individuals, in spite of them having the disease-causing mutation. This phenomenon is called *reduced penetrance* and it is responsible for the apparent *skipping of a generation* of certain dominant genetic traits or disorders, wherein an individual has an affected parent and an affected offspring, but is phenotypically normal. Penetrance of a genetic disorder is calculated as the proportion of individuals with a disease-causing genetic mutation who express the disease phenotype to the total number of individuals with the mutation. Examples of disorders with reduced penetrance include familial cancer syndromes. Variable expressivity and reduced penetrance are believed to result from the influence of other genetic and environmental factors that modify the phenotypic expression of the primary disease-causing gene mutation.

Like neurofibromatosis type 1, many genetic disorders affect multiple body systems with varied manifestations. This phenomenon wherein a single gene mutation results in multiple phenotypic manifestations involving different body systems is called *pleiotropy* and it is usually due to the involvement of the gene in a common metabolic/signaling pathway(s) present in the different body systems.

In many cases, the disorder may result from a mutation that has occurred newly in the affected individual rather than being inherited from a parent. Such a newly arisen mutation is called a *de novo mutation* and it occurs in the gamete (sperm or egg cell) or just after fertilization. In such cases, the affected individual would have normal parents, normal siblings and no affected relative in the previous generations. However, the risk of recurrence of the disease in his/her offspring would be 50%, as per the principles of autosomal dominant inheritance. Increase in paternal age has been noted to be associated with an increased risk of de novo mutations associated with some autosomal dominant disorders such as neurofibromatosis type 1, achondroplasia, Marfan syndrome and Crouzon syndrome. Increased mutability during spermatogenesis and accumulation of mutations in the sperm cell with age as well as possibility of the mutations conferring a survival advantage to the sperm cells have been postulated as possible mechanisms underlying this phenomenon.

There is another situation where an individual can have an autosomal dominant disorder without the disease being present in either parent or any of the preceding generations. This is a condition called *gonadal or germline mosaicism*, wherein the disease-causing mutation is present in only a proportion of the gonadal cells in a parent. As the mutation is not present in the somatic cells of the parent, the parent will be clinically normal and his/her blood DNA will also test negative for the mutation. If the egg or sperm cell is derived from the mutation-bearing gonadal precursor cell, the zygote and the resultant offspring will be affected with the disease. Gonadal mosaicism is difficult to demonstrate because only some of the germ cells in the parent carry the mutation and it is inferred when more than one offspring is born with an autosomal dominant disorder, in spite of both parents and previous generations being

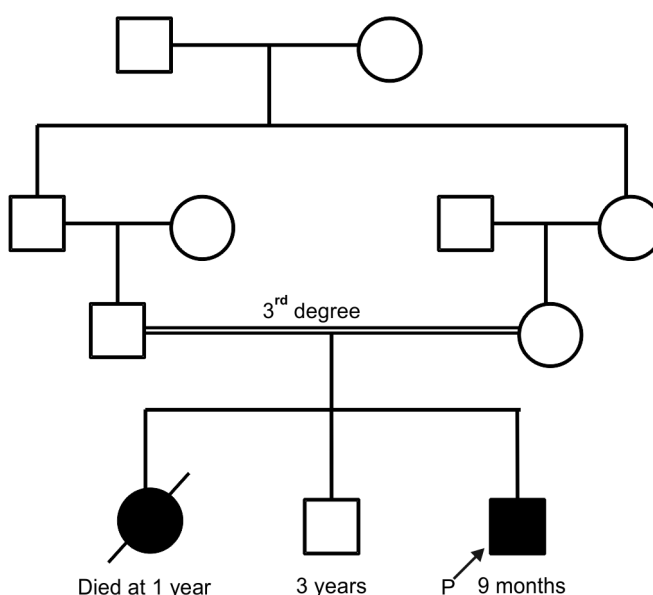
normal (as the same mutation cannot occur de novo in two or more offspring). The phenomenon of gonadal mosaicism should always be borne in mind while counseling a normal couple with one affected child, about the recurrence risk in future offspring; one might assume that the affected child has a de novo mutation as there are no other affected members in the family and give a negligible risk of recurrence, while in fact it might be a case of gonadal mosaicism with a significant recurrence risk. Exact recurrence risks cannot be usually predicted for cases with germline mosaicism, but empiric risks can be derived for each disorder based on previous case reports.

Sometimes, both alleles of a gene may be dominant and may get phenotypically expressed as with the AB blood group; this is referred to as *co-dominance*. The molecular mechanisms underlying autosomal dominant disorders include haploinsufficiency (wherein the protein function is dosage dependent and disease occurs because the mutation reduces the amount of functional protein to half of the normal amount, e.g., Marfan syndrome), dominant negative effect (wherein the mutant allele product interferes with the function of the normal allele product, e.g., some forms of osteogenesis imperfecta caused by mutations in *COL1A1* or *COL1A2* genes) and gain of function (mutation leads to increase of protein function or imparts a new function to the protein product, e.g., achondroplasia).

## Autosomal Recessive Inheritance

### Case 2

R, a 9-month-old male infant, was brought for evaluation of severe chronic anemia with hepatosplenomegaly. He had received a blood transfusion at 6 months of age. He was the third offspring of third degree consanguineous parents and his elder sister had died at 1 year of age due to severe anemia (Fig. 2). His hemogram showed severe microcytic, hypochromic anemia (hemoglobin of 4 g/dL) and hemoglobin electrophoresis revealed markedly elevated fetal hemoglobin (95.7%). Hemoglobin electrophoresis of both parents showed elevated hemoglobin A<sub>2</sub> (>3.5%) suggesting  $\beta$ -thalassemia carrier status. A diagnosis of  $\beta$ -thalassemia major was made and the parents were counseled accordingly.



**Figure 2** Pedigree of Case 2 characteristic of autosomal recessive inheritance

Beta-thalassemia major, one of the most common genetic disorders in India, is an autosomal recessive disorder. As in the given case scenario, one or more individuals in the same generation are affected, while members of previous generations are usually clinically normal. Phenotypic manifestations of the disease are seen only in individuals with mutations in both copies of the disease-associated gene. If mutations in both alleles of the gene are identical, the individual is said to be *homozygous*, whereas if the two mutations (one on each allele of the gene) are different, the individual is said to be *compound heterozygous*. Parents of affected individuals, though usually asymptomatic, are obligate carriers, i.e., each of them has one mutant allele and one normal allele. As the chance of each offspring of carrier parents getting both mutations (one from each parent) is 1 in 4, the risk of recurrence of the disorder in siblings of affected individuals (irrespective of the sex) is 25%. If one parent is affected (homozygous or compound heterozygous) and the other is a carrier (heterozygous), the possibility of the offspring getting the affected parent's mutation is 1 and of getting the carrier parent's mutation is 1 in 2. The risk of recurrence of the condition in the offspring in this scenario increases to 50% ( $1 \times \frac{1}{2}$ ). In such cases, the pedigree will look like that of an autosomal dominant disorder and therefore, the phenomenon is referred to as *pseudodominance*.

The principles of autosomal recessive inheritance are enumerated in **Box 2**. Other examples of autosomal recessive disorders include sickle cell anemia, oculocutaneous albinism, most inborn errors of metabolism, spinal muscular atrophy and cystic fibrosis. Most autosomal recessive conditions occur due to the *loss of function* mechanism, i.e., mutations on both alleles of the gene result in significant reduction in the amount or function of the protein product.

#### BOX 2 Principles of inheritance of autosomal recessive disorders

- Both copies of a gene should be mutated to produce disease phenotype
- Parents of an affected individual, though usually asymptomatic, are obligate carriers
- Horizontal pedigree pattern with one or more siblings affected
- Both males and females are equally affected
- Parental consanguinity increases the risk of autosomal recessive disorders in offspring
- Risk of recurrence in siblings is 25%.

Sometimes, mutations in different genes can produce the same phenotype, i.e., the phenotypic manifestations of mutations in Gene A may be the same as those of mutations in Gene B. This phenomenon of more than one gene being associated with the same phenotype is called *locus heterogeneity*. Classic examples of disorders with locus heterogeneity include sensorineural deafness and retinitis pigmentosa. An individual who is a heterozygous carrier of a mutation in two different genes is called a *double heterozygote*. Double heterozygotes for recessive mutations do not manifest the disease even if the mutations are associated with the same phenotype. This explains why sometimes even when both the husband and wife are affected with genetic sensorineural deafness, their offspring may be normal. If the husband has mutations on both alleles of one deafness-associated gene and the wife has mutations on both alleles of a different deafness-associated gene, each offspring will be a double heterozygote (carrier of a mutation on only one allele of each of the two genes) and will therefore be phenotypically normal.

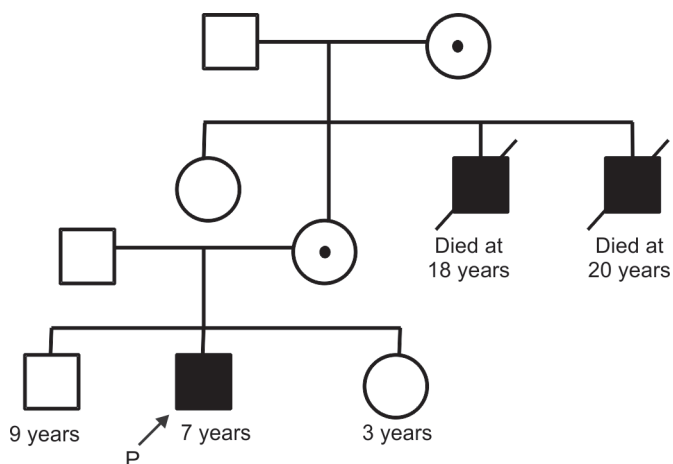
*Consanguinity*, mating between blood relatives, increases the risk of autosomal recessive disorders in the offspring but is not the sole responsible factor. Absence of consanguinity does not rule out the possibility of a condition being autosomal recessive;

likewise, presence of consanguinity does not necessarily imply that the condition has a recessive inheritance. Autosomal recessive disorders, especially those which have a relatively higher carrier frequency in the general population (e.g.,  $\beta$ -thalassemia in India and the Mediterranean countries and cystic fibrosis in Western Europe) are more likely to occur because of a chance mating between two unrelated carriers. However, consanguinity does contribute to a higher incidence of rare autosomal recessive disorders and the risk of autosomal recessive disorders in offspring of consanguineous couples is around one and a half times more than that of nonconsanguineous couples. When the husband and wife are related, the likelihood of both, being carriers of the same gene mutation increases, due to their descent from a common ancestor. Consanguinity is measured by the *coefficient of inbreeding* which is the proportion of loci at which a person is homozygous for an allele from the same ancestral source. Another entity which increases the risk of autosomal recessive disorders is *inbreeding*, wherein individuals from a small population tend to choose their mates from the same population for cultural, geographic or religious reasons.

### X-Linked Inheritance

#### Case 3

S, a 7-year-old male child, presented with a history of difficulty in getting up from sitting and squatting positions and in climbing stairs since 5 years of age. On examination, he was found to have a waddling gait, proximal muscle weakness, positive Gower's sign and bilateral calf muscle hypertrophy. His serum creatine phosphokinase was 4,080 U/L. Parents gave history of similar illness in two maternal uncles both of whom had become wheelchair-bound by around 12–13 years of age and had died at around 18 years and 20 years, respectively (pedigree shown in **Figure 3**). Genetic testing of the Duchenne muscular dystrophy (DMD) gene revealed a deletion mutation and the diagnosis of DMD was confirmed. The parents were counseled accordingly.



**Figure 3** Pedigree of Case 3 showing X-linked inheritance

Duchenne muscular dystrophy is a genetic disorder with an X-linked recessive inheritance pattern. For any X-linked recessive disorder, all male members of the family with the gene mutation are clinically affected, while female members are just carriers of the mutation and are mostly normal or are only mildly affected. This is because males have only one copy of the X-linked gene, i.e., they are *hemizygous*. As is evident from the given pedigree, X-linked recessive disorders show an oblique or *knight's move* transmission



pattern, wherein an affected male in a family is often found to have similarly affected maternal uncles. Male to male transmission does not occur, because the X chromosome in a male is always of maternal origin. All affected males in a family are related through carrier female relatives.

The principles of X-linked recessive inheritance are listed in **Box 3**. Other examples of disorders with X-linked recessive inheritance include hemophilia A, hemophilia B, Hunter syndrome, Fabry disease, and glucose-6-phosphate dehydrogenase deficiency.

Like autosomal dominant conditions, X-linked disorders can also result from de novo mutations; about one third of all DMD cases result from de novo mutations in the *DMD* gene. Gonadal mosaicism is also seen in X-linked disorders. The empiric risk of recurrence of DMD in male siblings of an affected boy due to gonadal mosaicism in the mother is around 15%. All these entities have to be considered when counseling a family about the recurrence risks. If the mother is a carrier for an X-linked recessive mutation, the risk for each of her male offspring being affected would be 50% and the chance of each of her female offspring being a carrier would be 50%. If however, the couple presents with only one affected male child, without a history of any other family member being affected, the recurrence risk in future male offspring can vary from 0% to up to 50%, depending upon whether it is a de novo mutation, a case of gonadal mosaicism or a maternally inherited mutation. If a male individual is affected with an X-linked recessive disorder, all of his daughters will be carriers but none of his sons will be at risk of being affected.

The other set of disorders that occur due to mutations on X-linked genes are the X-linked dominant disorders. Like dominant mutations on autosomal genes, dominant mutations on X-linked genes are also expressed in heterozygotes and therefore heterozygous females as well as hemizygous males are affected. However, due to the phenomenon of *lyonization* (random inactivation of one of the two X chromosomes in each cell in females), females are usually less severely affected than males. Some of the X-linked dominant disorders, such as Rett syndrome and Aicardi syndrome, have very severe manifestations in males leading to death in the antenatal/perinatal period and are compatible with survival only in females; for such disorders the pedigree will show only affected female members with intrauterine demise/stillbirths of male fetuses. An affected father will transmit the disorder to all his daughters but to none of his sons as male to male transmission of X-linked mutations does not occur. An affected mother will transmit the disorder to 50% of her sons and 50% of her daughters. The principles of X-linked dominant inheritance are listed in **Box 3**. Few more examples of X-linked dominant disorders are X-linked hypophosphatemic rickets (vitamin D resistant rickets), incontinentia pigmenti, orofaciocigital syndrome type 1, Goltz syndrome (focal dermal hypoplasia) and Melnick-Needles syndrome.

Several X-linked disorders, such as fragile X syndrome and ornithine transcarbamylase deficiency (a type of urea cycle defect), cannot be strictly categorized as X-linked recessive or dominant conditions, because they have very variable expression in female individuals. Phenotypic expression of X-linked disorders in females may depend upon a number of factors such as skewed X-inactivation (more of either mutation-free or mutation-bearing cells becoming inactivated instead of around 50–50 random inactivation) and somatic mosaicism. These can lead to manifestations of X-linked recessive disorders and suppression of the phenotype of X-linked dominant conditions in females. Therefore, it has been suggested that the terms *recessive* and *dominant* should not be used and all disorders caused by X-linked genes should be said to have *X-linked inheritance*.

### BOX 3 Principles of inheritance of X-linked disorders

- Disease caused by mutation in gene on X chromosome
- No male to male transmission

#### *X-linked recessive*

- Mostly males affected; carrier females are usually normal or only mildly affected
- Affected males in a family are always related to each other through carrier females
- For a carrier mother, risk of male offspring being affected is 50% and chance of female offspring being carrier is 50%
- For an affected father, risk of male offspring being affected is zero and chance of female offspring being carrier is 100%.

#### *X-linked dominant*

- Both males and females are affected but males usually have a more severe phenotype
- Some disorders are perinatally lethal in males and compatible with survival only in females; disease phenotype is seen only in females
- For an affected mother, risk of male offspring being affected is 50% and risk of female offspring being affected is 50%.

## Y-Linked Inheritance

Y-linked disorders would involve genes on the Y chromosome and therefore would affect only males and be transmitted from an affected male individual to all his sons and none of his daughters. Till date, no single-gene disorder has been identified to have Y-linked inheritance. *Hairy ears* and a type of deafness (Y-linked deafness) were believed to be associated with genes on the Y chromosome, but studies disproved this.

Y chromosome microdeletions involving the azoospermia factor regions that result in azoospermia/oligospermia and consequent male infertility show a Y-linked Mendelian inheritance-like pattern. These microdeletions can be transmitted from an affected male to his male offspring, if his sperms are used in assisted reproductive techniques such as intracytoplasmic sperm injection.

## NON-MENDELIAN INHERITANCE

### Trinucleotide Repeat Disorders

*Trinucleotide repeats* are stretches of repeats of three nucleotide sequences (such as CAG or CGG) which are normally present in some genes, within the exon, intron, 5' untranslated region or 3' untranslated region. When there is *repeat expansion*, i.e., increase in the number of repeats beyond the normal stable level or threshold, the disease occurs. There can be further expansion in the number of repeats during gametogenesis resulting in the affected offspring having a larger repeat number compared to the affected transmitting parent. This is why these mutations are called *dynamic mutations*. The increasing number of repeats leads to increasing severity and earlier onset of the disease in successive generations—a phenomenon known as *anticipation*, which is the hallmark of trinucleotide repeat disorders. For some disorders, the number of repeats can increase so much during gametogenesis that the offspring can get a very severe form of the disease, e.g., expansion of the CAG repeats in the Huntington disease (*HD*) gene during male gametogenesis can result in juvenile HD in the offspring of an affected male and expansion of the CTG repeats in the dystrophin myotonia-protein kinase (*DMPK*) gene during female gametogenesis can result in congenital myotonic dystrophy in the offspring of an affected female. **Table 2** lists some of the more common trinucleotide repeat disorders. Disorders are known to occur due to expansion of tetranucleotide repeats (e.g., CCTG repeat expansion in *ZNF9* gene in myotonic dystrophy type 2) and of other complex repeat motifs also.



**Table 2** Trinucleotide repeat disorders

Disorder	Inheritance	Gene	Trinucleotide repeat	Location of repeat
Fragile X mental retardation	X-linked	<i>FMR1</i>	CGG	5' UTR
Myotonic dystrophy	AD	<i>DMPK</i>	CTG	3' UTR
Huntington disease	AD	<i>HD</i>	CAG	Exon
Spinocerebellar ataxia	AD	<i>ATXN1</i> , <i>ATXN2</i> , <i>ATXN3</i> , <i>ATXN7</i> , etc.	CAG	Exon
Friedreich ataxia	AR	<i>FXN</i>	GAA	First intron
Spinobulbar muscular atrophy	X-linked	<i>AR</i>	CAG	Exon

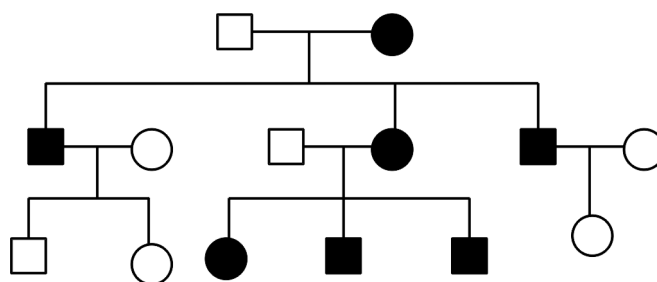
Abbreviations: AD, autosomal dominant; AR, autosomal recessive; UTR, untranslated region.

### Mitochondrial Inheritance

Disorders caused by mutations in genes in the mitochondrial genome show a mitochondrial inheritance pattern. Each cell has a few to several thousand mitochondria within it and each mitochondrion contains dozens of copies of the mitochondrial genome. Each mitochondrial genome is circular, is made up of around 16.5 kb of DNA and has 37 genes within it (of which 22 code for transfer RNAs, 2 code for ribosomal RNAs and 13 code for protein subunits of enzyme complexes of the oxidative phosphorylation system).

Mitochondrial mutations may be inherited or they may be acquired and accumulate during mitotic cell divisions. A given mutation may be present in only some of the mitochondrial genomes within a mitochondrion and in only a proportion of the mitochondria within a cell, leading to a heterogeneous population within an individual, within a tissue, within the same cell and even within the same mitochondrion, a condition referred to as *heteroplasmy*. If the mutation is present in all or at least a majority of the mitochondrial genomes of an individual, the condition is called *homoplasmy*. Expression of a mitochondrial disorder in an individual and in each body tissue occurs only when the number of mutated mitochondrial genomes in that tissue exceeds a baseline, a phenomenon referred to as *threshold expression*. In addition, there is a rapid change in the heteroplasmy levels between generations and a heteroplasmic state produced by new mutations arising in the female germline is usually transient and resolves itself within a few generations; this is attributed to the *mitochondrial genetic bottleneck* hypothesis. As per this hypothesis, only a limited number of mitochondrial DNA (mtDNA) templates are used during gametogenesis and there is several fold amplification of mtDNA copy number accompanying the maturation of the primary to the preovulatory oocyte, reducing the effective number of mtDNAs that contribute to the next generation.

A typical pedigree associated with an inherited mitochondrial disorder is shown in **Figure 4**. As only the egg cell contributes mitochondria to the zygote, the mitochondrial mode of inheritance is strictly maternal and affected males do not pass on the mutation to their offspring. However, the proportion and distribution of abnormal mitochondrial genomes can vary remarkably, resulting in great variability in the clinical severity amongst the affected individuals in a family. The phenomena of heteroplasmy and mitochondrial genetic bottleneck make prediction of disease

**Figure 4** Pedigree of an inherited mitochondrial disorder

severity, counseling for risk of recurrence in offspring/siblings of affected cases and phenotypic prognostication of prenatally detected mitochondrial mutations difficult.

Some disorders caused by mutations in the mitochondrial genome include Leber hereditary optic neuropathy, chronic progressive external ophthalmoplegia, some types of Leigh disease, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes syndrome, myoclonic epilepsy with ragged red fibers syndrome, Kearns-Sayre syndrome and neuropathy, ataxia and retinitis pigmentosa syndrome. Mitochondrial diseases usually affect organs with greater energy utilization and with greater rates of oxidative phosphorylation, e.g., muscles, brain, eyes, heart and endocrine organs and possibility of a mitochondrial etiology should be suspected in any multisystemic disorder, especially involving these systems.

### Imprinting Related Disorders

*Genomic imprinting* refers to the differential expression of alleles of certain genes based upon their parental origin. For such genes, only one of the two alleles, either the paternally derived one or the maternally derived one, would be actively expressed, while the other allele would be silenced through epigenetic mechanisms such as methylation. Therefore, a mutation will have phenotypic effects only if it is present on the active allele but not if it is on the silenced allele. For example, if for a given gene the maternally derived allele is imprinted, then a female affected with a disease-causing mutation in that gene will have phenotypic manifestations of the disorder but her offspring who inherit the mutation from her will not be affected. Some disorders associated with imprinted genetic loci are listed in **Table 3**.

### Uniparental Disomy

Normally, of the two homologues of each chromosome in an individual, one is derived from the father and one from the mother. Occasionally, both the chromosomes may be derived from the same parent, a condition referred to as *uniparental disomy*. Further, if both chromosomes are derived from a single chromosome of a parent and are identical it is called *uniparental isodisomy*, and if the two chromosomes are derived from both of the homologous pair of chromosomes of the parent, it is called *uniparental heterodisomy*. Uniparental disomy at an imprinted locus can result in an imprinting-related disorder as mentioned above, as both the chromosomes would be derived from the parent whose allele is silenced. In addition, uniparental isodisomy of a recessive mutation-bearing allele from a carrier parent would result in homozygosity for the mutation and thereby disease in the offspring even when the other parent is not a carrier for a mutation in that gene.

### Mosaicism

The presence of two or more genetically distinct cell lines in an individual, all of which are derived from a single zygote, is referred

**Table 3** Disorders associated with imprinted genetic loci

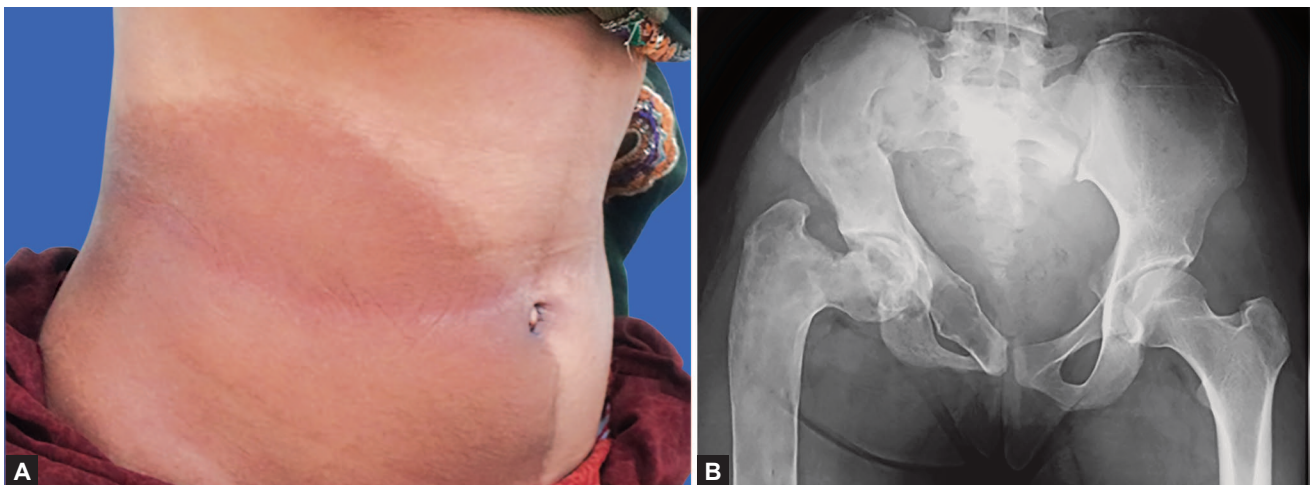
Disease	Chromosomal locus	Genetic alterations
Prader-Willi syndrome	15q11-q13	<ul style="list-style-type: none"> <li>• Deletion of paternal-origin 15q11-q13</li> <li>• Uniparental disomy of maternal-origin 15q11-q13</li> <li>• Imprinting center mutations</li> </ul>
Angelman syndrome	15q11-q13	<ul style="list-style-type: none"> <li>• Deletion of maternal-origin 15q11-q13</li> <li>• Uniparental disomy of paternal-origin 15q11-q13</li> <li>• Imprinting center mutations</li> <li>• Mutation in the maternal-origin allele of <i>UBE3A</i> gene</li> </ul>
Beckwith-Wiedemann syndrome	11p15.5	<ul style="list-style-type: none"> <li>• Imprinting center mutations</li> <li>• Uniparental disomy of paternal-origin 11p15.5</li> <li>• Deletion of maternal-origin 11p15.5 or duplication of paternal-origin 11p15.5</li> <li>• Mutation in the maternal-origin allele of <i>CDKN1C</i> gene</li> </ul>
Russell-Silver syndrome	7p11.2 and 11p15.5	<ul style="list-style-type: none"> <li>• Imprinting center mutations</li> <li>• Uniparental disomy of maternal-origin 7p11.2</li> <li>• Hypomethylation of imprinting center on paternal origin chromosome 11p15.5</li> </ul>
Pseudohypoparathyroidism type 1	20q13.2	<ul style="list-style-type: none"> <li>• Uniparental disomy of paternal-origin 20q13.2</li> <li>• Imprinting center mutations</li> <li>• Microdeletions near <i>GNAS</i> disrupting methylation</li> <li>• Mutation in the maternal-origin allele of <i>GNAS</i> gene</li> </ul>

to as *mosaicism*. Mosaicism usually results from a postzygotic mutation event, wherein one or more of the early embryonic cells acquire a mutation, which gets passed on to all the subsequent populations of cells derived from that precursor cell. Distribution of genetically distinct cell lines in different body tissues is called *somatic mosaicism*. Disorders with somatic mosaicism may show a mosaic or patchy involvement of tissues, e.g., patches or streaks of skin pigmentation changes, asymmetric overgrowth, focal bony lesions, etc. (**Figs 5A and B**). Tissue biopsy from affected sites will show a greater proportion of cells with the mutation while biopsy from normal appearing sites will have mostly genetically normal cells. An individual with somatic mosaicism will have normal parents. If the mutation is confined to somatic cells and does not affect any gonadal cells, his/her offspring will also be normal. Examples include McCune-Albright syndrome (somatic mosaicism of mutations in the *GNAS* gene) and Proteus syndrome (somatic mosaicism of *AKT1* gene mutations). Proteus syndrome-associated *AKT1* gene mutation can exist only in the somatic

mosaic form because if the mutation were to be present in all the cells of the embryo, it would be lethal.

### Oligogenic Inheritance

While monogenic disorders have been classically described to be caused by mutations within a single gene, of late some so called Mendelian disorders have been found to be caused by simultaneous mutations within two or more loci, a phenomenon referred to as *oligogenic inheritance* (*oligogenic* meaning caused by a few genes). For example, though Bardet-Biedl syndrome has been classically described to have an autosomal recessive inheritance pattern, in some cases it has been found that an individual with mutations in both alleles of the *BBS2* gene may not manifest the disorder unless there is a mutation present in at least one allele of a second gene, i.e., *BBS6*. The different genes involved in oligogenic inheritance are believed to have synergistic/modifier effects on each other. Other disorders reported to have oligogenic inheritance include one type of retinitis pigmentosa



**Figures 5A and B** (A) Large hyperpigmented patch on the abdomen; (B) Focal fibrous dysplasia involving the right pelvis and right femur in a girl with McCune-Albright syndrome

(*ROM1* and *RDS* gene related) and Hirschsprung disease (*RET* gene with other loci).

### Multifactorial Inheritance

Disorders which are caused by a complex interaction of many different genes and environmental influences are called *multifactorial disorders*. Individual alleles involved in the causation of multifactorial disorders may individually follow any of the Mendelian or non-Mendelian inheritance patterns described above, but the disorder per se, which is a composite manifestation of the different alleles, follows a complex inheritance called *multifactorial inheritance*. Multifactorial disorders include congenital malformations, such as neural tube defects, cleft lip, cleft palate and congenital hypertrophic pyloric stenosis, as well as adult onset disorders such as diabetes mellitus and coronary artery disease.

Characteristics of multifactorial inheritance are as follows: (i) the probability of an affected offspring increases with increase in the number of predisposing risk alleles in the parents; (ii) the risk to relatives decreases as the relationship to the index case becomes more distant (therefore first degree relatives have the highest risk); (iii) the recurrence risk is higher when more than one family member is affected; (iv) the risk of recurrence in relations increases with increase in the severity of the disease in the index case; and (v) for a disorder which exhibits a marked difference in incidence with sex, if the less frequently affected sex is affected, the risk of recurrence is higher in members of the more frequently affected sex in the family (e.g., for congenital hypertrophic pyloric stenosis, the incidence is much higher in male infants compared to female infants; therefore, if a female infant is affected in a family, the risk of recurrence of the malformation in males in the family would be much higher).

### CONCLUSION

Thorough understanding of the patterns of inheritance is essential for appropriate genetic counseling of patients and families with genetic disorders. Once the pattern of inheritance is known, one can predict the risk of recurrence of the disorder in offspring, siblings and other relatives of the index case and offer appropriate interventions such as prenatal diagnosis and presymptomatic diagnosis. Knowledge of the inheritance patterns of diseases also helps in identifying their causative genes through techniques like linkage analysis, homozygosity mapping and more recently whole exome/whole genome sequencing. However, while the classical textbook descriptions of Mendelian and non-Mendelian inheritance patterns are still relevant and useful especially in the clinical setting, the strict distinction between monogenic and

multifactorial diseases is gradually getting blurred with elucidation of newer non-Mendelian forms of inheritance and better understanding of modifier genes. Phenomena like oligogenic inheritance, reduced penetrance and variable expressivity suggest that even the so called monogenic disorders are significantly influenced by other genes and environmental factors. As our understanding of molecular mechanisms of genetic diseases improves, conventional concepts about inheritance patterns are likely to significantly change in the future.

### IN A NUTSHELL

1. Mendelian inheritance patterns, i.e., the patterns of inheritance which follow Mendelian laws of heredity, include autosomal dominant, autosomal recessive, X-linked and Y-linked inheritance.
2. Monogenic disorders follow Mendelian patterns of inheritance.
3. Autosomal dominant disorders show vertical transmission, with a 50% risk of recurrence in each offspring of an affected individual.
4. Autosomal recessive disorders have a recurrence risk of 25% in each offspring of carrier parents.
5. X-linked recessive disorders have a recurrence risk of 50% in each male offspring of a carrier mother and do not have male to male transmission.
6. Non-Mendelian mechanisms of inheritance include trinucleotide repeat expansion, mitochondrial inheritance, genomic imprinting, uniparental disomy, mosaicism, oligogenic inheritance and multifactorial inheritance.

### MORE ON THIS TOPIC

- Bachmann N, Bergmann C. Epigenetics and imprinting. *Arch Pediatr*. 2012;19:1145-7.
- Bamshad MJ, Ng SB, Bigham AW, et al. Exome sequencing as a tool for Mendelian disease gene discovery. *Nat Rev Genet*. 2011;12:745-55.
- de Sanctis L, Delmastro L, Russo MC, et al. Genetics of McCune-Albright syndrome. *J Pediatr Endocrinol Metab*. 2006;19 Suppl 2:577-82.
- La Spada AR, Taylor JP. Repeat expansion disease: progress and puzzles in disease pathogenesis. *Nat Rev Genet*. 2010;11:247-58.
- Nussbaum R, McInnes RR, Willard HF. Patterns of single-gene inheritance. In: Nussbaum R, McInnes RR, Willard HF. *Thompson and Thompson Genetics in Medicine*. 7<sup>th</sup> ed. Philadelphia: Elsevier Saunders; 2007. pp. 115-50.
- Schäffer AA. Digenic inheritance in medical genetics. *J Med Genet*. 2013;50: 641-52.
- Turnpenny P, Ellard S. Patterns of inheritance. In: Turnpenny P, Ellard S. *Emery's Elements of Medical Genetics*. 14<sup>th</sup> ed. Philadelphia: Churchill Livingstone Elsevier; 2012. pp. 109-28.



## Chapter 2.3

# Clinical Dysmorphology: An Approach to Bedside Diagnosis

Ratna Dua Puri

Every pediatrician at some time or the other is involved in the diagnosis of a child with abnormal physical features. This article deals with the approach to diagnosis of syndromes associated with developmental abnormalities of body structure.

David Smith defined *dysmorphology* in 1966 as a study of abnormality of body structure that originates before birth. Hall BD described this expertise as a clinical skill, an inexpensive visual diagnostic modality that can be acquired by all who so desire. Reardon and Donnai in their review note that no branch of science offers as much opportunity, challenge and excitement as is there in the diagnosis of a rare disorder or a syndrome in clinical genetics. However, it is not a profession of stamp collectors but one that affords affected families with an answer why their child is different, anticipates and treats complications, and prevents recurrence in affected families.

## WHY STRIVE FOR A DYSMORPHOLOGY DIAGNOSIS?

Dysmorphology diagnosis is not for a collection of rare syndromes. There are definite implications for management, anticipation, evaluation and treatment of complications like atlantoaxial dislocation in Larsen syndrome as well as prevention of recurrence in subsequent pregnancies. It also provides answer to the family why their child is different and halts a diagnostic odyssey and frustration of endless consultations with doctors. Advances in technology now allow identification of genes in cohorts of patients with similar phenotypes as well as identification of new syndromes. Understanding of pathogenesis permits better management and research into treatment of rare disorders. As for all other branches of medicine, a definite diagnosis is essential for improved care and counseling of families with a child with dysmorphism.

## APPROACH TO DIAGNOSIS

A multiple malformation syndrome is defined as a recognizable pattern of a combination of major and minor malformations that occurs due to an underlying etiology. There are more than 5,000 entries in the "*London Dysmorphology Database*" (LDDb) and it is impossible to memorize them all. The approach to diagnosis of a child with dysmorphism or congenital anomalies is not different from one in other disciplines of medicine and comprises a good history with a three generation family history, systemic examination combined with good power of observation. Some specific, salient features in history and examination that have dysmorphology diagnostic relevance are noted below.

## History

In addition to the details of the presenting complaints, this should include the timeline of the malformations, natural course, associated behavior phenotypes, progression/regression of symptomatology if any. There are some syndromes where the phenotype evolves with time, e.g., Prader-Willi syndrome, Noonan syndrome, as well as those where it becomes less apparent and photographs at different ages can hence be helpful. A specific

behavior patterns can aid in diagnosis, e.g., hyperphagy in Prader-Willi syndrome, happy phenotype in Angelman syndrome, disturbed sleep patterns in Smith-Magenis syndrome, and over-friendly behavior in Williams syndrome children; being some of the characteristic behaviors.

A three generation family history and consanguinity history are important because if present, inheritance patterns can be ascertained (**Case 1**). Parental ages at conception, teratogen exposure, history of abortions and stillbirth or abnormalities in the fetus in previous conceptions should be noted. History of maternal disorders like diabetes and infections during pregnancy should be taken (**Table 1**). Prenatal ultrasonography records may provide information about abnormal growth pattern, oligoamnios or polyhydramnios. Events at birth, including fetal distress, birthweight, length and head circumference, and neonatal behavior and feeding history should be sought. Details of development history and behavior with formal assessment are very important. A look into the old records, noted findings and treatment as well as anthropometry details with growth charting over time can assist to reach a conclusive diagnosis in some cases.

## Case 1: The Importance of Family History

*A family was referred to the out patient department for evaluation of intellectual disability in three children. The first child, female had mild intellectual disability and she was not dysmorphic on examination. There were no other significant abnormalities on evaluation. She had twin brothers who were hyperactive with intellectual disability. Except for prominent ears, there were no other abnormalities on examination.*

*On further questioning, the mother of the children was slow in her daily tasks and thinking abilities, though she had completed her graduation. Her father too was reported to be slow intellectually, but was employed and never required assistance for daily living. On direct questioning his maternal uncle was not as bright as his peers and other sibling and had no children.*

The pedigree analysis suggests an X-linked semidominant inheritance. The females are relatively mildly affected and the phenomenon of anticipation is apparent. The behavior phenotype, subtle dysmorphism and the inheritance suggests a diagnosis of the commonest X-linked mental retardation syndrome, fragile X mental retardation syndrome. The diagnosis was confirmed by molecular testing.

## Examination

The first important component is to observe the child and his parents to see if the child resembles them or looks different. It is important to do this unobtrusively so as not to discomfort the family. A detailed head to toe physical examination with recognition of facial dysmorphism, congenital anomalies and anthropometric measurements, should be taken. Abnormalities of growth, body proportions, asymmetry also should be looked for. Knowledge of normal and abnormal phenotypic features and their appropriate description is very important as the first step for diagnosis. "*American Journal of Medical Genetics* [2009:149A(1)]" has given standard terminologies used in description of elements of morphology and is very useful in describing dysmorphic features. The issue of the journal is available free online (<http://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.v149a:1/issuetoc>). A keen observation is important to recognize congenital anomalies. Recognize variations present in one of the parents and child as these may be normal variants and not of clinical significance.

Congenital anomalies could be either isolated or in combination (multiple). Amongst *single anomalies*, *malformations* are developmental defects of a body part and occur early in life. They could be major or minor. A *major malformation* is severe and

**Table 1** History: Important points and their significance

	Details of history	Significance
Family history	3 generation family history	Pattern of inheritance can be identified
	Consanguinity	<ul style="list-style-type: none"> <li>Increased risk of malformations</li> <li>Increased risk of autosomal recessive disorders</li> </ul>
	Recurrent abortions, stillbirths	Chromosomal translocation carrier, X-linked dominant disorder with lethality in males, e.g., Rett syndrome
	Parental age	Advanced maternal age—trisomy 21,18,13 Advanced paternal age—Marfan syndrome, Apert syndrome, achondroplasia
Antenatal history	Drugs—anticonvulsants, methotrexate, retinoic acid, periconceptional folic acid	Fetal phenytoin/valproate syndrome
	Maternal illness—diabetes mellitus, phenylketonuria	Infant of diabetic mother, cardiac and other malformations. Congenital phenylketonuria characterized by cardiac anomalies and microcephaly
	Infections—TORCH (toxoplasmosis, other (syphilis), rubella, CMV, HSV)	Congenital rubella syndrome, etc.
	Abnormal screening test— ↑ AFP ↓ E3 ↑ hCG	Neural tube defect Smith-Lemli-Opitz syndrome Down syndrome
	Abnormal Ultrasound	Malformations detected antenatally/IUGR
Neonatal history	Birthweight, length, head circumference	Primordial dwarfism—Seckel syndrome, Silver-Russel syndrome, de Lange syndrome
	Feeding difficulties Floppy baby	Prader-Willi syndrome
Details of developmental history		MR as a part of the syndrome
Behavioral patterns		Angelman syndrome, Prader-Willi syndrome, Williams syndrome

Abbreviations: CMV, cytomegalovirus; HSV, Herpes simplex virus; IUGR, intrauterine growth restriction; MR, mental retardation.

interferes with function; e.g., cleft lip and palate, heart defects. Some major malformations suggest a specific disorder:

- Left sided heart defects namely, coarctation of aorta, bicuspid aortic stenosis in Turner syndrome
- Atrioventricular canal defects in Down syndrome
- Duodenal atresia in Down syndrome

**Minor malformations** are mostly of cosmetic significance, e.g., prominent ear crus, ear tag, polydactyly. However, they serve as tools for diagnosis of a malformation syndrome. In the presence of 1 minor anomaly only 3% of the babies have an associated major malformation compared with babies with 2 and 3 or more minor anomalies where 11% and 90% babies, respectively, have associated major malformations.

- Malformations have to be differentiated from:
  - (i) **Deformations** like clubfoot due to antenatal oligohydramnios which occur due to abnormal mechanical forces causing abnormality of shape and form. This will not recur in the absence of the initiating factor.

- (ii) A **disruption** is a sporadic defect that occurs due to an abnormal extrinsic factor that interferes with otherwise normal morphogenesis. An amniotic band syndrome is a disruption presenting with asymmetric limb amputations with associated bizarre malformations of central nervous system (CNS) and cleft lip or palate. This is a sporadic event with a negligible recurrence risk.

- (iii) A **dysplasia** is the morphological consequence of an abnormal organization of a specific tissue type during morphogenesis. Examples include ectodermal dysplasia comprising abnormal development of structures derived from the ectoderm, e.g., teeth, inability to sweat due to abnormality of sweat glands, and poor hair growth.

When multiple anomalies come together the resulting phenotype is either a multiple malformation syndrome, an association or a sequence. A multiple malformation syndrome has been defined before in this chapter. This has to be differentiated from an *association* which includes an unrelated group of abnormalities but whose occurrence occurs together more often than by chance alone. Examples include VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal, limb). Some cases previously described as associations are found to be caused by genetic defects. One example is *CDH7* gene mutations in CHARGE syndrome (C-coloboma of iris or retina, H-heart defects A-atresia of the choanae, R-retardation of growth and development, G-genital anomalies, mostly in the male and E-ear abnormalities) thought to be CHARGE association previously. A knowledge of these is important so that a pediatrician can search for the other associated anomalies after one is identified.

**Sequence** is a specific pattern of abnormality that results due to a cascade of events due to one malformation or disruption. In Potter sequence, renal agenesis is the primary malformation that causes oligohydramnios that in turn results in clubfeet, flat facies and hypoplastic lungs.

Important points in examination for syndrome diagnosis are noted in **Table 2**. *Pearls of dysmorphology* refer to features that signify a specific diagnosis. Some common *pearls of dysmorphology* are noted in **Table 3**. Documentation with a detailed description of the phenotype, measurements and photographs is the key step in dysmorphology diagnosis. Photographs are important in dysmorphology and speak for multiple words and lengthy descriptions. Consent for this should be taken from the parents or proband as applicable.

## Investigations

Investigations in a child with a developmental defect depend on the nature of the defect. Some investigations are important to identify diagnostic handles in the process of diagnosis making whereas other are diagnostic tests to confirm a clinical suspicion.

- **Imaging** Radiographs for bone age and skeletal abnormalities where there are abnormalities of growth and skeletal defects. Brain CT scan or MRI is very useful in syndromes with known abnormalities of CNS, e.g., acrocallosal syndrome, Walker-Warburg syndrome, other cases like craniosynostosis, microcephaly and macrocephaly.
- **Echocardiography** It should be done in all cases with an abnormal cardiac examination as well as in some syndromes known to be associated with cardiac defects, e.g., Down syndrome, Williams syndrome, Turner syndrome.
- **Chromosomal analysis** This is an important investigation in dysmorphology and common indications include:
  - Presence of a typical defined chromosomal syndrome like Down syndrome, trisomy 18.
  - Malformations associated with a high incidence of chromosomal defect, e.g., omphalocele, holoprosencephaly.



**Table 2** Examination points in dysmorphology

Feature	Abnormality	Syndromes
i Growth parameters	Growth restriction	Proportionate Primordial short stature Seckel syndrome, de Lange syndrome
		Postnatal GR Noonan syndrome
	Disproportionate	Skeletal dysplasia Diastrophic dysplasia Chondrodysplasia punctata
	Overgrowth	Overgrowth syndromes Sotos syndrome, Beckwith-Wiedemann syndrome, etc
ii Asymmetry		Goldenhar syndrome Silver-Russell syndrome
iii Genitalia	Abnormal genitalia/delayed puberty	Smith-Lemli-Opitz syndrome
iv Intellectual disability	Common feature of many syndromes	Down syndrome, Fragile-X mental retardation
v Eye examination	Chorioretinal lacunae Salt and pepper retinitis	Aicardi syndrome TORCH infections
Consider variable features present in the child and parent as <i>normal variants</i>		

Abbreviations: GR, growth retardation; TORCH, toxoplasmosis other (syphilis) rubella cytomegalovirus (CMV) herpes simplex (HSV).

**Table 3** Pearls of dysmorphology

Clinical feature	Syndrome
Pursed up lips ( <b>Fig. 1</b> )	Whistling face syndrome
Broad thumb/great toe ( <b>Figs 2A and B</b> )	Rubinstein-Taybi syndrome
Hyperextensible joints/skin	Ehlers-Danlos syndrome
Absent clavicles	Cleidocranial dysplasia
Heterochromia iridis ( <b>Fig. 3</b> )	Waardenburg syndrome
Bird-headed dwarfism ( <b>Fig. 4</b> )	Seckel syndrome
Inverted nipples and abnormal fat distribution ( <b>Figs 5A and B</b> )	Congenital disorder of glycosylation
Webbed neck	Turner syndrome, Noonan syndrome
Mitten hands	Apert syndrome

**Figures 2A and B** Broad toes and deviated broad thumbs: Rubinstein-Taybi syndrome**Figure 1** Pursed lips: Whistling face syndrome**Figure 3** Heterochromia iridis: Waardenburg syndrome

- A child with intellectual disability, physical retardation, ambiguous genitalia, malformations and dysmorphic features.
- A child with nonspecific dysmorphism not suggestive of a definite syndrome.
- **Fluorescence in situ hybridization (FISH)** A technique where the probe binds to a definite region of the chromosome, is indicated in cases of microdeletion syndromes. Unlike

- chromosomal analysis, for this test a definite microdeletion syndrome has to be suspected and tested for. Common microdeletion syndromes include Williams syndrome, 22q11 microdeletion, Prader-Willi syndrome, Miller-Dieker syndrome, Angelman syndrome.
- **Subtelomeric deletions** This group of disorders due to deletions in the sub telomeric regions is identified by defined FISH



**Figure 4** Prominent nose, high nasal bridge, micrognathia: Seckel syndrome

probes or multiplex ligation-dependent probe amplification (MLPA) technology. In a study by Kausik et al., an overall detection rate of 4.6% in children with intellectual disability, compares with 13% in children with associated dimorphism.

- **Cytogenomic microarray (CMA)** is a platform used for detection of chromosomal gains and losses of very small sizes which are undetectable by traditional karyotyping. CMA is very useful in the setting of intellectual disability, autism and/or congenital anomalies. CMA identifies chromosomal aberrations in additional 10–20% cases and is now recommended as a first-tier investigation. However in India, cost and interpretation expertise are current limiting factors and need to be considered before ordering the test.
- **Molecular diagnosis** The causative genes are now identified for many disorders, e.g., Coffin-Siris syndrome, Joubert syndrome, Crouzon syndrome and should be tested if indicated in a specific case. Most common indications for confirmatory molecular testing include an ambiguous diagnosis which needs confirmation, in preparation for prenatal diagnosis for the family and where predictive testing for unaffected family members or carrier testing for persons at risk is indicated.
- **Metabolic studies** Many metabolic disorders present with dysmorphism, e.g., Smith-Lemli-Opitz-syndrome, storage

disorders, galactosemia with cataract, peroxisomal disorders. The metabolic test ordered is case specific and based on the diagnosis entertained.

### Making a Dysmorphology Diagnosis

This involves synthesizing all the information of the history and clinical examination. Steps in making a diagnosis are as follows:

- Determine the underlying pathogenic mechanism, i.e., deformation, disruption, dysplasia or malformation.
- Where there are multiple malformations, syndrome identification proceeds as below:
  - Identification of the syndrome can be by fast recall of a facial gestalt and pattern recognition (**Case 2**). This is simple for common syndromes like Down syndrome, trisomy 13 (**Figs 6A to C**), Cornelia de Lange syndrome (**Fig. 7**), to name a few. However, as apparent, this is based on the experience and expertise of the examining physician and prone to errors. In our experience, even if a diagnosis is gestalt based, it is important to consider unusual features and refer to written text about that syndrome.

In other cases diagnosis occurs in stages. Few pivotal signs or *diagnostic handles* that are objective and not overly common are selected from the history, examination and investigations and these are correlated using search engines and databases (**Case 3**). Common online free search engines are Online Mendelian Inheritance in Man and PubMed. The computerized databases are LDDB and Pictures of Standard Syndromes and Undiagnosed Malformations. Based on the prioritization of the handles used a list of possible syndromes are suggested. These further have to be correlated with the phenotype of the proband. Books of malformation syndromes with pictures and phenotype help further to reach a probable diagnosis that then can be confirmed by a diagnostic test as indicated. Commonly used book is “*Smith’s Recognizable Patterns of Human Malformation*”. There are many excellent reviews with system wise detailed approach and diagnosis which can be referred to. It is also very useful to look at published case reports and compare the features of the case with the photographs and features of similar cases published. However, these databases and books are *systems for experts* and not experts to reach a diagnosis. Telemedicine and sharing pictures with expert



**Figures 5A and B** (A) Inverted nipples, and (B) Abnormal distribution of fat: Congenital disorder of glycosylation





**Figures 6A to C** Broad nose, microcephaly, cutis aplasia, polydactyly: Trisomy 13



**Figure 7** Cornelia de Lange syndrome

dysmorphologists can likely to aid in reaching a diagnosis.

- All listed features of a syndrome may not be present in each case and it is important to keep in mind the variability of phenotypes in different cases. This is especially true for autosomal dominant syndromes like Holt-Oram syndrome.
- A definite diagnosis of a syndrome where additional significant features are identified should be reported.
- Getting cases with features overlapping with two different syndromes is not unusual and suggests the possibilities of common etiologies like allelic disorders or genes involved in a common developmental pathway.

In evaluating a child with anomalies, it is important not to miss a treatable disorder like hypothyroidism, craniosynostosis, scoliosis, Smith-Lemli-Opitz syndrome. Equally important is surveillance for treatable associated malformations like atlantoaxial dislocation in syndromes with joint laxity. It is important not to rush to a diagnosis, as it is difficult to remove or correct an incorrect diagnostic label of a patient. Many times, despite all efforts a diagnosis is not defined. This must be noted as such and the child kept under follow up. Evolution of the syndrome with time, similar phenotypes that are published in literature and rapid advancement with new technology can help the family at a later follow-up.

### Case 2: Gestalt Diagnosis

A 28 years old second gravida was referred at 32 weeks for an antenatally detected fetal double bubble appearance. A possibility of trisomy 21 was kept and the family was offered amniocentesis. However, they declined amniocentesis. At birth, the neonate had duodenal atresia and looked different from his sibling and parents. He was hypotonic, had brachycephaly, bilateral upslant of eyes with epicanthic folds. The bridge of nose was depressed and ears were low set. The hands were small and there was fifth finger clinodactyly. There was increased distance between the first and second toe, referred to as a sandal gap. The pediatrician suspected Down syndrome that was confirmed on chromosomal analysis.

Based on gestalt, the diagnosis of Down syndrome was confirmed. Chromosomal analysis confirmed trisomy 21 and the family was counseled for management.

Gestalt diagnosis for Down syndrome is easy to make as this is not an uncommon syndrome and most pediatricians and all geneticists have seen these children. However, it is important to know and consider differential diagnosis of syndromes with a similar phenotype—Zellweger syndrome, 9q deletion, Smith-Magenis syndrome.

### Case 3: Evaluation Using Diagnostic Handles

A 2-month-old male child had an abnormal shape of the head with limb abnormalities. Examination showed a cloverleaf shaped skull, bilateral duplication of the great toe with postaxial polydactyly of one upper limb. There was hypertelorism with narrow palpebral fissures, midfacial hypoplasia and prominent anthelix. A previous similarly affected sibling was noted to have an abnormal shaped skull with ambiguous genitalia. The parents were normal and there was no other significant family history.

Good diagnostic handles in this case for a London Medical Database search are cloverleaf skull and hallux duplication. These are rare malformations present in few syndromes compared to hypertelorism, ambiguous genitalia and mid facial hypoplasia, which are nonspecific and present in many syndromes. Search with autosomal recessive craniosynostosis syndromes show 102 results, but when combined with polydactyly or hallux duplication, it narrowed it to two disorders, Carpenter syndrome and Baller-Gerold syndrome. Comparing the phenotypes and photographs of published cases, a final diagnosis of autosomal recessive Carpenter syndrome was made and confirmed by identification of mutations in *Rab23* gene.

### IN A NUTSHELL

1. Detailed head to toe clinical examination complements a good history.
2. Be careful of the sentiments of the family while evaluating the proband for dysmorphic features.
3. Take good photographs to document dysmorphism after informed consent.
4. Dysmorphology databases are not experts but tools for experts.
5. Confirmation of diagnosis is important for anticipatory management and counseling for recurrence risks.

### MORE ON THIS TOPIC

Aase JM. Diagnostic Dysmorphology. New York: Plenum Medical Book Co; 1990.

Aase JM. Dysmorphologic diagnosis for the pediatric practitioner. *Pediatr Clin North Am.* 1992;39:135-56.

Cassidy SB, Allanson JE. Management of Genetic Syndromes. New Jersey: John Wiley & Sons; 2001.

Dalal AB, Phadke SR. Morphometric analysis of face in dysmorphology. *Comput Methods Programs Biomed.* 2007;85:165-72.

Gorlin RJ, Cohen MM Jr, Hennekam RCM. Syndromes of the Head and Neck. New York: Oxford University Press; 2001.

Hall BD. The state of the art of dysmorphology. *Am J Dis Child.* 1993;147:1184-9.

Hall JG, Allanson JE, Gripp KW, Slavotinek AM. Handbook of Physical Measurements. New York: Oxford University Press; 2007.

Hennekam RCM, Kranz ID, Allanson JE. Gorlin's Syndromes of the Head and Neck. 5<sup>th</sup> ed. New York: Oxford University Press; 2010.

Jones KL, Jones MC, Campo MD. Smith's Recognizable Patterns of Human Malformation. 7<sup>th</sup> ed. USA: Saunders; 2013.

Puri RD, Verma IC. Dysmorphology diagnosis. *Indian J Pediatr.* 2004;71:535-9.

Reardon W. The Bedside Dysmorphologist: Classic Clinical Signs in Human Malformation Syndromes and their Diagnostic Significance. New York: Oxford University Press; 2008.

Taybi H. Handbook of Syndromes and Metabolic Disorders: Radiologic & Clinical Manifestations. Chicago: Mosby; 1998.

## Chapter 2.4

# Chromosomal Disorders

Shagun Aggarwal, Ashwin Dalal

Chromosomes or colored bodies (as the word means) have been recognized for more than 100 years when Walther Flemming first demonstrated them in mitotic tumor cells in 1882. They were given their name by Waldeyer in 1882 and the chromosomal theory of inheritance was proposed in 1900 by Sutton and Boveri. In the year 1923, Painter reported the human diploid chromosome number as 48 on the basis of his studies on meiotic cells in testicles. For a long 30 years this was believed to be the case, till better cytogenetic techniques and the advent of hypotonic treatment helped scientists study the chromosomes better. In 1956, the correct human diploid chromosome number, i.e., 46 was reported by Tijo and Levan. This was followed by the description of chromosomal basis of Down syndrome in 1959. Lejeune and his team reported 47 chromosomes in patients with Down syndrome and showed that the smallest chromosome, which we now know as chromosome 21 was 3 in number in these patients. Subsequently, in quick succession the Patau syndrome and Edward syndrome were described. The necessity of performing bone marrow aspiration for obtaining dividing cells was obviated in 1960s when Moorhead et al described a method of obtaining good quality metaphases from small amount of peripheral blood samples using combination of phytohemagglutinin for stimulation of lymphocyte culture and air-drying technique for metaphase preparation. However, the recognition of other chromosomal abnormalities was possible only after the chromosomal banding techniques were developed. In 1968, Caspersson and colleagues used quinacrine hydrochloride to differentially stain various regions of the chromosomes. This was followed by the development of the Giemsa banding technique by Drets and Shaw a year later, and this led to the identification of each of the human chromosome by their different banding patterns. The chromosomes could now be identified and arranged systematically, and the human karyotype (defined as the orderly arrangement of chromosomes) could be prepared. Subsequently, a number of chromosomal abnormalities were described like the various deletions, translocations and inversions. The era of cytogenetics had arrived and progressed further with the advent of fluorescence in situ hybridization (FISH) technology in the 1990s. This was followed by development of other molecular cytogenetic techniques like quantitative fluorescent-polymerase chain reaction (QF-PCR), multiplex ligation dependent probe amplification (MLPA) and chromosomal microarray which helped scientists study the chromosomes in much finer details and lead to the recognition of many new genetic disorders.

### NOMENCLATURE OF CHROMOSOMES

The diploid human chromosomes are 46 in number. Each chromosome in metaphase consists of two *chromatids* attached at the center by a structure called *centromere*. There are two arms of the chromosome on either side of the centromere, the p arm and the q arm. The ends of the chromosomes are known as *telomeres*. Individual chromosomes can be identified and numbered according to size, length of arms, position of centromeres and banding patterns.

There are 22 pairs of autosomes numbered 1 to 22 and one pair of sex chromosomes which are XX in females and XY in males. **Figures 1A to D** shows a diagram of the chromosome, the appearance of chromosomes under microscope and their

arrangements into a male karyotype and a female karyotype. The autosomes are arranged in the descending order of their size. Three main types of chromosomes can be distinguished depending on the position of the centromere. Chromosomes whose centromere is at the center are known as the *metacentric chromosomes*, e.g., chromosomes 1, 2, 3, 16, 19 and 20, those with centromere more towards one of the arms are called *submetacentric chromosomes*, e.g., chromosomes 4, 5, 6, 7, 8, 9, 10, 11, 12, 17, 18, X and the ones with centromere near the end of the q arm, the p arms being replaced by satellites are termed *acrocentric chromosomes*, e.g., chromosomes 13, 14, 15, 21, 22 and Y. These have also been grouped as Group A: the large metacentric chromosomes no. 1, 2, 3; Group B: the large submetacentric chromosomes no. 4, 5; Group C: chromosomes 6–12 and X; Group D: the large acrocentric chromosomes no. 13, 14 and 15; Group E: 16, 17, 18; Group F: 19, 20; and Group G: 21, 22 and Y.

Chromosomal banding refers to the differential staining of the different parts of a chromosome and this can be achieved by pretreatment with various chemicals before staining. On Giemsa banding after trypsin digestion, some regions of the chromosome stain lightly, these are mainly the guanine and cytosine (GC) rich regions; while others stain darkly, these being adenine and thymine (AT) rich. The banding characteristics of individual chromosomes help in identification of the chromosomes and the diagnosis of the various structural chromosomal abnormalities.

Chromosomal abnormalities may be inherited from the parents or may occur due to errors in meiotic segregation of chromosomes. Chromosomal abnormalities can be classified as numerical and structural chromosomal abnormalities.

### NUMERICAL CHROMOSOMAL ABNORMALITIES

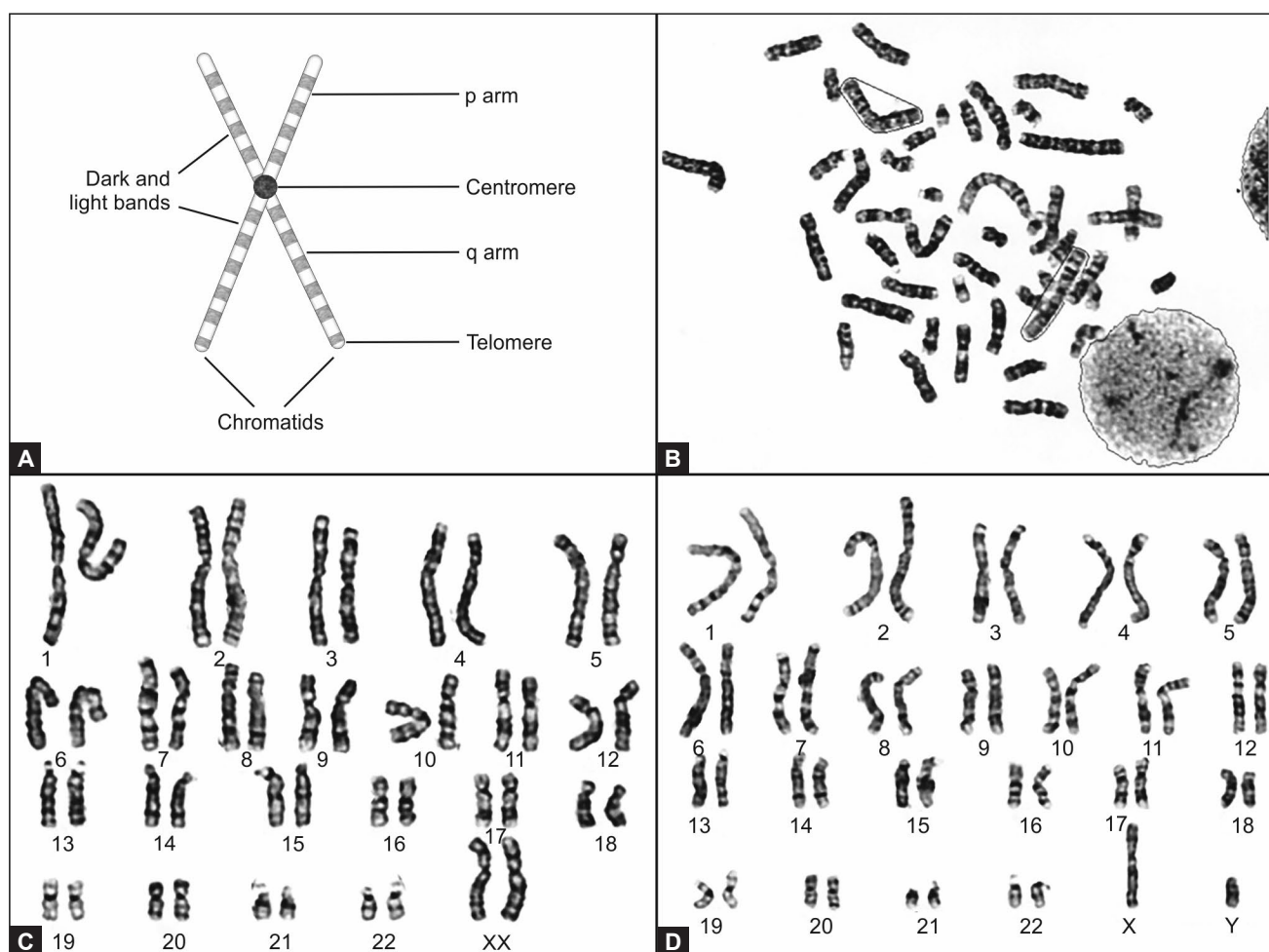
The normal human chromosome complement is made up of 46 chromosomes (diploid) which is double the euploid (haploid) complement of 23 chromosomes seen in gametes. Exact multiples of euploid chromosome complements can be diploid or polyploid, i.e., triploid or tetraploid consisting of three or four sets of chromosomes, respectively. Aneuploidy refers to the presence of extra copy of a specific chromosome (trisomy), as seen in Down syndrome (trisomy 21) or to the absence of a single chromosome (monosomy), as seen in Turner syndrome (monosomy X). Polyploidy and aneuploidy result from errors in segregation of chromosomes during cell division (meiosis) leading to either loss or gain of chromosome in the gametes. Similar errors in mitotic cell division of zygote (fertilized egg) can lead to simultaneous presence of both diploid and aneuploidy cell populations in an individual. This is termed as *mosaicism*. The clinical relevance of mosaicism depends on the proportion and tissue distribution of the aneuploid cells. On the other hand, presence of different cell lines derived from more than one zygote in an individual is called *chimerism*.

Polyploidy resulting from triploidy (69 chromosomes) or tetraploidy (92 chromosomes) is mostly lethal and seen frequently in spontaneous abortions. Most of the aneuploidies are also incompatible with life in humans, with exception of trisomy 13, 18, 21 and X chromosomal aneuploidies. Absence of a chromosome is more detrimental than presence of an extra chromosome.

### Down Syndrome: Trisomy 21

Down syndrome (trisomy 21) is a chromosomal abnormality that occurs in approximately one in every 800–1,000 livebirths. It was first described in 1866 by John Langdon Down, the superintendent of a facility for children with mental retardation in England. Jean Lejeune and his colleagues identified the genetic cause of Down syndrome in 1959.





**Figures 1A to D** (A) Diagram showing structure of a chromosome; (B) Chromosomes in metaphase as seen under 100X magnification; (C) A normal female karyotype; (D) A normal male karyotype

### Mechanism

Trisomy 21 can occur in one of the three forms:

**Meiotic nondisjunction** Meiotic nondisjunction is an error occurring during separation of the pair of chromosomes during meiotic cell division in the process of formation of gametes (sperm or egg). If it occurs for chromosome 21 then, the gamete will get 2 copies of chromosome 21 leading to trisomy 21 in the zygote. A patient with Down syndrome has 47 chromosomes in every cell (as compared with the normal 46). This is the most common cause of Down syndrome and it accounts for about 95% of cases. **Figure 2A** shows karyotype of a child with Down syndrome due to nondisjunction.

**Translocation Down syndrome** About 3% of patients with Down syndrome have the extra copy of chromosome 21 attached (translocated) to another chromosome. The other chromosome may be one of the acrocentric chromosomes, i.e., chromosome 13, 14, 15, 21 or 22. All cells have 46 chromosomes plus extra chromosome 21 material attached to another chromosome. About 50% of translocations occur spontaneously. The other half happens as a result of inheritance of translocated chromosome from a parent with a balanced translocation (the parent has 45 chromosomes, one free normal chromosome 21 and the other chromosome 21 attached to some other chromosome). **Figure 2B** shows a parent who is carrier of t(14; 21), and can give birth to a child with translocation Down syndrome.

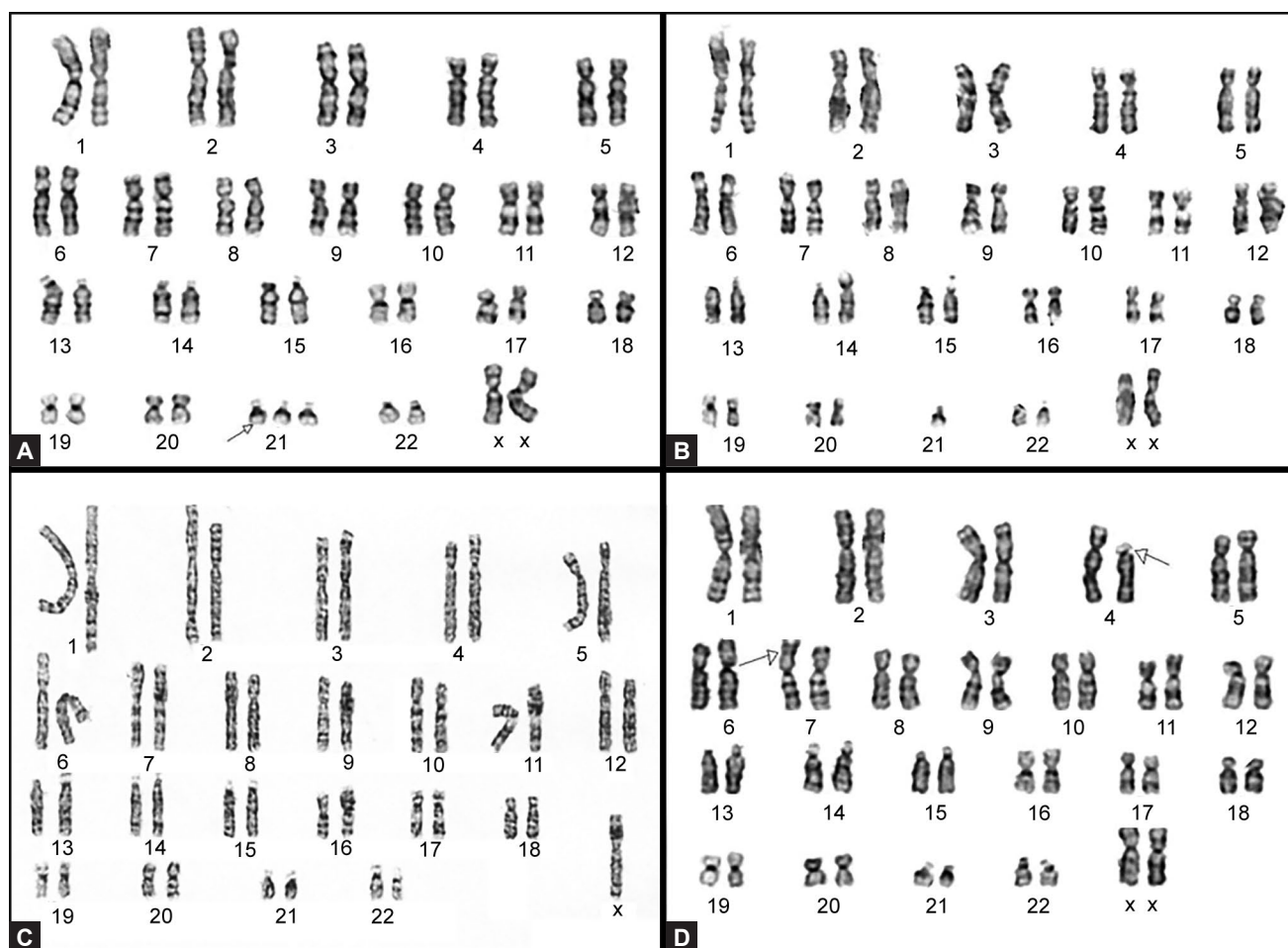
**Mosaicism** Approximately 2% of children with Down syndrome have mosaicism wherein the patient has both normal diploid cells as well as cells with trisomy 21.

### Clinical Features

Down syndrome is characterized by mental subnormality (intellectual disability), typical facial dysmorphism and malformations of different organs. All the characteristic facial features are not obvious in neonatal period and diagnosis may be difficult. Clinical signs in a neonate which point towards Down syndrome include small ears, wide space in between the first and second toe (*sandal gap*), small internipple distance, Brushfield spots, increased nuchal skinfold, brachycephaly, hypotonia, flat face, upward slant of palpebral fissures and transverse line in the palm of the hand (*simian crease*). As the child grows older, the facial features become more and more discernible. Apart from facial features, the child with Down syndrome is at risk of multiple clinical problems as detailed in **Table 1**.

### Diagnosis

Diagnosis of Down syndrome is obvious in most cases from the facial features (**Fig. 3A**). However, this needs to be confirmed in every patient by doing chromosomal analysis. Karyotype also helps to detect Down syndrome due to translocation and mosaicism which helps in providing accurate risk of recurrence (**Box 1**).



**Figures 2A to D** (A) Karyotype of a child with Down syndrome showing free trisomy 21; (B) Karyotype of a female  $t(14; 21)$  carrier; (C) Karyotype of a patient with Turner syndrome; (D) Karyotype of a female with  $t(4; 7)$

### Management

Down syndrome management is done through a multidisciplinary approach. The details of clinical problems associated with Down syndrome and their management are shown in **Table 1**.

### Prenatal Screening and Prenatal Diagnosis

The risk of having a baby with Down syndrome increases with maternal age. A lady at an age of 45 carries a risk of up to 1 in 15 of having a child with Down syndrome. This phenomenon has been used as a screening method for selecting patients for prenatal diagnosis. However, various screening protocols have evolved over last decade consisting of maternal serum markers and ultrasonographic markers with marked increase in the sensitivity and specificity. A brief list is presented in **Table 2**. All the screening protocols give a risk figure which is then compared with the risk of abortion following an amniocentesis. A risk of 1:250 or more is taken as significant and the couple is advised prenatal diagnosis. Prenatal diagnosis can be done by karyotyping the fetal cells obtained by chorionic villus sampling or amniocentesis. The couple can opt for termination of pregnancy in case the fetus is having Down syndrome or any other chromosomal abnormality.

### Genetic Counseling

Genetic counseling includes providing the family with confirmed diagnosis and information regarding prognosis in a child with

Down syndrome. It should be done as soon as the diagnosis is suspected or confirmed after birth. It is very important to convey to the parents regarding the clinical problems in Down syndrome as well as information about absence of any definitive treatment. Treatment of clinical problems detected and screening protocol for future needs to be discussed. Further the couple is explained about the risk of Down syndrome in subsequent pregnancy and the option of prenatal diagnosis (**Box 1**).

### Other Autosomal and Sex Chromosome Trisomies

Autosomal trisomies compatible with life in humans, other than Down syndrome are Edward syndrome (trisomy 18) and Patau syndrome (trisomy 13) as shown in **Figure 3B** and **Table 3**. Most of these children do not survive beyond 2 years of age.

Sex chromosome aneuploidies are less detrimental as compared to autosomal aneuploidies. This could be due to phenomenon of X chromosome inactivation and paucity of significant genes on Y chromosome. Clinical features of sex chromosome aneuploidies and their incidence is shown in **Table 3**.

### Turner Syndrome: Monosomy of X Chromosome

Turner syndrome is a chromosomal disorder caused due to partial or complete loss of one X chromosome. The disease incidence is approximately 1 in 2500 live born females. A 45, X karyotype is observed in 1–2% of conceptuses, 10% of miscarriages and 1% of stillbirths. More than 99% of 45, X conceptuses are spontaneously aborted.

**Table 1** Clinical problems and management in children with Down syndrome

<i>Clinical problem</i>	<i>Description</i>
Congenital heart defects (CHD)	<ul style="list-style-type: none"> <li>• Atrioventricular septal defect and ventricular septal defect are the most common forms of CHD (54% ASD and 33% VSD)</li> <li>• Surgical correction of significant defects usually at the age of 2–4 months, sometimes earlier (tetralogy of Fallot)</li> <li>• Echocardiography in the first month of life helps in early recognition of CHD for optimal management and prevention of pulmonary hypertension</li> </ul>
Vision disorders	<ul style="list-style-type: none"> <li>• Ocular features include epicanthal folds, narrowed or slanted palpebral fissures (the mongoloid slant) and Brushfield spots (38–85%)</li> <li>• Vision disorders include strabismus (20–47%), nystagmus (11–29%), congenital cataract (4–7%), acquired cataract (3–15%), blepharitis (7–41%), refractive errors (43–70%) and glaucoma (0.7%)</li> <li>• Ophthalmological examination is essential for detecting defects that can be treated</li> </ul>
Hearing disorders	<ul style="list-style-type: none"> <li>• High incidence of chronic middle ear disease and chronic rhinorrhea</li> <li>• Regular assessment of the hearing function is very important</li> </ul>
Obstructive sleep apnea syndrome	<ul style="list-style-type: none"> <li>• High incidence due to macroglossia, glossoptosis, recurrent enlargement of the adenoid tonsils and enlarged lingual tonsils</li> <li>• Baseline polysomnography recommended in all children with Down syndrome at 3–4 years of age</li> </ul>
Wheezing airway disorder	<ul style="list-style-type: none"> <li>• Major cause of morbidity and hospital admissions</li> <li>• Respiratory syncytial virus infections common</li> <li>• Exacerbation due to associated airway anomalies like tracheolaryngomalacia, pulmonary hypoplasia, and subpleural cysts</li> </ul>
Congenital defects of gastrointestinal tract	<ul style="list-style-type: none"> <li>• Duodenal stenosis/atresia (1–5%), esophageal atresia/trachea-esophageal fistula (0.3–0.8%), pyloric stenosis (0.3%), Hirschsprung disease (1–3%) and anal stenosis/atresia (&lt; 1–4%)</li> </ul>
Celiac disease	<ul style="list-style-type: none"> <li>• Screening for early detection of celiac disease helps in starting treatment and preventing complications such as failure to thrive, anemia, osteoporosis and malignancy</li> <li>• Screening by human leukocyte antibodies (HLA)-DQ2 and HLA-DQ8 typing in the first year of life</li> </ul>
Transient myeloproliferative disorder	<ul style="list-style-type: none"> <li>• Thrombocytopenia (up to 66%) and polycythemia (up to 33%)</li> <li>• Lowered T- and B-lymphocyte counts and functions</li> <li>• Increased risk for acute myeloid as well as lymphoblastic leukemia</li> </ul>
Thyroid disorders	<ul style="list-style-type: none"> <li>• Congenital hypothyroidism (1.8–3.6%), primary hypothyroidism, autoimmune (Hashimoto) thyroiditis (0.3–1.4%), compensated hypothyroidism (25–33%), hyperthyroidism (Graves' disease) (0–2%)</li> <li>• Screening once a year recommended</li> </ul>
Orthopedic problems	<ul style="list-style-type: none"> <li>• Atlantoaxial instability (15%), extra care in intubation</li> <li>• Acquired hip dislocation (30%), patellofemoral instability (10–20%), slipped capital femoral epiphysis</li> <li>• Physiotherapy helps the development of the basic gross motor skills</li> </ul>
Skin problems	<ul style="list-style-type: none"> <li>• Alopecia areata (3–20%), vitiligo (1–9%), seborrheic eczema (8–36%), folliculitis (10–26%) and syringoma (12–39%)</li> </ul>
Behavior problems	<ul style="list-style-type: none"> <li>• Mental development shows a deceleration between the ages of 6 months and 2 years, IQ values vary from 35 to 70</li> <li>• Delayed verbal short-term memory and expressive language</li> <li>• Attention deficit hyperactivity disorder (6%), conduct/oppositional disorder (5%) or aggressive behavior (6%), and obsessive-compulsive disorders</li> <li>• Autism (7%), epilepsy (8%)</li> <li>• Alzheimer disease after childhood</li> </ul>

**BOX 1 Case Study: Down Syndrome**

Baby Aayushi is taken to her pediatrician for the 6th week vaccination. She is the first child of a Punjabi mother and Bengali father. Her parents are concerned about her loose limbs and recurrent cold episodes. The pediatrician notices the presence of dysmorphic features like upslanting palpebral fissures, brachycephaly, epicanthic folds and simian crease in right hand. He advises peripheral blood karyotype for the child.

Aayushi's karyotype report is shown in **Figure 2A**. Can you identify the condition?

The pediatrician told the couple that Aayushi has a genetic disease called Down syndrome or Trisomy 21 and referred them to the geneticist.

Aayushi's parents were counseled by the geneticist regarding the prognosis for her developmental milestones and subsequent intellectual challenges. They were advised to consult a psychologist for guidance regarding management of these problems. Aayushi was advised to go for cardiac echocardiography and thyroid function assessment. She was advised for regular follow-up for development assessment, ophthalmic and ENT checkups. The couple was also told about the need for prenatal diagnosis in subsequent pregnancies.

For women with previous child with Down syndrome due to free trisomy 21 (like Aayushi), the average recurrence risk for subsequent pregnancies is 1%. These women are offered direct amniocentesis and do not undergo screening test. The recurrence risk for the translocation Down syndrome is much higher (1–5% if father is carrier and 5–15% if mother is carrier).



**Table 2** Prenatal screening for Down syndrome

Screening strategy	Criteria/Parameter	Sensitivity
Maternal age only	> 35 years	30%
Triple marker assay from maternal serum (15–22 weeks)	Free beta-hCG, alpha-fetoprotein Unconjugated estriol	60–75%
Quadruple marker from maternal serum (15–22 weeks)	Inhibin Free beta-hCG Alpha-fetoprotein Unconjugated estriol	80%
Double marker from maternal serum (11–14 weeks)	PAPP-A Free beta-hCG	65%
Fetal ultrasonography (11–14 weeks)	Nuchal translucency	65–75%
Combined test (double marker and USG)	PAPP-A, Free beta-hCG, Nuchal translucency	85–90%
Combined test and nasal bone	Nasal bone assessment, PAPP-A, free beta-hCG and nuchal translucency	95%

Abbreviations: hCG, human chorionic gonadotropin; PAPP-A, pregnancy associated plasma protein A.

### Mechanism

The most common type of Turner syndrome results from errors in meiotic segregation of chromosomes, leading to one gamete with two X chromosomes and another with no X chromosome. This type of abnormality is seen in about 45% of patients and karyotype is 45, X. The other mechanisms of Turner syndrome include isochromosome Xq (15–18%), mosaic 45, X/46, XX (7–16%), ring X chromosome or partial deletion of Xp or Xq.

### Clinical Features

The clinical features of Turner syndrome include short stature, ovarian failure, edema of hands or feet, nuchal folds, left-sided cardiac anomalies, low hairline, low set ears, small mandible, cubitus valgus, nail hypoplasia, hyperconvex nails, multiple pigmented nevi, characteristic facies, short fourth metacarpal, and high arched palate (**Fig. 3C**). Isolated deletion of the distal region of Xp including the *SHOX* (short stature homeobox) gene may result only in short stature in females and these patients may not get diagnosed with Turner syndrome. Similarly, individuals with deletions of Xq24 are typically diagnosed with premature ovarian failure since they do not have short stature. The girls with Turner syndrome usually do not have intellectual disabilities but may have learning disabilities in some areas.

**Table 3** Clinical features of patients with common autosomal or sex chromosome aneuploidy

Syndrome/Karyotype	Incidence (per 1,000 livebirths)	Clinical features
Edward/Trisomy 18	1 in 3,000	Multiple congenital malformations of many organs, low-set malformed ears, receding mandible, small eyes, mouth and nose, clenched fist with overlapping fingers, severe mental deficiency, congenital heart defects, horseshoe or double kidney, short sternum, posterior heel prominence
Patau/Trisomy 13	1 in 10,000	Severe mental deficiency, small eyes, cleft lip and/or palate, extra fingers and toes, cardiac anomalies, midline brain anomalies, genitourinary abnormalities
Klinefelter/47,XXY	1 in 1,000	Male, infertile with small testes, may have some breast development, tall, learning disability, long limbs, at risk for educational problems
Trisomy X/47,XXX	1 in 1,000	Female with normal genitalia and fertility, at risk for educational and emotional problems, premature ovarian failure
47, XYY	1 in 1,000	Tall male with normal physical/sexual development, normal intelligence, increased tendency for behavioral and psychological problems



**Figures 3A to C** (A) Photograph of a child with Down syndrome (Courtesy: Dr Shubha Phadke, Professor, Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow); (B) Photograph of a child with Edward syndrome; (C) Photograph of a girl with Turner syndrome

Source: Dr Shubha Phadke, Professor, Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow.

## Diagnosis

Chromosomal analysis is indicated in any female with short stature. Karyotype will reveal one of the different mechanisms of Turner syndrome described above (**Fig. 2C**). In addition, it is important to look for mosaicism for Y chromosome in these patients because of the risk of gonadoblastoma. Y chromosome mosaicism can be detected by cytogenetic analysis of chromosomes and detection of fluorescently labeled probes by FISH or by PCR-based methods.

## Management

A multidisciplinary team should oversee management of girls with Turner syndrome from diagnosis to adult life.

- Cardiovascular evaluation needs to be done at diagnosis, including physical examination and echocardiogram and/or MR angiography. Left-sided obstructive cardiac anomalies occur in 30% of girls with Turner syndrome. Bicuspid aortic valve (50%) and coarctation of aorta (30%) are commonly seen. Blood pressure should be measured annually, including arm and leg.
- Renal assessment needs to be done for urinary tract anomalies (30%) like renal rotational abnormalities and double collecting systems. Risks include hypertension, urinary infection and hydronephrosis.
- Free T4 and thyroid stimulating hormone at diagnosis and annually thereafter since primary hypothyroidism occurs in 10–30% of individuals with Turner syndrome.
- Hearing and visual assessment and management of problems detected.
- Patients are at risk of celiac disease and inflammatory bowel disease. Hence, antibody screening is indicated.
- Growth hormone (GH) therapy should be considered in all girls with Turner syndrome whose height is below the 5th centile for Turner syndrome and are not exhibiting significant catch-up on disease specific charts by 3–4 years age. Therapy with GH accelerates growth in patients with Turner syndrome and final height increments range from 5 cm to 15 cm. GH therapy also contributes to achievement of peak bone mass in combination with estrogen.
- Hormone replacement therapy under supervision of pediatric endocrinologist. Estrogen is essential for the physical changes of puberty including breast development, uterine and pelvic growth, and the psychological, social, emotional and sexual evolution of puberty. But, since estrogen also potentially accelerates fusion of bony epiphyses, the timing of its commencement must be coordinated to avoid undue delaying of onset of puberty.

## STRUCTURAL CHROMOSOMAL ABNORMALITIES

Abnormalities in the structure of one or more chromosome constitute an important group of chromosomal disorders. These abnormalities can be broadly categorized into two types:

1. **Unbalanced chromosomal abnormalities** These are associated with net loss or gain of chromosomal material and constitute the deletions, duplications and unbalanced chromosomal translocations (**Figs 4A and B**).
2. **Balanced chromosomal rearrangements** These do not lead to change in genomic content and consist of the inversions and the balanced translocations (**Figs 4C and D**).

### Unbalanced Chromosomal Abnormalities

The unbalanced chromosomal abnormalities present with phenotypic abnormalities of various types depending on the location and extent of the genomic imbalance.

**Deletions** involve loss of a part of a chromosome. These can occur as pure deletions or as part of a derivative or recombinant. The common pure deletions which can be detected on a karyotype are as follows:

- **4p-deletion/Wolf Hirschhorn syndrome** This is a subtelomeric deletion involving the terminal end of p arm of the chromosome 4. The cardinal clinical features are mental retardation, a *Greek helmet* appearance of nose, cleft lip or palate, preauricular tags and multisystem malformations.
- **5p-/Cri-du-Chat syndrome** This is a subtelomeric deletion involving the terminal end of the chromosome 5. The cardinal clinical features are a cat like cry, mental retardation, hypertelorism, microcephaly and downturned angles of mouth.
- **1p36 deletion syndrome** This is a subtelomeric deletion involving terminal part of p arm of chromosome 1. These children present with severe mental retardation, seizures, multiple malformations and facial dysmorphism in the form of straight eyebrows and deep set eyes.

Besides these large deletions which can be seen on a karyotype, many chromosomal deletions are too small to be seen under microscope. These are known as the microdeletions and are described in the subsequent section.

**Duplications** involve gain or duplication of part of a chromosome. Many duplications are tandem duplications where a segment of a chromosome is contiguously duplicated. Most tandem duplications are not easily seen on a karyotype and we need various molecular cytogenetics techniques to detect them. However, sometimes the extra or duplicated chromosome material can be present as a derivative chromosome, a recombinant, a dicentric, an isochromosome or a separate fragment in the cell called a marker chromosome. Some duplications detected on a karyotype are as follows:

**Tetrasomy 12p/Pallister-Killian syndrome** is a mosaic tetrasomy of p arm of chromosome 12, in which a metacentric isochromosome composed of two p arms of chromosome 12 is present in a proportion of body cells. The clinical features include polydactyly, mental retardation, hyperpigmented streaks on skin and coarse facial features. **Cat eye syndrome** due to tetrasomy of q arm of chromosome 22 presents with iris coloboma, anal atresia, preauricular tags and mental retardation. **Pseudodicentric 15** due to tetrasomy of part of chromosome 15 presents with mental retardation, autism and facial dysmorphism.

### Unbalanced Chromosomal Translocations

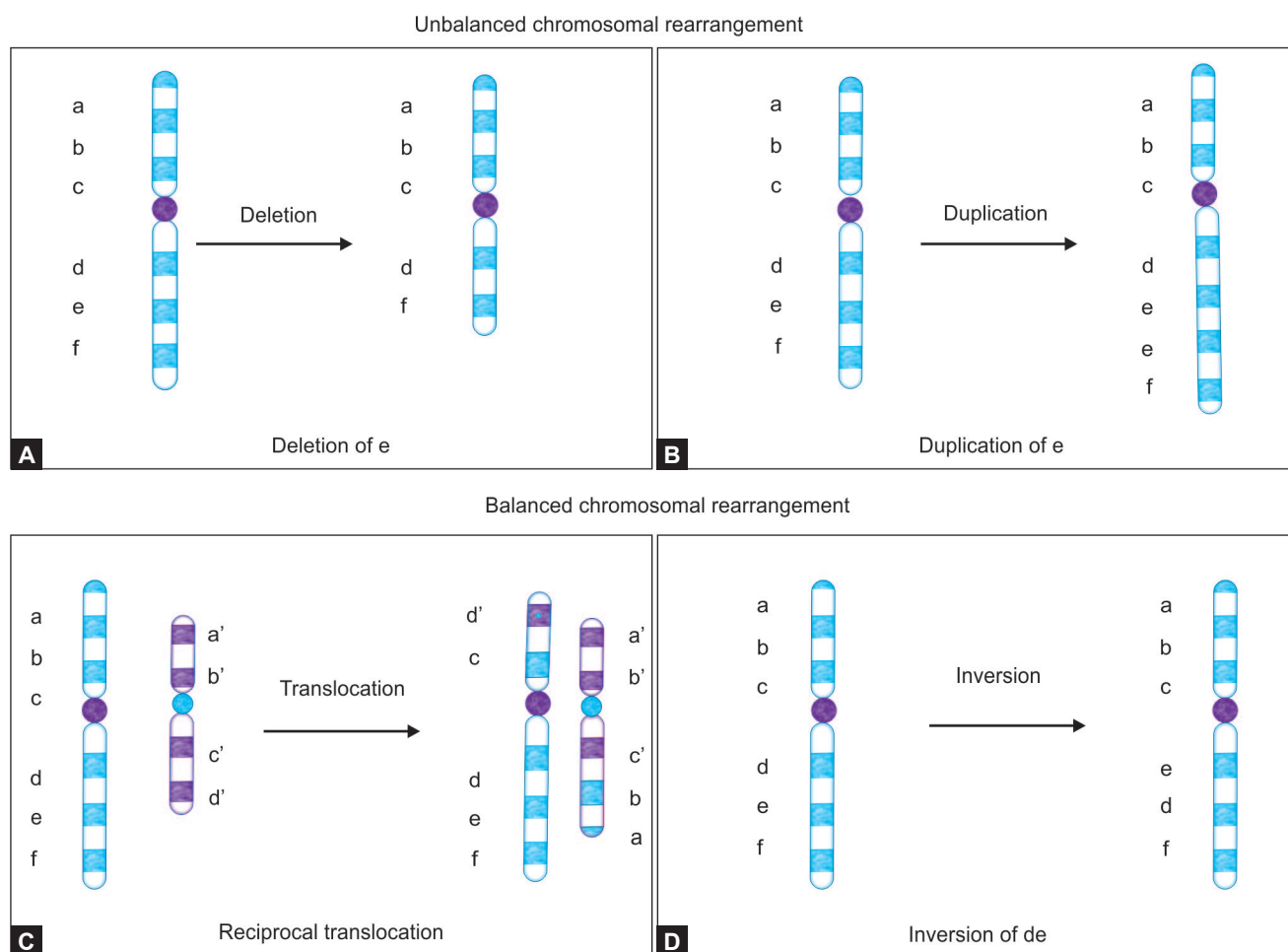
Translocations involve the exchange of genomic material between two or more chromosomes. This exchange can be balanced, where no material is lost or gained and this is discussed in the next subsection. Sometimes a translocation can involve gain or loss of chromosomal segments at the breakpoints. Usually, in karyotypes with unbalanced translocation, there is duplication (trisomy) of one segment and deletion (monosomy) of one segment of the involved chromosomes. Some of such unbalanced translocation may be inherited from a parent with balanced translocation. In these cases the patient develops a phenotype depending on the deleted and/or duplicated material.

## Balanced Chromosomal Abnormalities

### Inversions

These are intrachromosomal rearrangements where a segment of chromosome breaks and gets reinserted in the same place in a reverse orientation. One in 1,000 individuals is a carrier of an inversion. These are of two types: pericentric inversions, where the breakpoints of the inversion lie on either side of the centromere





**Figures 4A to D** (A) Diagram depicting a deletion; (B) Diagram depicting a duplication; (C) Diagram depicting a reciprocal translocation; (D) Diagram depicting an inversion

and the paracentric inversions, where both the breakpoints are in one of the arms. Many inversions are recurrent in the human population and 85–90% are inherited from one of the parent. Inversion carriers are asymptomatic individuals, however, some of the inversions can lead to reproductive problems due to abnormal meiotic recombination. The risk of an abnormal offspring in an inversion carrier is approximately 5–10%.

### Translocations

These arise due to exchange of material between two or more chromosomes. One in 500 individuals is a carrier of a balanced translocation. These are of two main types:

1. **Reciprocal translocation** The exchange of genomic material between two non-homologous metacentric or submetacentric chromosomes. **Figure 2D** shows karyotype of a translocation carrier.
2. **Robertsonian translocation** Translocations involving the extreme ends of two acrocentric chromosomes leading to loss of the satellites and fusion of their q arms.

### Clinical Presentation of Balanced Translocation Carriers

Individuals with balanced translocations are phenotypically normal. However, they can present with reproductive problems due to formation of abnormal synapses during meiosis 1. Five percent of couples with recurrent abortions and 1% of couples with

unexplained infertility have balanced chromosomal translocations. Usually the male partner presents with infertility as abnormal synapse formation leads to gametogenesis arrest in males. The female partner presents with recurrent pregnancy losses or recurrent abnormal offspring. The risk of abortion is approximately 25% for the female carrier of a translocation. The risk of abnormal offspring varies according to various factors like the mode of ascertainment, sex of carrier parent, type of rearrangement and predicted segregation patterns. On an average, if there is history of a liveborn abnormal offspring, the risk of recurrence is 5–30% and if the translocation was ascertained due to reproductive problems, the risk of an abnormal live offspring is 0–5%. Usually the risk is 5–15% if the carrier is the female partner and 0–5% if it is the male partner (**Box 2**).

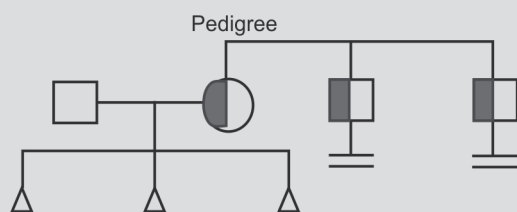
Other rare structural chromosomal rearrangements are the insertions, ring chromosomes and centromere fissions.

### MICRODELETION AND MICRODUPLICATION SYNDROMES

The resolution of routine cytogenetic testing is about 5 Mb. This means that any deletion or duplication of less than 5 million base pairs will not be detected. However, the availability of high resolution methods like FISH and array comparative genomic hybridization (CGH) has enabled detection of smaller chromosomal rearrangements. Microdeletions or microduplications are

**BOX 2 Case Study: Translocation Carrier**

A couple was referred to the geneticist from their gynecologist in view of recurrent pregnancy losses in the first trimester with no identifiable cause. On pedigree analysis it was found that the wife's two brothers were infertile. A peripheral blood karyotype was done for the couple and the results are depicted in **Figure 2D**. The wife was found to be carrier of t (4; 7) and the couple was told that this was the possible cause of the recurrent pregnancy losses. The same translocation was found in the brothers of the wife.



The couple was also told about the need for prenatal diagnosis by amniocentesis in subsequent pregnancies as this translocation could lead to birth of a phenotypically abnormal child.

small (< 5 Mb) chromosomal rearrangements and the disorders resulting from alteration of gene dosages due to which these rearrangements are known as microdeletion or microduplication syndromes. They are frequently associated with mental subnormality and multiple congenital anomalies. The phenotype

is a cumulative result of haploinsufficiency or overexpression of a set of genes involved in the rearrangement. A list of common microdeletion or microduplication syndromes is shown in **Table 4**. Clinical photographs of some patients are shown in **Figures 5A to C**.

Microdeletions or microduplications can be detected by FISH using locus specific fluorescently labeled probes for a particular genomic region. However, newer techniques like MLPA can detect multiple microdeletions or microduplications in a single assay. The advent of array CGH has made it possible to scan the genome with resolution of few hundred base pairs and this has led to description of large number of novel microdeletion or microduplication syndromes in recent past.

**CYTOGENETIC TESTING****Chromosomal Analysis (Box 3)**

The karyotype of an individual can be investigated by studying the chromosomes in metaphase. These are obtained from any living body cells like peripheral blood lymphocytes, amniocytes, skin fibroblasts and chorionic villus cells by a series of steps in the cytogenetics laboratory. These involve cell culture, metaphase arrest using colcemide, treatment with hypotonic saline and fixative, spread of chromosomes on slide and staining followed by visualization under a microscope (**Fig. 6A**). Peripheral blood sample for karyotyping should be collected in a heparin vial under aseptic precautions. Blood samples need to reach the laboratory with 48 hours for chromosomal analysis.

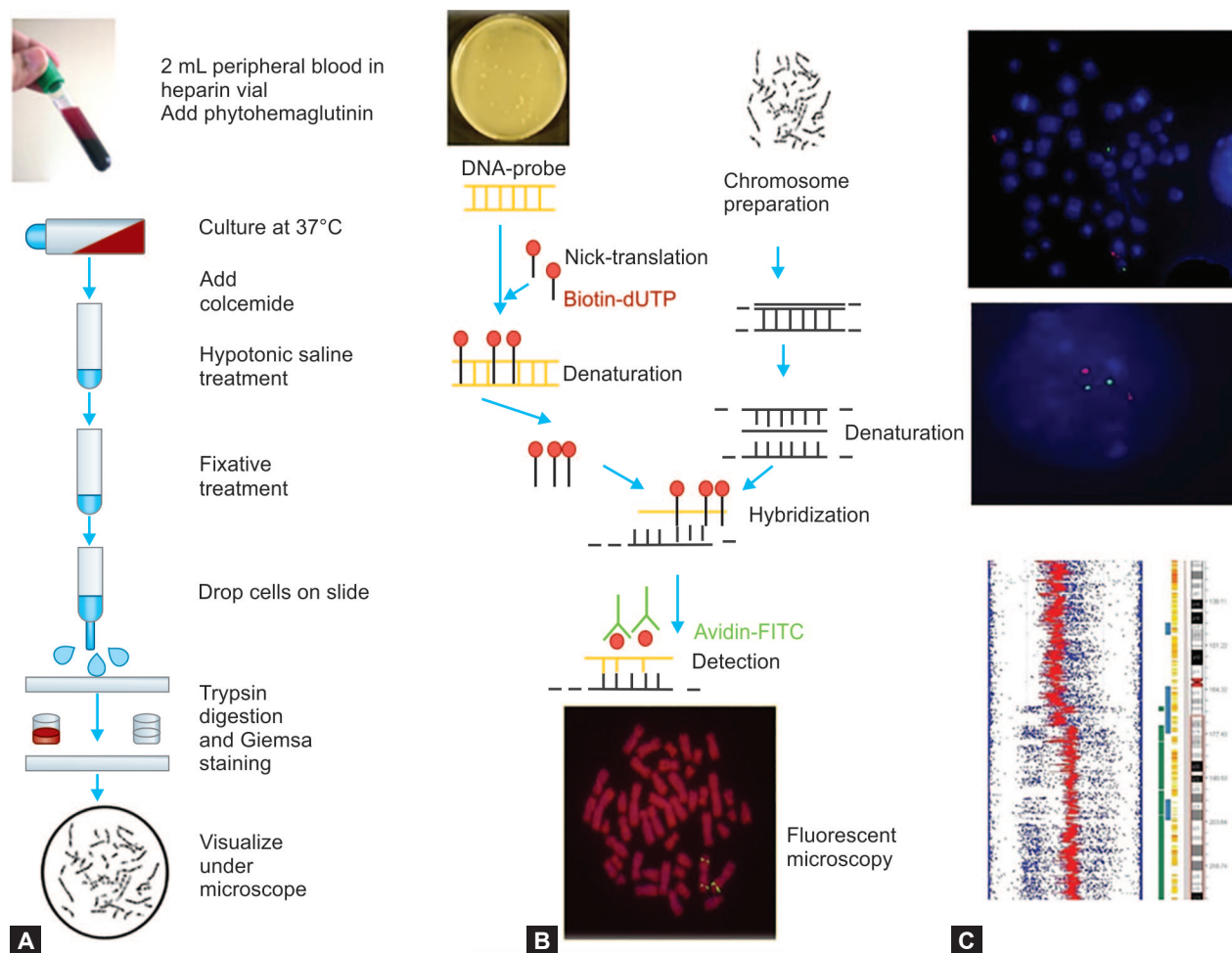
**Table 4** Common microdeletion/microduplication syndromes

Syndrome	Chromosome region	Clinical features
<b>Microdeletion syndromes</b>		
Prader-Willi syndrome	15q11-13	Developmental delay, intellectual disability, almond shaped eyes, inverted V-shaped upper lip, decreased muscle tone, obesity, small genitals, excessive appetite, hypopigmentation
Angelman syndrome	15q11-13	Developmental delay, intellectual disability, microcephaly, truncal ataxia/unstable gait, absence of speech, hyperactivity, spontaneous laughter, hypopigmentation, hypertonia
Williams syndrome	7q11.23	Cardiac anomalies (supravalvular aortic stenosis and pulmonic valvular stenosis), characteristic facies with periorbital puffiness, long philtrum and prominent lips, growth retardation, gregarious disposition, hoarse voice, hypocalcemia, hyperacusis, intellectual disability
Velocardiofacial syndrome	22q11.2	Facial dysmorphism (long broad nose with bulbous tip, hypertelorism, low set ears), palatal abnormalities (velopharyngeal incompetence, submucous cleft palate), hypocalcemia, developmental delay/intellectual disability, conotruncal cardiac defects (tetralogy of Fallot, truncus arteriosus), T-cell immunodeficiency
Miller-Dieker syndrome	17p13.3	Severe intellectual disability, developmental delay, seizures, hypotonia, feeding difficulties, distinctive facial features (prominent forehead, midface hypoplasia, small upturned nose, low-set and abnormally shaped ears, thick upper lip). Malformations include lissencephaly, renal, cardiac anomalies
Smith-Magenis syndrome	17p11.2	Mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems, facial features (broad, square-shaped face with deep-set eyes, full cheeks, and a prominent lower jaw)
<b>Microduplication syndromes</b>		
Charcot-Marie-Tooth neuropathy 1A	17p12	Decreased reflexes, progressive distal muscular wasting, decreased muscle tone, sensory neuropathy
Potocki-Lupski syndrome	17p11.2	Hypotonia, failure to thrive, mental retardation, pervasive developmental disorders, and congenital anomalies
22q11.2 duplication syndrome	22q11.2	Developmental delay, intellectual disability, slow growth leading to short stature, hypotonia
Pelizaeus-Merzbacher disease	Xq21-22	Neuroregression, nystagmus, spastic quadriplegia, ataxia, and developmental delay



**Figures 5A to C** (A) Photograph of a patient with Williams syndrome; (B) Photograph of a patient with Prader-Willi syndrome; (C) Photograph of a patient with velocardiofacial syndrome

Source: Dr Shubha Phadke, Professor, Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow.



**Figures 6A to C** (A) Method of chromosome analysis/karyotyping from peripheral blood; (B) Method of fluorescence in situ hybridization; (C) FISH and Array CGH, Metaphase FISH (Top), Interphase FISH (Middle), Array CGH showing partial duplication of chromosome 2 (Bottom)

**BOX 3 Indications of karyotyping***Postnatal indications*

- Clinically apparent chromosomal disorder like Down syndrome, Patau syndrome, etc.
- Mental retardation
- Multiple malformations
- Disorders of sex development
- Primary amenorrhea or short stature in females
- Recurrent pregnancy losses
- Azoospermia in males
- X-linked recessive disorder manifesting in a female.

*Prenatal indications*

- Advanced maternal age
- Previous child with Down syndrome
- Soft markers on ultrasound
- Malformations in a fetus detected on prenatal ultrasonographic evaluation
- Parent is a carrier of balanced chromosomal abnormality.

**Fluorescence In Situ Hybridization**

The resolution of karyotyping is about 5 Mb. Hence, in order to detect abnormalities of lesser size, FISH is used. DNA probes are prepared in form of oligonucleotides which are complementary to the region of interest. These probes are labeled with fluorescent dye. A metaphase spread is prepared on a glass slide as described above. Both the probe and the DNA in metaphase spread are denatured by heating, followed by hybridization of probe onto the metaphase on slide. The DNA probe binds the complementary region in the metaphase. The location of probe binding on the metaphase can be visualized by a fluorescence microscope which uses light at a particular frequency and detects the emission of fluorescence (**Figs 6B and C**). Microdeletion leads to absence of probe binding. FISH is used for detection of microdeletions or microduplications, aneuploidy screening for rapid prenatal diagnosis, screening for copy number alterations and translocations in cancers, etc. (**Fig. 6B**). The resolution of FISH is about 1 Mb; hence abnormalities of few kilobases will not be detected by this method. However, FISH can look at one or a few regions at a time and clinical suspicion of a microdeletion or duplication syndrome is necessary before ordering FISH.

**Array Comparative Genomic Hybridization**

Microarray-based array CGH is a revolutionary platform that has been recently developed to screen entire genome for copy number abnormalities with resolution beyond the capacity of light

microscope (5–10 Mb). This technology was first developed as a research tool for the investigation of genomic alterations in cancer.

Array comparative genomic hybridization is based on the same principle of complementary DNA hybridization. Whole genomic DNA is labeled with fluorophores and used as probes that are hybridized onto nucleic acid targets on a microarray. Presence of deletion or duplication is inferred based on fluorescent intensity at each target site (**Fig. 6C**). The yield of karyotyping is about 5% in patients with intellectual disability. Use of array CGH increases the yield up to 20%. In view of this high detection rate, array CGH has been recommended as the first line of investigation in patients with intellectual disability, autism and multiple congenital anomalies.

**IN A NUTSHELL**

1. Chromosomal disorders form an important group of genetic disorders and are of various types. Majority present with mental retardation.
2. Karyotyping is the gold standard test to study the chromosomes.
3. Diagnosis of a chromosomal disorder is important for the management of patient, genetic counseling and prenatal diagnosis in future pregnancies.
4. Some patients with reproductive problems can have chromosomal abnormalities.
5. Molecular cytogenetic techniques help in studying chromosomes and the genome in greater detail.

**MORE ON THIS TOPIC**

- ACOG Committee on Practice Bulletins. ACOG Practice Bulletin No. 77: screening for fetal chromosomal abnormalities. *Obstet Gynecol.* 2007;109:217-27.
- Gardner RJM, Sutherland GR, Shaffer LG. *Chromosome Abnormalities and Genetic Counseling*. 4<sup>th</sup> ed. New York: Oxford University Press; 2012.
- Gersen S, Keagle MB. *The Principles of Clinical Cytogenetics*, 3<sup>rd</sup> ed. New York: Springer; 2013.
- Ivan DL, Cromwell P. Clinical practice guidelines for management of children with Down syndrome: Part I. *J Pediatr Health Care.* 2014;28:105-10.
- Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet.* 2010;86:749-64.
- Palomaki GE, Lee JE, Canick JA, et al. Technical standards and guidelines: prenatal screening for Down syndrome that includes first-trimester biochemistry and/or ultrasound measurements. *Genet Med.* 2009;11:669-81.
- Pinsker JE. Clinical review: Turner syndrome: updating the paradigm of clinical care. *J Clin Endocrinol Metab.* 2012; 97:E994-1003.
- Weise A, Mrasek K, Klein E, et al. Microdeletion and microduplication syndromes. *J Histochem Cytochem.* 2012;60:346-58.



## Chapter 2.5

# Management of Genetic Disorders and Genetic Counseling

Shubha R Phadke

Genetic disorders of chromosomal and monogenic etiologies are being diagnosed and many of them are being treated appropriately for many decades. However, tremendous developments in the field of genetics in recent times have resulted in a marked change in the approach to genetic disorders, leading to the establishment of the specialty of clinical genetics. With decrease in the infant mortality rate in India, the contribution of genetic disorders to morbidity and mortality in children is increasing. Genetic disorders involve every system of the body and clinical presentations of these disorders may be similar to many common *nongenetic* disorders. As new diagnostic techniques and new forms of treatments have now become available, it is imperative for clinicians to suspect genetic disorders in appropriate clinical situations, so that the fruits of research in the field of genetics reach patients with genetic disorders and their families. This chapter after briefly reviewing the traditional treatments of genetic disorders, will present an overview of newer treatments based on better understanding of molecular pathophysiology and the future possibilities.

## TRADITIONAL TREATMENTS

Many genetic diseases were being treated successfully even before their causative genes were identified. The treatments involved diet management, removal of offending agents, drugs, megavitamin therapies, surgical treatments and recently bone marrow and other organ transplantations. **Table 1** shows examples of such therapies which have shown very good results.

Many of these treatments are associated with very good outcome, though some require lifelong treatment. Bone marrow transplantation or stem cell therapy has been extended to many diseases other than hematological disorders such as lysosomal storage disorders. Some treatments are though effective in ameliorating symptoms, exact mechanisms of action are not clear. One example is efficacy of hydroxyurea in reducing the painful crisis in sickle cell disease. Surveillance for early diagnosis of treatable complications has been effective in many disorders especially familial cancers and cancer prone syndromes. Inborn errors of metabolism are an important group of genetic disorders for many of which considerable success in treatment has been reported over decades, even though for some disorders the treatment continues to be only partially successful.

## NEWER TREATMENTS

In addition to the treatable genetic disorders mentioned above and some more, many genetic disorders still do not have any therapeutic options other than supportive treatments and continue to have a poor prognosis. The treatments which have come into clinical practice over the last decade or more are discussed here.

### Growth Hormone Therapy for Turner Syndrome and Achondroplasia

Short stature is the major problem with Turner syndrome and achondroplasia, the problem being more severe with the latter. Availability of growth hormone as a drug has led to its use in various

genetic conditions with short stature. Consistent utility of growth hormone therapy in increasing the final height has been observed only in achondroplasia and Turner syndrome. The additional gain of height shown in various studies is 6–8 cm; the gain makes a significant difference to girls with Turner syndrome who usually have a height of a little less than 5 feet. For while for patients with achondroplasia this much gain may not be of much help in changing the quality of life and improving body image. Growth hormone therapy should preferably be started in early childhood and continued till completion of growth by fusion of epiphysis. The need for such a long-term treatment and cost of treatment and possible adverse effects need to be discussed with the child and the parents in the perspective of realistic gain of height, before starting the treatment.

### Bisphosphonates for Osteogenesis Imperfecta

Osteogenesis imperfecta is a common genetic bone disorder with great clinical variability, many cases being markedly deformed with severe physical disability. Bisphosphonates act by inhibiting osteoclast function of bone resorption. This drug treatment has found to be effective in reducing pain and frequency of fractures to a large extent in most of the cases causing marked change in the quality of life and reducing the extent of deformities. Even severe deforming type III cases with fractures at birth have been able to stand and walk if the treatment is started early. In the past few years, more than ten genes other than *COL1A1* and *COL1A2* have been identified to cause osteogenesis imperfecta. These genes are responsible for the autosomal recessive type of osteogenesis imperfecta and their proteins have important functions on post-translational modifications of collagen. There is limited information about the efficacy of bisphosphonates in these types of osteogenesis imperfecta. As bisphosphonate molecules get permanently deposited in bone tissue, some issues like duration of treatment and adverse effects with long-term therapy still remain unresolved.

### Therapies for Lysosomal Storage Disorders

Enzyme replacement therapy (ERT) for lysosomal storage disorders is the great success story which has created hope for other metabolic disorders and many other genetic disorders in general, in the 21st century. Providing deficient enzyme as a treatment was being tried for a long time, but became successful only when targeting of the enzyme to its intracellular location of action was achieved by attaching the mannose 6-phosphate molecule to the recombinant enzyme. This allows the enzyme to enter the cell through the mannose 6-phosphate receptors on the cell surface. With this strategy, successful enzyme replacement therapy came into clinical practice for type I Gaucher disease in 1991. ERTs for other diseases got approval from 2001 onwards. At present ERTs are available for mucopolysaccharidosis (MPS) I, MPS II, MPS IV, MPS VI, Pompe disease and Fabry disease, with very impressive results. The skin and joint changes and organomegaly decrease in MPS, while in Gaucher disease there is normalization of the hematological profile, with reduction in the size of the liver and the spleen. The results of ERT for Pompe are variable; cases started on ERT early in the course of the disease show marked improvement, but the outcome may not be good if ERT is started in an advanced stage. For this reason, some countries have included Pompe disease in the newborn screening program and the babies put on ERT pre-symptomatically have been found to achieve normal motor milestones with no cardiac involvement. Fabry disease is difficult to diagnose due to nonspecific symptoms like neuralgic pains in limbs and lack of clinical signs in many cases. Most of the cases develop stroke, renal failure or cardiac symptoms by young adulthood. It is responsible for 1% of cases with end-stage renal disease. As ERT can reduce the incapacitating limb

**Table 1** Successful traditional therapies for genetic disorders

Strategy of treatment	Diseases	Comment
Diet modification to limit a specific component	<ul style="list-style-type: none"> <li>Phenylketonuria</li> <li>Galactosemia</li> <li>Congenital fructose intolerance</li> <li>Urea cycle disorders</li> <li>Maple syrup urine disease</li> </ul>	<ul style="list-style-type: none"> <li>Phenylalanine restricted diet</li> <li>Avoidance of milk and milk products</li> <li>Avoidance of fruits</li> <li>Low protein diet</li> <li>Restriction of branched chain amino acids</li> </ul>
Removal of offending agent	<ul style="list-style-type: none"> <li>G6PD deficiency</li> <li>Porphyria</li> </ul>	<ul style="list-style-type: none"> <li>Avoidance of drugs like primaquine, etc.</li> <li>Avoidance of drugs like phenobarbitone, etc.</li> </ul>
Avoidance of triggering factor	<ul style="list-style-type: none"> <li>Fatty acid oxidation defects</li> <li>Glycogen storage disease I</li> <li>HMG CoA Lyase deficiency</li> <li>Fructose-1,6 biphosphate deficiency</li> </ul>	<ul style="list-style-type: none"> <li>Avoid fasting</li> <li>Avoid fasting</li> <li>Avoid fasting</li> <li>Avoid fasting</li> </ul>
Replacement of deficient product	<ul style="list-style-type: none"> <li>Thalassemia major</li> <li>Hemophilia A</li> <li>Primary carnitine deficiency</li> <li>Congenital adrenal hyperplasia</li> <li>Congenital hypothyroidism</li> </ul>	<ul style="list-style-type: none"> <li>Red blood cells</li> <li>Factor VIII</li> <li>Carnitine</li> <li>Adrenocortical hormone</li> <li>Thyroxine hormone</li> </ul>
Augmentation of deficient protein by drugs	<ul style="list-style-type: none"> <li>Crigler-Najjar syndrome II</li> <li>Mild hemophilia A</li> </ul>	<ul style="list-style-type: none"> <li>Phenobarbitone</li> <li>Desmopressin (DDAVP)</li> </ul>
Megavitamin therapy	<ul style="list-style-type: none"> <li>Sideroblastic anemia</li> <li>Thiamine responsive megaloblastic anemia</li> <li>Homocystinuria</li> <li>Pyridoxine responsive seizures</li> <li>Vitamin D dependent rickets I</li> <li>Biotinidase deficiency</li> </ul>	<ul style="list-style-type: none"> <li>Vitamin B<sub>6</sub></li> <li>Vitamin B<sub>1</sub></li> <li>Vitamin B<sub>6</sub></li> <li>Vitamin B<sub>6</sub></li> <li>Vitamin D</li> <li>Biotine</li> </ul>
Removal of an organ	<ul style="list-style-type: none"> <li>Hereditary spherocytosis</li> <li>Familial adenomatous polyposis</li> <li>Familial carcinoma breast</li> <li>Multiple endocrine neoplasia II</li> </ul>	<ul style="list-style-type: none"> <li>Splenectomy</li> <li>Colectomy</li> <li>Mastectomy</li> <li>Thyroidectomy</li> </ul>
Specific drug therapy	<ul style="list-style-type: none"> <li>DOPA responsive dystonia</li> <li>Hypophosphatemic rickets</li> </ul>	<ul style="list-style-type: none"> <li>Dopamine</li> <li>Phosphate and high dose calcitriol</li> </ul>
Removal of toxic product	<ul style="list-style-type: none"> <li>Tyrosinemia</li> <li>Urea cycle disorders</li> <li>Maple syrup urine disease</li> </ul>	<ul style="list-style-type: none"> <li>Nitisinone (NTBC)</li> <li>Sodium benzoate/sodium phenylacetate/ dialysis</li> <li>Hemodialysis/ hemofiltration</li> </ul>
Organ/tissue transplantation	<ul style="list-style-type: none"> <li>Thalassemia major</li> <li>Osteopetrosis</li> <li>Mucopolysaccharidosis</li> <li>Immunodeficiency disorders</li> <li>Gaucher disease</li> <li>Autosomal dominant polycystic kidney disease</li> <li>Maple syrup urine disease</li> <li>Tyrosinemia</li> <li>Cardiomyopathy</li> <li>Epiphyseal dysplasia</li> </ul>	<ul style="list-style-type: none"> <li>BMT</li> <li>BMT</li> <li>BMT</li> <li>BMT</li> <li>BMT</li> <li>Kidney transplantation</li> <li>Liver transplantation</li> <li>Liver transplantation</li> <li>Heart transplantation</li> <li>Joint replacement</li> </ul>
Surgical treatment of malformation	<ul style="list-style-type: none"> <li>Cardiac malformation in Holt-Oram syndrome</li> <li>Cleft palate in velocardiofacial malformation</li> </ul>	<ul style="list-style-type: none"> <li>Surgical repair</li> <li>Surgical repair</li> </ul>
Management of symptoms	<ul style="list-style-type: none"> <li>Tuberous sclerosis</li> <li>Stickler syndrome</li> <li>Conduction defects of heart</li> </ul>	<ul style="list-style-type: none"> <li>Anticonvulsants</li> <li>Myopia correction and laser therapy to seal retinal holes</li> <li>Pacemaker implantation</li> </ul>

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase deficiency; BMT, bone marrow transplantation.

pains and also reduce the risk of life-threatening complications, it is important to suspect it in appropriate clinical situations even if the characteristic angiofibromas are absent on the skin. Asymptomatic relatives of a confirmed case of this X-linked disease including carrier females should be evaluated for pre-symptomatic diagnosis. Similar high level of suspicion is necessary for diagnosing patients with Pompe disease and milder forms of MPS, who will be benefited by ERT. It needs to be mentioned that ERT is still ineffective for the neurological effects of the disease as it cannot cross the blood brain barrier. For MPS cases with neurological involvement bone marrow

transplantation before significant neurological involvement may arrest further progression of the neurological component as well.

Other than ERT, substrate reduction therapy is another form of therapy available for those cases of lysosomal storage disorders that have some residual enzyme activity. This is aimed at blocking the synthesis of glycosphingolipids by blocking glucosylceramide synthase. Thus, the deposition of sphingolipids responsible for the pathogenesis of the disease is reduced. The orally available molecule miglustat is effective in many cases of Gaucher disease type I and Niemann-Pick disease type C.

### Fetal Therapy

Many genetic disorders can now be easily diagnosed prenatally by invasive or non-invasive methods. Effective treatments for fetal tachyarrhythmia and corticosteroid treatment for congenital adrenal hyperplasia (started immediately after confirmation of pregnancy to prevent genital ambiguity) are being practiced. Interventions for hydrocephalus and obstructive uropathy have been shown to be feasible, but have limited utility as there is not much difference in the outcomes of cases with pre- and postnatal treatment. Open surgery for meningocele before 26 weeks of pregnancy is being done at a few centers and has been found to have a definitely better outcome as regards to the neurological outcome. However, invasive nature of this procedure poses risks, both to the fetus and the mother. Stem cell therapy of the fetus is still in the research phase, but has been tried for hematological disorders like thalassemia and immunodeficiency disorders.

### POST GENOME ERA SUCCESSES

The Human Genome Project led to the identification of causative genes for many monogenic disorders, development of many molecular techniques used in gene mapping and the understanding of molecular pathogenesis of various diseases. This, in turn, led to the application of new molecules and strategies to the treatment of genetic disorders. These therapeutic strategies are more specific to the genetic defect and better targeted to the pathology. Some examples are discussed here.

#### Ivacaftor for Cystic Fibrosis

Cystic fibrosis is caused by mutations in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene. The protein functions as a gated anion channel to increase conductance for certain ions like chloride. Hundreds of mutations have been identified in the *CFTR* gene. In 2012, ivacaftor was approved for treatment of patients of cystic fibrosis with a specific mutation, i.e. G551D which affects the gating function at the cell surface of the *CFTR* protein. This molecule was selected from more than 2 lac drug molecules due to its ability to potentiate the activity of *CFTR*. Within a short span of a few years, studies on cell lines and human patients have confirmed the beneficial effect of the drug. The drug is now approved for cases with the specific mutation which accounts for a small proportion of cases of cystic fibrosis and studies on its efficacy on other types of *CFTR* mutations are ongoing. This is an example of personalized medicine, but the cost is exorbitant at present. It is important to mention here that the Cystic Fibrosis Foundation has contributed to the development of the drug.

#### Sapropterin for Phenylketonuria (PKU)

Phenylketonuria caused by the deficiency of phenylalanine hydroxylase has been treated for more than six decades with special diets free of phenylalanine. Lifelong strict diet control is a challenge to the patient and the family. Tetrahydrobiopterin is a cofactor in the enzymatic conversion of phenylalanine to tyrosine by phenylalanine hydroxylase, which is deficient in PKU. Some scientists in 1999 observed that oral tetrahydrobiopterin intake reduces the phenylalanine level in some patients with mildly raised levels of phenylalanine even without altering the diet; this was confirmed later by other studies. This has led to the development of sapropterin hydrochloride, a drug approved in the US and Europe for management of PKU. It reduces or eliminates the need for dietary therapy in some cases of PKU. It has now been found that the efficacy of sapropterin is not due to its effect on the metabolism of phenylalanine, but due to its efficacy as a chaperon molecule. It helps a misfolded protein to gain some of its function and hence is effective in patients with mutations which lead to misfolding of the protein. This chaperon like activity of sapropterin may also make it

useful in other diseases caused by mutations leading to misfolding of proteins.

#### Losartan for Marfan Syndrome

Marfan syndrome is caused by mutations in the *FBN1* gene which encodes for fibrillin protein, which is a component of the connective tissue. Weakness of connective tissue was considered to explain the cardiac, eye and other connective tissue abnormalities in patients with Marfan syndrome. It was later observed that mutation in the *FBN1* gene leads to activation of the transforming growth factor (TGF) beta pathway and manipulation at this level seemed easy as the already approved drug losartan was known to inhibit the TGF beta pathway. Use of losartan in mice with Marfan syndrome showed very impressive results with total absence of the eye and heart phenotype. Recently, human trials have convincingly shown that losartan prevents dilatation of the aortic ring. This is a successful and easy treatment which works by modifying the downstream pathway rather than correcting the gene or giving the deficient protein.

Similar therapies based on understanding of pathways are also being explored in other groups of disorders caused by disturbances of molecular pathways. An example is the RASopathies, a group of clinically similar disorders (Noonan, Costello, LEOPARD and cardiofaciocutaneous syndromes) caused by mutations in any of the genes in the RAS-MAPK pathway (*BRAF*, *HRAS*, *KRAS*, *PTEN11*, *SPRED 1*, etc.). This pathway is well studied and is an attractive target for inhibition using small molecules used to treat cancers.

### PHARMACOGENOMICS

Genetic defects not only cause diseases but they also determine the dose requirement and toxicity of drugs prescribed for nongenetic disorders and hence this aspect also needs to be considered as a part of genetics and treatment. Hemolysis due to certain drugs in individuals with G6PD (Glucose-6 phosphate dehydrogenase) deficiency is a well known example of the varying effects of drugs in different individuals. Genes affecting the dose requirement for various drugs and susceptibility to the adverse effects are being studied. Nucleotide variations in Cytochrome P450 and *VKORC1* genes have been identified to contribute to variability of the required dosage for the coumarin group of drugs. Though genetic variations account for only a part of the drug dose variability, the US Food and Drug Administration (FDA) has approved the test for genotyping and the drug label also mentions that the genotype information can be used for initial dose selection. Another example of a strong correlation between genetic variation and drug toxicity is that of anticancer drugs like 6-Mercaptopurine, where the level of the drug metabolizing enzyme thiopurine S-methyltransferase (TPMT) is governed by polymorphisms in the *TPMT* gene. With techniques like whole genome sequencing and SNP microarray to look at the whole genome in one go, more associations of genotypes with drug toxicity are being explored and medicine may be marching towards personalized medicine with lower risks of adverse effects.

### INTERESTING STRATEGIES IN THE PIPELINE

As has been highlighted by successful new therapies, better understanding of disease pathologies at the molecular level and the ability to manipulate the genome is likely to transform the therapeutic options for genetic disorders in the 21st century. Many interesting and logical strategies for monogenic disorders are being conceptualized and tried in laboratories and a few have also been tried in patients. Very attractive results have been observed in the experiments in cell lines and sometimes in animal models. However, in spite of extensive efforts of scientists, only a very few

treatment modalities have reached the stage of clinical trials. Many new therapies in the pipeline may not have shown clinically significant outcomes yet, but promises for the future are evident. Some strategies and drugs in various stages of research are listed in **Table 2**. Use of small RNA molecules complementary the RNA transcript those interfere with its abnormal function or abnormal protein formation has been showing a great promise as a treatment of choice for not only monogenic diseases like triplet repeat disorders and Duchenne muscular dystrophy but also for cancers and viral infections.

After experiments on cell line, trials in animal models become very important in development of any therapeutic strategy. Naturally occurring or artificially created (by knocking down a gene) animal models are available for research for many disorders like Fragile X syndrome, Huntington chorea, Duchenne muscular dystrophy, etc. Their contribution to the drug developments is very important.

## GENE THERAPY STORY: SUCCESS AND HURDLES TO CROSS

With development of the ability to manipulate the gene, correction of genetic defects at DNA level appeared the most logical treatment. The first gene therapy was attempted for beta thalassemia in 1980, but was not successful. First success for gene therapy was recorded in a girl with immunodeficiency due to adenosine deaminase deficiency, but she was continually receiving the recombinant enzyme as well, raising doubts about the efficacy of gene therapy. First long-term success with gene therapy for X-linked immunodeficiency for more than 10 patients was documented by a French group. Two of the patients however, developed a leukemia-like disease, confirming the risk of malignancy due to gene therapy. Another important setback to gene therapy trials was the death of Jesse Gelsinger who participated in a gene therapy trial for ornithine transcarbamylase deficiency (OTC). He died on the fourth day of gene therapy probably due to an immune reaction to the adenovirus used as a vector to carry the gene. Till date more than 1,800 gene therapy

trials have been completed or are ongoing under strict guidelines and supervision of ethics committees.

The best vector to transfer the gene of interest is currently an important limitation. The best vector should be harmless, should be able to carry a large sized gene to the target cells, get incorporated into the nuclear DNA without disturbing any important gene, and should be able to produce the necessary gene product in adequate amounts and over a long period. At present most gene therapy protocols use viral vectors and the possibility that they may become infectious, carcinogenic or cause immune reaction continues to pose a big threat. Recent studies have tried liposomes or gene packed in lipids to avoid the use of viral vectors. However, the search for the ideal vector continues.

Of all gene therapy trials at present, only 10% are being done for single gene disorders. Though a complete cure has not been achieved, clinically significant successes are being reported for some diseases such as Leber congenital amaurosis caused due to *RP65* gene mutations and hemophilia B. Diseases like hemophilia B, where a small amount of the gene product is sufficient for clinical efficacy, are good candidates for gene therapy. Diseases like thalassemia need a regulated expression of the gene and hence are more challenging. For diseases like Duchenne muscular dystrophy the target tissue is big and gene expression in all muscle cells is necessary to be clinically effective. The other challenge for Duchenne muscular dystrophy is the very large size of the gene; a carrier vector for transporting such a large gene is not available. To overcome this, a minigene construct containing only the very important regions of the dystrophin gene has been tried with limited success. Another strategy called exon skipping therapy is being tried for Duchenne muscular dystrophy. It involves the use of small oligonucleotide segments to block the expression of the defective part of the gene and restore the reading frame of the gene sequence, so that the gene product contains the normal sequence of amino acids before and after the defect. Exon skipping therapy has shown some benefit in Phase II trials and Phase III trials are underway. Though not completed yet, positive results are being reported for gene therapy trials for eye diseases like retinitis pigmentosa, Stargardt disease, age related macular degeneration

**Table 2** Novel treatment strategies for genetic disorders, in various stages of experimentation and trial

Disease	Treatment strategy	Drug	Comment
Duchenne muscular dystrophy	Exon skipping	Using antisense oligonucleotides	Phase II, III trials
	Read through stop codon	PTC124* (Ataluren)	Phase II Phase III trial for cystic fibrosis
	Upregulation of Utrophin	SMT C1100-A small molecule – moderator of utrophin expression	Animal models
	Gene therapy	Insertion of minigene With important exons of dystrophin gene	Animal models, cell lines
Spinal muscular atrophy	Modulation of alternate splicing of <i>SMN 2</i> gene to increase its expression	Antisense RNA	Animal model
Fragile-X syndrome	mGluR-5 antagonist	MPEP	Animal model
Fragile-X tremor ataxia syndrome	Silencing by small interfering RNA (siRNA)	Antisense RNA	Also being tried in many disorders like myotonic dystrophy, SCA 8, and cancers
Rett syndrome	Increasing BDNF (Brain-derived neurotrophic factor)	Ampakines	Phase II
	IGF1 (Insulin like growth factor)	IGF 1	Phase I
Achondroplasia	Suppressing activated fibroblast growth factor receptor 3 (FGFR3) signaling	Meclozine, an antihistaminic	Cell lines

Note: \*- also tried in Cystic fibrosis, Rett syndrome and MPS I due to stop codon mutations, MPEP – 2-Methyl 6-phenylethynyl pyridine.



and choroideremia. Gene therapy trials are also underway for cystic fibrosis, Niemann-Pick disease, X-linked adrenoleukodystrophy and hyperlipidemias.

In addition to monogenic disorders gene therapy trials are also being done for cardiovascular diseases, HIV, autoimmune diseases and for cancers. Products of gene therapy have been approved for patients in China and Europe. The *Gene Pill* might become a treatment for every genetic and many nongenetic diseases in this century, but *when* is a question that only time can answer.

## STEM CELL THERAPY AND REGENERATIVE MEDICINE

Transplantation of hematopoietic stem cells from the bone marrow has been an accepted therapy for some genetic hematological disorders and is being used for patients. But the number of diseases for which this option is effective is still small. A lot of basic information about stem cells is becoming available including their sources and ubiquitous presence. In research settings, trials using stem cells from the peripheral blood or the umbilical cord, for various genetic disorders as well as stroke, ischemic heart disease, spinal cord injury, etc. are being done. Though stem cells take part in the normal regenerative and repair processes of the body, there is no convincing, unambiguous proven benefit of such stem cell therapy. Available data does not show any success of stem cell therapy for muscular dystrophies, developmental disabilities like intellectual disability, autism and neurodegenerative disorders. Success has been achieved in transforming human pluripotent cells into disease specific cells. The ability to transform the human pluripotent cells into target cells like pancreatic cells or neurons for use of transplantation has opened up new avenues. This is an important step towards obtaining an unlimited source of cells and may be considered a major step in the direction of regenerative medicine. At present no developed country has approved such type of stem cell therapy for patients.

### Umbilical Cord Blood Banking

Umbilical cord blood is a very good source of hematopoietic stem cells and can be used as an option for human leukocyte antigen (HLA)-matched siblings or unrelated recipients for the treatment of hematological disorders like thalassemia major, aplastic anemia or immunodeficiency disorders. Hence umbilical cord banking has come into practice. Cord blood banking for personal use is not recommended unless there is a family member affected with one of the above mentioned disorders for which stem cell therapy is an accepted option. For a child to need his or her cord blood stem cells in the future is a remote possibility. Stored cord blood of an individual is of no use for the treatment of genetic disorders in the same individual, as the stem cells also have the same genetic defect. Public banking is a good option and the stored cord blood can be used for the needy person with a good HLA match.

## EFFECT OF DIAGNOSTIC ADVANCES ON TREATMENT OUTCOMES

The first and the most important requisite for effective treatment is accurate diagnosis. Tremendous advances have been made in DNA based diagnostics for genetic disorders. Causative genes for more than two-thirds of the 6,000 odd known monogenic disorders have been identified. The technical hurdle of large sizes of genes and genetic heterogeneity has been crossed by next generation high throughput techniques which can sequence multiple genes or the whole genome at a time. Sequencing coding regions (exons) of all genes (termed as the exome) is used as a diagnostic test for undiagnosed disorders suspected to have a genetic etiology. In 2012, for the first time, treatment based on diagnosis obtained

by exome sequencing was done. This was for a young child with Crohn disease-like illness. He was extensively investigated for immune deficiency disorders; but without any success. His exome sequencing identified a sequence variation in an apoptosis inhibitor gene which explained the clinical picture. Based on the diagnosis bone marrow transplantation was done and the child was cured. Similarly in a patient with clinical features of hereditary spastic paraparesis exome sequencing identified a mutation in the gene causing dopa-responsive dystonia. The patient improved markedly with treatment with L-dopa. Such types of diagnostic surprises leading to access to curative treatments is becoming a part of clinical practice, thanks to next generation sequencing. Hence, the contribution of diagnostic techniques to the progress in the management of genetic diseases needs to be emphasized.

Newborn screening has been in patient care for the last five decades. Over the last two decades there has been a number of additions to the diseases included in the newborn screening programs, the latest addition being severe combined immunodeficiency (SCID). The treatment of SCID is bone marrow transplantation which has very good success if done before the onset of symptoms; i.e., before contracting infections. This early pre-symptomatic diagnosis can only be achieved by newborn screening. The progress in diagnosis and management will keep on going hand in hand.

Sequencing the whole genome or whole exome (all coding sequences) has been done for thousands of individuals by now and is possible to be done from the sample taken on filter paper for newborn screening. It has also been done from free fetal DNA (ffDNA) in maternal plasma. All monogenic disorders hence can be diagnosed at or before birth. As more and more disorders become treatable, the pre-symptomatic diagnosis at birth may be the first step to a long and healthy life in future.

## GENETIC COUNSELING

The 21st century holds many promises for genetic disorders. But still many genetic diseases are untreatable, handicapping or associated with morbidity and mortality. The other implication of genetic diseases is the possibility of recurrence in the family. This makes genetic counseling an integral part of the management of genetic disorders.

### Definition

The American Society of Human Genetics has defined genetic counseling as *"a communicative process which deals with human problems associated with the occurrence and/or recurrence of a genetic disorder in a family"*. This process involves an attempt by one or more appropriately trained persons to help an individual or a family to: (i) comprehend the medical facts, including the diagnosis, probable course of the disorder and available management; (ii) understand the manner in which heredity contributes to the disorder, and the risk of recurrence in the family; (iii) understand the alternatives for dealing with the risk of occurrence or recurrence; (iv) choose a course of action which seems to them appropriate in view of this risk, their family goals, ethical and religious standards and to act in accordance with the decision; and (v) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

This makes one understand that the aim of genetic counseling is to educate the family about the genetic disorder and help them to cope with the problem and the risk of recurrence of the disorder.

### Principles and Steps

Genetic counseling is a communication process of management but based on latest scientific and medical knowledge of the

disease. So the process has to be nondirective as against other situations involved in medical advice. Accurate diagnosis, complete family history, latest review of the disease in concern and communication of the information in simple and local language are the steps of genetic counseling. The information provided in the genetic counseling session should be simple and provided to the concerned family members preferably together. The privacy, emotional complexities, socio-economic and religious background and expectations of the family should be taken into consideration to make genetic counseling a success.

A person who seeks genetic counseling is called a consultand or *counselee*, and the person who gives the advice is called the counselor. In association with a medical specialist, persons from various backgrounds such as nursing, sociology, psychology or genetics can be trained as genetic counselors.

### Indications for Genetic Counseling

The following clinical presentations indicate the need for referral to a clinical geneticist and genetic counseling:

- *Congenital malformations* Lethal or nonlethal, isolated or multiple, prenatal or postnatal.
- Unexplained still births/perinatal deaths with or without malformation.
- Developmental delay or mental retardation with or without malformations, facial dysmorphism and/or neurological deficit.
- Neurodegenerative diseases presenting as focal neurological deficit, ataxia, spasticity, hypotonia, seizures or psychomotor regression.
- Myopathies and muscular dystrophies.
- A neonate or an infant with acute sickness, failure to thrive or recurrent episodes of vomiting, acidosis and/or convulsions.
- Ambiguous genitalia or abnormalities of sexual development like primary amenorrhea and delayed puberty.
- Infertility and poor obstetric history like recurrent spontaneous abortions and fetal losses.
- Proportionate or disproportionate short stature.
- Childhood deafness.
- Known monogenic disorders like thalassemia, Wilson disease, hemophilia A, MPS, etc.
- Down syndrome and other chromosomal disorders.
- Familial cancers or cancer prone disorders.
- Relatives of an individual having a structural abnormality of a chromosome or chromosomes.
- Any unusual disease of the skin, eyes, bones or unusual facial features.
- Any disease which is familial.
- Exposure to a known or possible teratogen during pregnancy.
- Consanguineous marriage.
- Advanced maternal age.
- Carrier of a genetic disorder.
- Positive screening test for a genetic disorder.

### PRENATAL DIAGNOSIS

Many a times, helping the family to take reproductive decisions and organizing prenatal diagnosis is the aim of genetic counseling. Availability of invasive and noninvasive diagnostic tests makes things easier for the family and the counselor. A variety of tissues can be collected from the fetus for chromosomal, DNA and biochemical analysis. These include chorionic villi (at 11–12 weeks of gestation) and amniotic fluid (at 16–20 weeks of gestation). Rarely, fetal skin, muscle, liver biopsy or blood sample may be collected for biochemical or tissue analysis. For DNA-based prenatal diagnosis of monogenic disorders mutation detection of the proband or of the carrier parent or parents in the family is

a prerequisite. Analysis of fetal DNA from mother's blood has become technically possible and can be used for fetal Rh typing, single gene disorders and aneuploidy detection. Pre-implantation diagnosis is a good option for families who do not approve of termination of pregnancy.

High resolution ultrasonography can detect a number of structural malformations of the central nervous system, gut, kidneys, limbs, spine and heart. Detection of associated malformations and chromosomal analysis is useful for providing counseling in a case with prenatally detected malformation. But for counseling regarding next pregnancy, examination of the baby or fetus after delivery or termination (fetal autopsy) is important, because in 30–40% cases associated malformations may be missed or may not be detectable on ultrasonography.

### FUTURE AHEAD

Medicine has entered the molecular era. There is a paradigm shift in the diagnosis and management of genetic disorders. Gene therapy may or may not become a reality for all disorders; many new pathway-based drugs and other methods to modify translation and transcription of target genes or modifier genes may open up new avenues for genetic disorders. Success of ERT for lysosomal storage disorders and ivacaftor for cystic fibrosis has also brought another problem to the forefront. This problem is the exorbitant costs of these new treatments due to the heavy cost of research which goes into the development of new therapy. The scientists and the society have to take up this problem.

When one peeps into the future, the other possibility that comes to mind is the treatment of the embryo. Testing of the embryo by testing fDNA in maternal plasma is now possible for chromosomal as well as single gene disorders. Scientists have successfully sequenced the exome of fetus from fDNA, making identification of any inherited or de novo mutations in the fetus possible. A group of scientists have even shown that the extra copy of chromosome 21 in cell lines from a Down syndrome child can be silenced and the normal diploid functional genome can be restored. This makes one dream of the possibility of diagnosis and treatment of embryos and fetuses with genetic disorders.

### IN A NUTSHELL

1. For all cases in which a genetic disorder is diagnosed or suspected, complete evaluation of the affected individual and genetic investigations are important.
2. Latest information about available treatments is the responsibility of a clinician. Missing a diagnosis of a treatable disorders will be a misfortune for the patient and may be considered negligence on the part of the doctor.
3. Genetic counseling is an integral part of the management of a case with a genetic disorder. It is the responsibility of the primary care physician to suspect cases with a probable genetic disorder and refer them to a clinical genetics center. As clinical geneticists are few in number, pediatricians, obstetricians and physicians may have to take up the responsibility of providing diagnosis and counseling for common genetic disorders.
4. New treatment strategies based on the understanding of molecular pathology have become available for some disorders like cystic fibrosis, Marfan syndrome and lysosomal storage disorders and many more in pipeline are showing promises.
5. Gene therapy expected to find cure for all genetic diseases has been successful in immunodeficiency disorder, but many hurdles need to be crossed till it becomes a reality for many other genetic disorders and cancers.

## MORE ON THIS TOPIC

- Cideciyan AV, Jacobson SG, Beltran WA, et al. Human retinal gene therapy for Leber congenital amaurosis shows advancing retinal degeneration despite enduring visual improvement. *Proc Natl Acad Sci USA*. 2013;110:E517-25.
- Dietz H. A healthy tension in translational research. *J Clin Invest*. 2014;124:1425-9.
- Dietz HC. New therapeutic approaches to mendelian disorders. *N Engl J Med*. 2010;363:852-63.
- Fairclough RJ, Wood MJ, Davies KE. Therapy for Duchenne muscular dystrophy: renewed optimism from genetic approaches. *Nature Rev Genet*. 2013;14:373-8.
- Harrison MJ, Murphy DM, Plant BJ. Ivacaftor in a G551D homozygote with cystic fibrosis. *N Engl J Med*. 2013;369:1280-2.
- Muntau AC, Gersting SW. Phenylketonuria as a model for protein misfolding diseases and for the development of next generation orphan drugs for patients with inborn errors of metabolism. *J Inher Metab Dis*. 2010;33:649-58.
- Muro S. New biotechnological and nanomedicine strategies for treatment of lysosomal storage disorders. *Rev Nanomed Nanobiotechnol*. 2010;2:189-204.
- Rabbani B, Tekin M, Mahdiah N. The promise of whole-exome sequencing in medical genetics. *J Hum Genet*. 2014;59:5-15.
- Rauen KA. The RASopathies. *Annu Rev Genomics Hum Genet*. 2013;14:355-69.
- Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. *N Engl J Med*. 2011;364:1144-53.
- Worthey EA, Mayer AN, Syverson GD, et al. Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genet Med*. 2011;13:255-62.

## Chapter 2.6

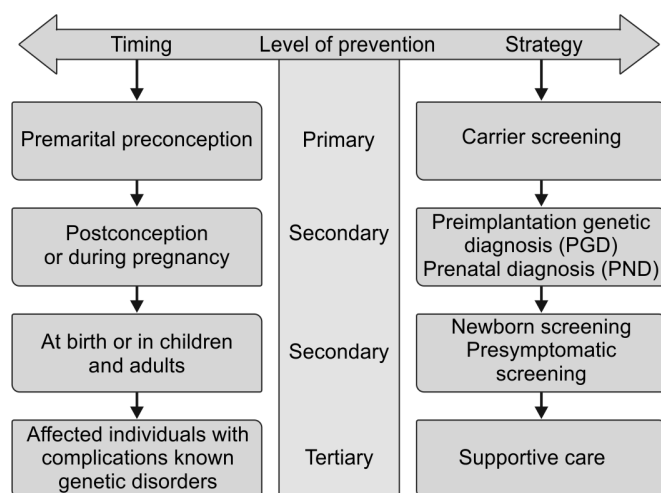
# Prevention of Genetic Disorders

Neerja Gupta, Madhulika Kabra

*An ounce of prevention is worth a pound of cure*—a quote by Benjamin Franklin correctly stresses the importance of prevention which plays a major role in the management of genetic disorders. Several single-gene, chromosomal and multifactorial disorders occur at a high frequency in every population. Over years, better understanding of the pathophysiological mechanisms of genetic disorders has paved way for several newer therapies for various genetic disorders, however, their use does not lead to complete clinical cure for many and is available for a limited number of disorders only. Moreover, the cost of therapy involved in such therapies, the associated morbidity of the disorder and the poor quality of life for the family as a whole, prevention is the focus for all genetic disorders. The prevention of genetic disorders can be done at three levels:

1. **Primary prevention** To prevent the occurrence of the disease, i.e., preventing birth of an affected child. It reduces the incidence and prevalence of a genetic disorder.
2. **Secondary prevention** To prevent clinical manifestations in affected individuals by appropriate early intervention such as by early detection through prenatal diagnosis, newborn screening and presymptomatic screening. It basically detects the disease at a preclinical stage and decreases or ameliorates its severity. It also targets to prevent the recurrence of disease in a particular family by providing high doses of vitamins, such as folic acid, to prevent neural tube defects.
3. **Tertiary prevention** To provide better care and rehabilitation to the patients with disease. It basically means providing best supportive care to the affected patients with various chronic genetic disorders.

The different levels of prevention pass through various life stages for ultimately providing a good quality of life to the individual, family and society at large. **Figure 1** depicts the levels of prevention at different life stages using different strategies.



**Figure 1** Strategies for prevention of genetic disorders

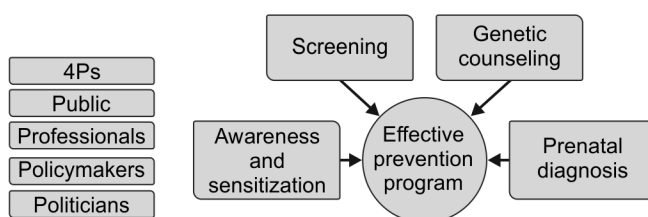
## COMPONENTS OF PREVENTION PROGRAM FOR GENETIC DISORDERS

The three important components of an effective prevention program are awareness, screening and genetic counseling (**Fig. 2**). Increased awareness amongst policy makers, health professionals, paramedics, social health workers and the community requires involvement of mass communication and media. The next step is providing services for various screening tests for genetic disorders. A genetic screening test has to be accompanied by appropriate pretest and post-test counseling. An effective prevention program at various levels, not only reduces the incidence of that particular disorder, morbidity, the psychological and social trauma associated with rearing individuals with these disorders but also gives an opportunity to live with pride and independence to these individuals. **Figure 3** demonstrates the Cyprus model wherein timely introduction of a comprehensive screening program in 1970s led to massive reduction in the incidence of  $\beta$ -thalassemia by 1990s. The decisions to adopt any particular prevention program relies upon the burden of the disorders, ethnic distribution of the disorder, attitudes toward genetic screening, acceptability of termination based upon the religious background, resources and political will. The success of any effective prevention program can be judged on the basis of reduction in the incidence of that particular disorder.

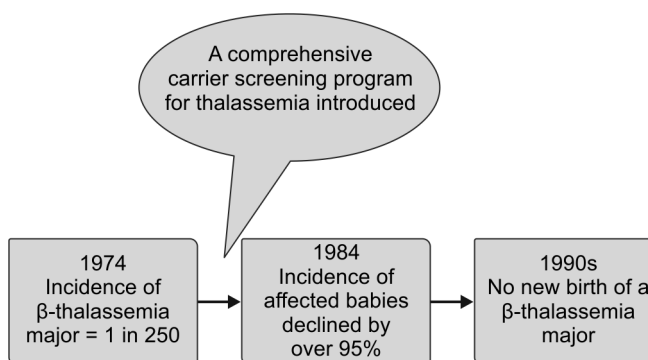
Next section focuses on the strategies that can be used at various levels of prevention for genetic disorders. **Table 1** briefly outlines the various strategies.

## PRIMARY PREVENTION

The disorders most amenable to primary prevention are birth defects such as neural tube defects and chromosomal disorders. Prevention of birth defects is possible through appropriate maternal nutrition, providing supplementation or fortification with folic acid and adequate control of maternal diabetes. A landmark randomized double-blind prevention trial on prevention of neural tube defect by Medical Research Council Vitamin Study Research



**Figure 2** Components of prevention programs



**Figure 3** Cyprus as a success model for effective prevention program for thalassemia



**Table 1** Strategies for primary, secondary and tertiary prevention of genetic disorders

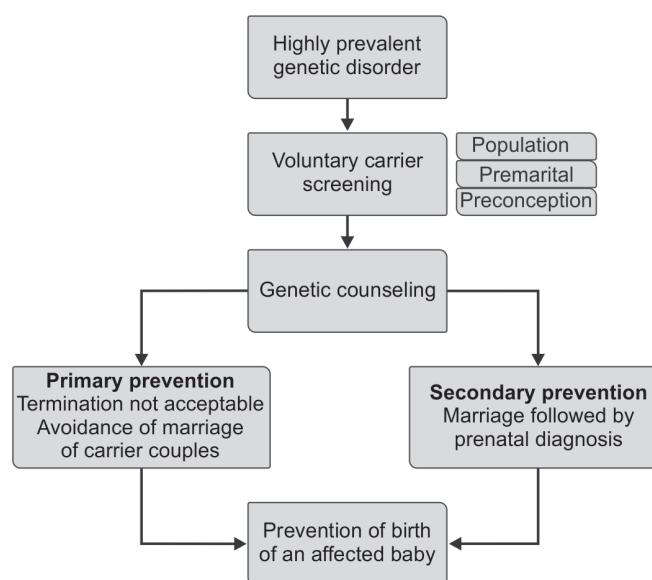
<i>Suggested primary prevention package (preconception and premarital)</i>	<i>Suggested secondary prevention package (pregnancy, neonate, child, and adults)</i>	<i>Suggested tertiary prevention package (neonate, child, and adults)</i>
<ul style="list-style-type: none"> <li>Improved maternal nutrition and folic acid supplementation 400 µg daily</li> <li>Universal rubella immunization</li> <li>Family planning between reproductive age of 20–35 years</li> <li>Identification of high-risk genetic factors and patients, and families (carrier screening) for appropriate genetic counseling at primary health care</li> <li>Control of maternal health and obesity associated conditions such as diabetes</li> <li>Raise awareness about effect of maternal drugs for maternal illnesses on fetuses during pregnancy</li> <li>Identification of families at high-risk of genetic disorders by family history</li> </ul>	<ul style="list-style-type: none"> <li>Control of maternal health associated conditions such as diabetes</li> <li>Shift to safer drugs for maternal illnesses during pregnancy</li> <li>Carrier screening and genetic counseling for common genetic disorders like thalassemia</li> <li>Antenatal biochemical screening for chromosomal and neural tube defects</li> <li>Prenatal diagnosis of malformations by ultrasonography followed by counseling</li> <li>Newborn screening for metabolic disorders and birth defects</li> <li>Presymptomatic screening for at risk family members if medical intervention is possible and feasible</li> </ul>	<ul style="list-style-type: none"> <li>Improved access to medical facilities for children with chronic genetic disorders</li> <li>Multidisciplinary, supportive care</li> <li>Monitoring growth and development of child, complications anticipated for any particular genetic disorders</li> <li>Psychosocial support of affected individuals and their families</li> </ul>

Group in 1991 across 11 countries, demonstrated a 72% protective effect of folic acid in women at high risk of having a pregnancy with a neural tube defect, because of a previous affected pregnancy. Universal rubella immunization and avoidance of teratogenic drugs are other important steps toward primary prevention of birth defects. Avoidance of pregnancy during advanced maternal age can avoid common chromosomal disorders, such as Down syndrome, to some extent, but this is not a practical feasible strategy in the present era. More so majority of babies with Down syndrome in India are born to young mothers. A preconception screening program involving modifiable risk factors, like screening for maternal diabetes, thyroid, syphilis, rubella immunization and folic acid supplementation, is actually lacking in our country as a standard of care even in the majority of big hospitals.

*Primary prevention by carrier screening* for highly prevalent genetic disorders (e.g.,  $\beta$ -thalassemia) in a particular high-risk community comes under this category. Carrier screening during premarital period is a very sensitive issue and should be preceded by appropriate nondirective pretest counseling. Testing should be strictly voluntary as it may avoid marriage of at risk couples. This strategy is particularly useful when abortion is not acceptable, but may not be acceptable for some families as it is difficult to influence personal issues like marriage and reproduction. The usual strategy for any carrier screening program is depicted in **Figure 4**. The objective is to identify all the individuals who themselves are healthy but at risk of having children with a severe autosomal recessive or X-linked disorder. Criteria for carrier screening are given in **Box 1**.

#### BOX 1 Criteria for carrier screening

- Disease should be an important health problem and should be severe but amenable to prevention
- Screening is directed toward high-risk population
- The test should be safe, inexpensive, easily available and should have high sensitivity and specificity
- The screening program should be socially, ethically and morally acceptable to the target population
- Participation in the screening program must be entirely voluntary with prior informed consent and confidentiality must be ensured
- Detailed information about that particular disorder and a pretest and post-test counseling should be available
- At risk carrier couple should have access to various reproductive options (prenatal diagnosis, treatment).

**Figure 4** Strategy for a carrier screening program

The timing of any carrier screening program is program specific. It could either be at population level, during premarital period or can be done preconceptionally. **Table 2** provides the carrier frequency of various genetic disorders in different ethnic groups.

#### Target Disorders for Carrier Screening in Indian Context

Although exact prevalence of most disorder is not known in India due to lack of any registry; a large data available about hemoglobinopathies support it to be a major prevalent group of disorders in our population. The carrier rate of  $\beta$ -thalassemia is 5–15% amongst the Sindhis and Punjabis. Based on various surveys, prevalence of sickle gene is found to vary between 0 and 35% in various regions of our country, being highest in central India. With the current population estimate and birth, it is estimated that over 42 million are carriers and over 12,000 infants are born each year with a major and clinical significant hemoglobinopathy.

**Table 2** Frequency of selected disorders requiring carrier screening in various ethnic groups

Disorder	Ethnic group	Carrier frequency
Alpha thalassemia	Southeast Asians and Chinese	1/25
Beta thalassemia	India, Greek/Italian, Cyprus Sardinia	1/25–1/30
Cystic fibrosis	Northern Europeans	1/25
Phenylketonuria	Northern Europeans	1/50
Sickle cell disease	African-American Central India Specific tribal population	1/12 ~1/15
Spinal muscular atrophy	Asian	1/30
Tay-Sachs disease	Ashkenazi Jews	1/30

Few other disorders, such as megalencephalic leukodystrophy and spinocerebellar ataxia type 12, are frequent genetic disorders in Agarwal community. Other prevalent genetic disorders are glucose-6-phosphate dehydrogenase deficiency, cystic fibrosis, spinal muscular atrophy, Tay-Sachs disease, Duchenne muscular dystrophy, fragile X syndrome and hemophilia.

## SECONDARY PREVENTION

Secondary prevention focuses on avoiding the birth of affected fetus [prenatal screening, prenatal diagnosis and preimplantation genetic diagnosis (PGD)], early detection of the disorders, appropriate medical intervention to minimize the manifestations (newborn screening) or detecting the genetic predisposition for a condition with onset in the later life (presymptomatic screening).

### Prenatal Screening

Objective of the prenatal screening and diagnosis is to identify the mothers at high risk of having an affected fetus with a genetic disease. This includes biochemical screening and evaluation by ultrasonography; noninvasive prenatal testing. Once the fetus is found to be affected, option for termination of pregnancy (the legal age of which in India is 20 weeks) or prepare themselves psychologically for adequate management and care of affected child after birth.

*Indications for prenatal screening and diagnosis are:*

- Advanced maternal age
- Previous child with any chromosomal abnormality
- Previous child with a common single-gene disorder like thalassemia, cystic fibrosis, Duchenne muscular dystrophy, spinal muscular atrophy or multifactorial disorder like neural tube defects, cleft lip/palate
- Abnormal findings in ultrasonographic evaluation of the fetus
- Abnormal maternal screening
- Maternal infection
- Teratogen exposure.

### Neural Tube Defects

Maternal serum  $\alpha$ -fetoprotein (AFP) levels are measured at 16–18 weeks of gestation. A cut-off of more than 2.5 multiple of the median detects more than 90% cases of anencephaly and 80% cases of open spina bifida. Though the specificity of the test is not very high, AFP levels are increased in impending abortion, twin pregnancy, and exomphalos. The test is used widely and has led to a striking decline in the incidence of open neural tube defect.

## Down Syndrome

**Biochemical screening** Antenatal screening is a useful test that detects the likelihood of baby being born with Down syndrome. The American College of Obstetrics and Gynecology and the American College of Medical Genetics and Genomics (ACMG) recommend antenatal screening for women of all age groups. Antenatal screening can be done either during first trimester or second trimester depending upon the availability of the test and the timing of the first visit by a pregnant lady. First trimester screening incorporates maternal age risk, nuchal translucency measurement by ultrasonography along with maternal serum beta human chorionic gonadotropin and pregnancy-associated plasma protein A levels between 11 to 13 completed weeks. The detection rate of first trimester screen varies between 80% and 82% at a false positive rate of 3%. Amongst the second trimester screening, quadruple test is preferred to triple test. It includes maternal age risk and estimation of maternal serum human chorionic gonadotropin, unconjugated estriol, AFP and inhibin A levels between 15 weeks and 19 weeks. If combined with 18 weeks anomaly scan, the detection rate is approximately 80% at a false positive rate of 3%. If the risk for Down syndrome exceeds the cut off of 1:250, prenatal diagnosis either by chorionic villi sampling at 11–12 weeks or amniocentesis 16–18 weeks may be offered to examine the fetal chromosomes. The results are usually available in 2–3 weeks. Rapid prenatal diagnosis in 48 hours can also be provided using quantitative fluorescent polymerase chain reaction or interphase fluorescence in situ hybridization.

Recently, a very reliable noninvasive prenatal screening strategy for common chromosomal aneuploidies using next-generation sequencing technology has come into clinical practice with very high sensitivity and specificity in early gestation.

**Ultrasound screening** Routine fetal anomaly scan is done at 18–20 weeks to look at the major malformations. Significant sonographic findings are seen in nearly all fetuses with trisomy 13, 77–100% of trisomy 18 and 33–50% of fetus with Down syndrome. Presence of multiple abnormalities raises the risk of chromosomal abnormality to 35%.

### Prenatal Diagnosis and Preimplantation Genetic Diagnosis

This is possible for single-gene disorders and any structural chromosomal rearrangement in one of the partners. Most common indications are known single-gene disorder or chromosomal abnormality in a previous affected child in the family. These tests can also be offered if the married couple is found to be carrier for any prevalent single-gene disorder on routine screening and mutations have been identified in the couple. Prenatal diagnosis for above mentioned disorders are widely available in India, however, experience with PGD for single-gene disorders is still limited in India.

### Newborn Screening (Also see Chapter 3.19)

Newborn screening (NBS) screens all newborns for disorders in which symptoms are not clinically evident and an early treatment can prevent or at least ameliorate the consequences. It is a comprehensive system of secondary prevention. Like any other screening program, it requires education, screening, diagnosis, management, follow-up and evaluation. It needs financial and personnel resources for sustainability and often challenged by economic, political and cultural considerations. The criteria for NBS program is given in **Box 2**. The list of disorders commonly included in a newborn screening program is given in **Table 3**.

**BOX 2** Criteria for newborn screening

- Should be an important health problem
- Facilities for diagnosis and treatment should be available
- Simple method of sample collection
- High benefit to cost ratio
- High sensitivity (no false negative) and high specificity (few false positive)
- The natural history should be adequately understood
- Appropriate follow-up of abnormal results so that affected children can be diagnosed and treated in a timely fashion.

**Table 3** List of disorders included in a newborn screening program

Phenylketonuria	Biotinidase deficiency
Hypothyroidism	Toxoplasmosis
Galactosemia	Hemoglobinopathies
Maple syrup urine disease	Deafness
Homocystinuria	Cyanotic congenital heart disease
Cystic fibrosis	Congenital adrenal hyperplasia
Tyrosinemia	Glucose-6-phosphate dehydrogenase deficiency

**Current Situation of Newborn Screening in India**

There have been several individual programs across India, e.g., program in Chandigarh, Goa, Gujarat, Kerala, UP, now very recently a program is launched in Haryana. Indian Council of Medical Research recently funded a multicenter feasibility study including five regions of the country screening 100,000 babies for congenital hypothyroidism (CH) and congenital adrenal hyperplasia. A high incidence of CH was detected (unpublished) and it was concluded that implementation in the country will be feasible in a phased manner. So far, there is no national NBS program.

**Presymptomatic Screening**

It includes screening of presymptomatic individuals at risk for adult-onset genetic disease where effective surveillance for the disease is the mainstay for at risk persons and the family. The benefits of this testing are targeted surveillance, prognosis assessment, and solving uncertainties. It has many debatable ethical and legal issues. Examples are familial hypercholesterolemia, factor V Leiden mutation, hereditary hemochromatosis, adult onset polycystic kidney disease, breast cancer, colon cancer, etc.

**TERTIARY PREVENTION**

Tertiary prevention includes providing supportive and rehabilitative care of individuals with various complications of genetic disorders to minimize the disability and dependency of these individuals and their family. The various strategies could be anticipatory guidance for prevention of complication such as obesity in achondroplasia, prophylactic posterior cervical fusion for Morquio syndrome, prophylactic mastectomy for individuals with high risk of breast cancers, proactive monitoring to avert development of complications, and providing rehabilitative and occupational services to maximize the potential of these differently able individuals such as providing orthosis for disorders with joint involvement, physiotherapy in neuromuscular disorders, hearing aids or speech therapy. Another most important but often neglected component is psychological support of these individuals and their families with genetic disorders. Year 2013

has been a landmark year as a very ambitious national program on *child health screening and early intervention services* [Rashtriya Bal Suraksha Karyakram (RBSK)] for universal screening, early detection and management has been launched by Government of India under the National Rural Health Mission of the Ministry of Health and Family Welfare. It targets approximately 27 crore children in the age group of 0–18 years with an objective to improve the overall quality of life of children through early detection of 4Ds (birth defects, diseases, deficiencies, development delay including disabilities). This program basically provides both secondary and tertiary prevention for nine common structural birth defects [neural tube defect, Down syndrome, cleft lip and palate/cleft palate alone, talipes (club foot), developmental dysplasia of the hip, congenital cataract, congenital deafness, congenital heart diseases and retinopathy of prematurity]. It also includes few important functional defects such as developmental delay, CH, sickle cell anemia, and  $\beta$ -thalassemia.

**Ethical Dilemmas in Genetic Screening**

To protect the child's autonomy, in the absence of any medical relevance, routine carrier testing or screening for recessive conditions and late onset disorders during childhood is not recommended by the American Academy of Pediatrics and ACMG. Possible *negative consequences of genetic screening* include stigmatization, labeling, or discrimination in work place or in insurance. It also carries a potential risk of misunderstanding the difference between affected and carrier.

**Challenges in the Development of Population-based Prevention Programs for Genetic Disorders in India**

The main challenges are other health priorities, limited political will, lack of awareness, limited resources both financial and personnel and lack of integration of genetic services with the existing programs. Countries, like India, are still struggling to achieve an appropriate control of other priority conditions, such as infection and malnutrition, and not yet attained Millennium Development Goal 4. Inclusion of these preventive strategies was not under the purview of government until last year. With RBSK, we are yet to recognize the actual burden (both social and economical) of these disorders and generate a political will to make prevention programs for genetic disorders universal. Recognizing the magnitude of genetic disorders in the community, it is imperative that more preventive measures for genetic disorders are integrated with the above strategies not only to decrease the burden but also to seed the soil by building up the capacity for genetic services at grass root levels.

**IN A NUTSHELL**

1. Genetic disorders are quite prevalent in the vast population of India.
2. In the absence of absolute cure for most of the genetic disorders, there is a need to develop effective preventive programs at various levels.
3. Prevention of genetic disorders requires mass education (both at community level and amongst health professionals) about common genetic disorders, availability of various screening tests, prenatal diagnosis and appropriate genetic counseling.
4. Any genetic screening tests should follow the principles of screening and should be accompanied with detailed information, pretest and post-test counseling and should maintain the autonomy and privacy of the individual being tested.

**MORE ON THIS TOPIC**

Bianchi DW1, Parker RL, Wentworth J, et al. DNA sequencing versus standard prenatal aneuploidy screening. *N Engl J Med*. 2014;370:799-808.

Cuckle HS, Benn PA. Multi-marker maternal serum screening for chromosomal abnormalities. In: Milunsky A, Milunsky JM. *Genetic Disorders and the Fetus: Diagnosis, Prevention, and Treatment*. 6th ed. USA: Wiley Blackwell; 2010. pp. 771-819.

Kapoor S, Kabra M. Newborn screening in India: current perspectives. *Indian Pediatr*. 2010;47:219-24.

McGinniss MJ, Kaback MM. Heterozygote testing and carrier screening. In: Rimoin DL, Pyeritz RE, Korf BR. *Emery and Rimoin's Principles and Practice of Medical Genetics*. 6th ed. USA: Academic Press; 2013.

Mohanty D, Das K. Genetic counselling in tribals in India. *Indian J Med Res*. 2011;134:561-71.

Verma IC, Saxena R, Kohli S. Past, present and future scenario of thalassaemic care and control in India. *Indian J Med Res*. 2011;134: 507-21.



## Section 3 METABOLIC DISORDERS

**Section Editors** Madhulika Kabra, Neerja Gupta

### Chapter 3.1

## Approach to Inborn Errors of Metabolism

Chitra Prasad, CA Rupar

Inborn errors of metabolism (IEM) are in essence the *new kid on the block*. With improved detection and management of infectious diseases, attention is now focused on these genetic IEM with newer advances in diagnosis and management. Over a hundred years ago, in 1908, Sir Archibald Garrod, father of metabolic medicine, gave the prestigious Croonian lectures on four IEMs in London, UK (alkaptonuria, albinism, cystinuria and the benign pentosuria, **Figs 1A to C**). At the time these diseases were considered a variation, as a genetic trait that was not of clinical significance. However, the identification of phenylketonuria (PKU; the prototype of IEM) by Dr Asbjørn Følling a few years later in two mentally retarded siblings brought a chemical discovery into realm of management for mental retardation. It has been 80 years since PKU was first discovered. Early diagnosis through newborn screening (NBS) and dietary management of PKU has revolutionized the field of medicine.

Inborn errors of metabolism are individually rare; however, collectively their number increases everyday. There are close to 1,000 known metabolic disorders. Many of these disorders present in neonates, infants and children; hence, for a pediatrician it is essential that these disorders be recognized and managed appropriately as some of them are amenable to early detection and treatment. IEM are also genetic disorders, thus making genetic counseling around recurrence risk imperative for individuals who have had one affected child.

### EPIDEMIOLOGY

There are more than 1,500 articles, reviews and case reports on IEM from India and other nearby developing countries in the last 10 years. This highlights that IEM are certainly not rare in Southeast Asia. Reasons for increased interest and recognition are better awareness and availability of newer modalities of diagnosis for IEM. Many of these patients were previously labeled as having sepsis or other illnesses. Diagnosing and managing IEM in India and other developing countries is a challenge since some of the biochemical tests are not routinely available. Therapies of IEM are lifelong for most of the disorders and can be very expensive. We believe that IEM represent a true example of potential of collaborative medicine whereby families, many specialists, allied professionals, politicians and health-care advocates can play an important role. The information exchange is taking place at a pace never previously imagined. With access to the Internet even in remote areas, parents and families may be aware of the conditions before physicians. However, local innovations for therapies and diagnosis will need to take place in developing countries so that cost of diagnosis and management is no longer prohibitive.

### PATHOGENESIS

Metabolism is the process of renewal and breakdown of the tissues of the body. Enzymes are the catalysts in conversion of one chemical to another. Mutations affecting enzyme activity can cause the build-up of the substrate with subsequent deficiencies of the product. Accumulation of substrate can be diagnostically important; for example, phenylalanine in PKU (**Table 1**). Accumulation of substrate is one of the ways in which many IEM present (**Flow chart 1**). Other pathogenetic mechanisms involve the deficiency of the product, e.g., vitamin B<sub>12</sub> deficiency in transcobalamin deficiency. There can also be an accumulation of a minor metabolite, such as galactitol in galactosemia, which can cause cataracts.

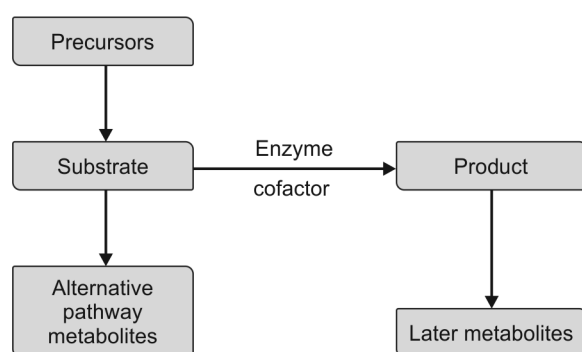


**Figures 1A to C** Alkaptonuria showing pigmentation on the (a) ears; and (b) in the eyes; (c) Albinism: a 6-year-old boy with light pigmentation of eyes and hair

Source: Prasad C, Galbraith PA. Clin Genet. 2005;68:199-203. With permission from Blackwell Munksgaard.

**Table 1** Pathogenesis of inborn errors of metabolism (IEM)

Accumulated substrates proximal to the enzyme block
<ul style="list-style-type: none"> <li>• Storage disorder</li> <li>• Hyperammonemia in organic acidemia (indirect)</li> </ul>
Deficient products distal to the block
<ul style="list-style-type: none"> <li>• Biotinidase deficiency</li> <li>• Neurotransmitter deficiency (e.g. dopamine) in phenylketonuria</li> </ul>
Accumulation of unusual intermediates
<ul style="list-style-type: none"> <li>• Galactitol—galactosemia</li> <li>• Causing secondary carnitine deficiency in organic acidemia</li> </ul>
Other pathogenesis
<ul style="list-style-type: none"> <li>• Energy deprivation—mitochondrial disorders</li> <li>• Hypoglycemia and lactic acidosis in disorders of gluconeogenesis</li> <li>• Protein glycosylation abnormalities in congenital disorders of glycosylation</li> </ul>

**Flow chart 1** Pathogenesis of inborn errors of metabolism

Source: Dr Mark Korson, Associate Professor of Pediatrics at Tufts University School of Medicine.

Another disease-causing class of mutations can occur in genes that encode transporter proteins, e.g., the mitochondrial ornithine transporter, which transports ornithine across the inner mitochondrial membrane in the hyperammonemia, hyperornithinemia, homocitrullinemia syndrome. This results in intramitochondrial ornithine deficiency, which then leads to hyperammonemia. Bioppterin deficiency, which is a cofactor for phenylalanine hydroxylase, can cause features similar to infantile parkinsonism. Thus, IEM have many different underlying mechanisms. Some of the other examples of pathogenetic mechanisms are given in **Table 1**.

## INHERITANCE, GENETIC COUNSELING AND PRENATAL DIAGNOSIS

Most of the IEM are inherited in an autosomal recessive manner. With the increased incidence of consanguinity (inbreeding) that is commonly seen in various part of India and other countries, there is an increased incidence of autosomal recessive disorders. However, even within metabolic disorders, there are notable exceptions to autosomal recessive inheritance such as ornithine transcarbamylase (OTC) deficiency, Menkes disease, Hunter syndrome and Fabry disease (all X-linked), acute intermittent porphyria and hereditary hypercholesterolemia (autosomal dominant inheritance), and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy and ragged red fibers (MERRF; maternal inheritance). A family history should always be obtained when there is a suspicion of IEM. Even within a very busy clinic, this information is too

important to be neglected. Once a formal diagnosis is made, a genetic counselor should ideally meet with the patient's family and explain the recurrence risk (e.g., in autosomal recessive disorders, there is a 1 in 4 risk for having an affected child and a 2/3 risk of being a carrier). These concepts should be explained with the use of diagrams and other genetic counseling aids. Where mutations are available, prenatal diagnosis can be done using molecular studies (preferable to enzymatic diagnosis since it can be difficult to differentiate carrier versus affected). Chorionic villus sampling or amniocentesis can be used. Since genetic counselors are not commonly available in India and developing countries, physicians should become familiar with basic genetic concepts.

The disease phenotype can vary remarkably within the family, a reminder that disease causing mutation may be influenced by gene-gene interaction and by gene-environment interaction.

## CLASSIFICATION

It is a daunting task to try and classify IEM. A number of classifications have been proposed for IEM. One is based on organelle involved: lysosomal disorders; peroxisomal disorders; mitochondrial disorders; and prelysosomal diseases. Another classification is based on size of the affected molecules:

- *Small molecule diseases* Diseases of amino acids, organic acidemia, and simple sugars (galactosemia, etc.), disorder of creatine metabolism (causing developmental delay, seizures and dystonia).
- *Complex molecule disease* Lysosomal disorders, mucopolysaccharidosis II (I-cell) disease, Gaucher disease, Hurler and Hunter syndrome.

## CLINICAL FEATURES

Inborn errors of metabolism are great mimickers of other disease processes, particularly sepsis. Almost all organ systems can be affected by IEM singly or in a multisystemic manner. Thus, it is helpful to keep IEM in the differential diagnosis of many medical conditions. The classic clinical scenario of IEM is of a healthy term infant who decompensates in the first few days after birth. During pregnancy, the fetus is protected, as the intermediate metabolic products cross placental barrier and are filtered through the mother's system.

## CLINICAL APPROACH TO INBORN ERRORS OF METABOLISM

Inborn errors of metabolism should be considered at all ages. Typical stresses, such as fasting, surgery, illness, constipation, excess protein, can worsen patients of IEM (intoxication type), such as amino acidopathies, maple syrup urine disease (MSUD), urea cycle disorders, organic acidemia and mitochondrial disorders. Of note, disorders of lysosomal metabolism (chronic neurodegenerative disorders), e.g., storage disorders, such as Batten disease, Hurler syndrome and Hunter syndrome, are not typically affected with acute stresses mentioned above. A few pointers in history of IEM are listed in **Box 1**. Some of the more common presentations and period of onset of IEM are discussed in **Box 1**.

### Pregnancy

A minor fraction of patients with hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome cases are caused by fetal homozygous long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency. OTC deficiency can present with increased sleepiness and coma in female carriers.

**BOX 1** History pointers which may be useful for inborn error of metabolism

- Diminished exercise intolerance (e.g., mitochondrial disorders)
- Unusual severity of symptoms during illness (e.g., organic acidemia, mitochondrial disorders)
- Unusual odors (e.g., MSUD)
- Avoidance/intolerance of certain foods, e.g., urea cycle disorders (e.g., avoidance of protein)
- Family history of metabolic-oriented symptoms and consanguinity (e.g., autosomal recessive disorders)
- Sudden infant death syndrome [SIDS, medium-chain acyl-CoA dehydrogenase deficiency (e.g., MCAD)]
- Regression of milestones (e.g., metachromatic leukodystrophy)

**Fetus****Nonimmune Hydrops**

A number of lysosomal disorders can present as nonimmune hydrops. Disorders such as sialidosis, mucopolysaccharidosis VII (MPS VII), and congenital disorders of glycosylation (CDG) should be considered when nonimmune hydrops are identified. Prognosis is usually poor.

**Lack of/Poor Fetal Movements/Arthrogryposis/  
Polyhydramnios**

Glycogen storage type IV, CDG can present with poor fetal movements and arthrogryposis.

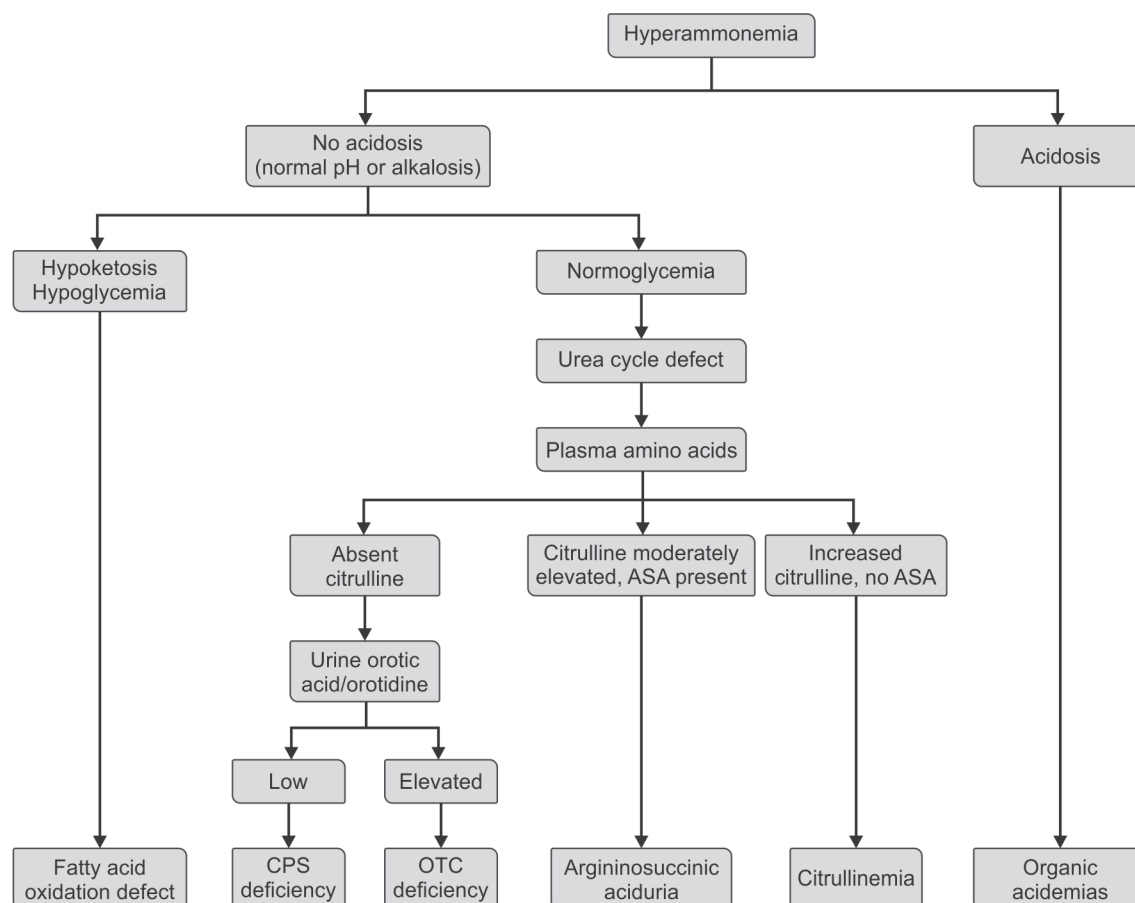
**Neonatal Period**

Neonates have a very limited repertoire by which they manifest disease symptoms. IEM symptoms during neonatal period are indistinguishable from sepsis, such as vomiting, cyanosis, lethargy, seizures, hypotonia, poor feeding, poor sucking and hiccups. Hence, IEM should always be considered in the differential diagnosis of sepsis. Some of the common IEM to consider in this age group are aminoacidopathies, urea cycle disorders, organic acidemia, Zellweger syndrome and seizure disorders such as pyridoxine dependency.

A child who is normal at birth can present in the newborn period with a catastrophic illness or encephalopathy. Such a child should be screened for biochemical disturbances including hyperammonemia, hypoglycemia, metabolic acidosis and lactic acidosis.

**Hyperammonemia**

Deficiency of any of the six enzymes in the urea cycle results in the accumulation of ammonia and leads to encephalopathy. Episodes of encephalopathy and associated symptoms are unpredictable and, if untreated, are lethal or produce devastating neurologic sequelae in long-term survivors. Urea cycle disorders are typically associated with respiratory alkalosis. Rising ammonia level is a medical emergency as there is a risk of raised intracranial pressure. High ammonia can also be caused by organic acidemia and fatty acid oxidation disorders. In this situation, there will be metabolic acidosis associated with hyperammonemia (**Flow chart 2**). Arginase deficiency (the last enzyme) typically presents with spastic diplegia rather than hyperammonemia in the newborn period.

**Flow chart 2** Approach to hyperammonemia

Abbreviations: ASA, argininosuccinic aciduria; OTC, ornithine transcarbamylase; CPS, carbamoyl phosphate synthetase.

Source: Modified from Burton B. Inborn errors of metabolism in infancy: a guide to diagnosis. *Pediatrics*.1998;102:e69-77 and Summar M. Current strategies for the management of neonatal urea cycle disorders. *J Pediatr*. 2001;138:S30-9.

*In any lethargic, septic-appearing neonate, child, adult without a diagnosis measure blood ammonia levels!!*

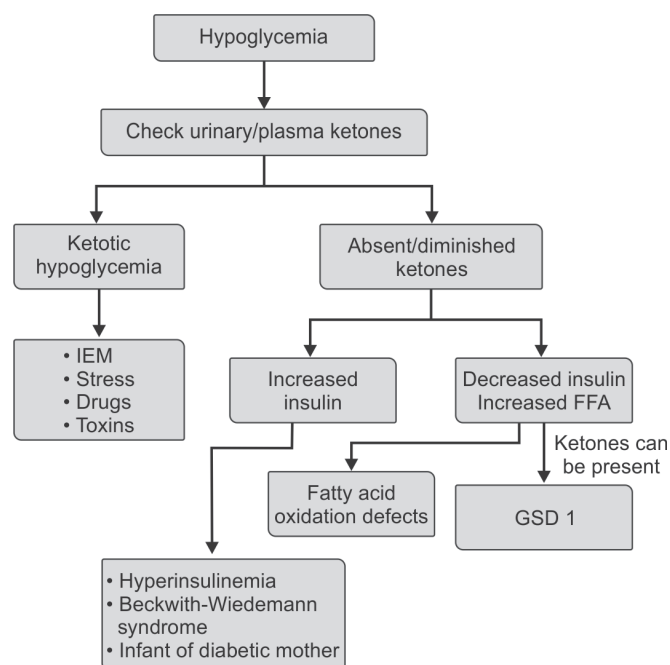
### Hypoglycemia

Although hypoglycemia can be a presenting feature of many unrelated conditions (sepsis, drugs, insulin, cardiac conditions, etc.), nevertheless, some hypoglycemic episodes could be due to IEM, particularly in cases of multisystemic involvement (**Flow chart 3**). Glycogen storage disease (GSD) type 0, I, III, VI and IX; glucose transporter 2 deficiency; fatty acid oxidation [medium-chain acyl-CoA dehydrogenase (MCAD)]; ketogenesis disorders; and gluconeogenesis disorders can cause hypoglycemia. Other ketogenesis disorders [3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) lyase deficiency], and gluconeogenesis disorders (fructose-1,6-biphosphatase deficiency) can also cause hypoglycemia in neonate and infancy.

### Metabolic Acidosis

Metabolic acidosis is characterized by decreases in arterial blood pH (pH < 7.30), plasma bicarbonate and pCO<sub>2</sub>. This is classically caused by organic acidemia. A number of these disorders are due to defects in the catabolic pathways for the branched chain amino acids, or other amino acids after deamination. Examples of organic acidemia include methylmalonic acidemia, propionic acidemia (PA), and isovaleric acidemia (IVA). These disorders may present in the neonatal period with an increased anion gap (>15) metabolic acidosis (**Flow chart 4**). The most severe presentation is of a healthy newborn infant who becomes very ill within the first 24–48 hours with profound metabolic acidosis, hyperammonemia (which is due to secondary impairment of the urea cycle), urine ketosis and encephalopathy. Features of cerebral edema with a bulging fontanel may be present. Presence of ketones in the urine may be a clue for organic acidemia as urinary ketones are normally not seen in a neonate.

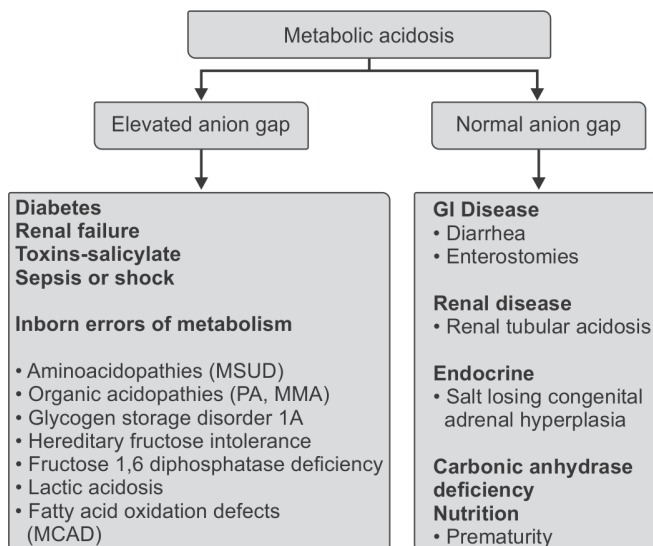
**Flow chart 3** Approach to hypoglycemia



**Abbreviations:** IEM, inborn errors of metabolism; FFA, free fatty acids; GSD, glycogen storage disease.

**Source:** Mark Korson, Associate Professor of Pediatrics at Tufts University School of Medicine.

**Flow chart 4** Approach to metabolic acidosis



**Abbreviations:** MSUD, maple syrup urine disease; MCAD, medium-chain acyl-CoA dehydrogenase; GI, gastrointestinal; PA, propionic acidemia; MMA, methylmalonic acidemia.

**Source:** Dr Mark Korson, Associate Professor of Pediatrics at Tufts University School of Medicine; and modified from Prasad C, Rupar CA. Inborn errors of metabolism in infancy and childhood presenting with metabolic acidosis. Indian Journal of Practical Pediatrics. 2010;12:155.

### Lactic Acidosis

Lactic acidosis is the most common metabolic acidosis. It can be caused by shock or poor perfusion from a variety of causes including congenital heart defects (e.g., coarctation of the aorta and hypoplastic left heart syndrome). Lactate levels less than 10 mmol/L may not result in an elevated anion gap; however, high anion gap metabolic acidosis can be due to lactic acidosis (levels > 10–15 mmol/L). There are primary lactic acidosis disorders such as pyruvate dehydrogenase (PDH) deficiency, pyruvate carboxylase deficiency and respiratory chain disorders. Elevations in lactate reflect increased concentrations of pyruvate, the assay of which is not easily available in most laboratories. Accumulated pyruvate is also converted to lactate and alanine. The ratio of plasma lactate concentration to pyruvate reflects the redox potential within the cytosol. A decreased lactate/pyruvate ratio of less than 10 indicates PDH deficiency and an increased lactate/pyruvate ratio (>25) is suggestive of pyruvate carboxylase deficiency or mitochondrial respiratory chain abnormalities. Secondary lactic acidosis is also a feature of organic acidemia and fatty acid  $\beta$ -oxidation disorders.

### Clinical Clues in Neonates/Children

#### Unusual Smells

A specific smell may be an indication of IEM. However, on other occasions this may not be reliable. Common examples include smell of maple syrup (MSUD), sweaty feet odor (IVA, type II glutaric aciduria), fishy odor (trimethylaminuria, carnitine therapy) and cat urine odor (3-methylcrotonylcarboxylase deficiency).

#### Liver Disease

Cholestatic jaundice should also be investigated for IEM. Niemann-Pick C,  $\alpha$ -1 antitrypsin deficiency, galactosemia, hereditary fructose intolerance, tyrosinemia. GSD IV can present with predominant hepatomegaly. Wilson disease presents with liver disease in early childhood and later causes neurological involvement.



### Hepatosplenomegaly

There should be suspicion of a storage disorder with hepatosplenomegaly. Differential diagnoses include hematological and autoimmune disorders, Gaucher disease, Niemann-Pick A, Niemann-Pick B, mucopolysaccharidoses. In many instances there will be other systemic features as well.

### Neurologic Disease

Neurological system is affected in many IEM. The IEM also affect different parts of nervous system causing different symptomatology. Neurological symptoms and respective disorders of metabolism are listed in **Box 2**.

### Psychiatric Symptoms

Unusual behaviors and psychiatric manifestations are now recognized for some of the IEM. Urea cycle disorders, for example, OTC deficiency can present with bizarre behaviors and may be wrongly diagnosed as a psychiatric disorder. Porphyrrias (hepatic) have psychiatric manifestations. A baseline metabolic workup should be done when there are atypical features or a family history of IEM.

### Cardiomyopathy

**Pompe disease** (glycogen storage disorder Type II): It can cause cardiomyopathy. A history of sweating during feeding should prompt cardiac investigations. Carnitine transporter deficiency presents with cardiomyopathy. Prognosis is good if carnitine is supplemented early and given for life. Fabry disease may also present with hypertrophic cardiomyopathy.

### Storage Disease

Coarse facies, hepatosplenomegaly, skeletal dysplasia, vision and hearing involvement, neurodegenerative course are typical for mucopolysaccharidoses, mucopolipidosis II (**Fig. 3**) and oligosaccharidoses.

### Skin

A thorough clinic examination at initial assessment may reduce the chances of missing a diagnosis. For example, one of our patients labeled as having a psychiatric disorder was later found to have classic angiokeratoma and was diagnosed with Fabry disease.

### BOX 2 Neurological signs and symptoms of inborn errors of metabolism

- Hypotonia
  - Disorder of peroxisomal biogenesis (prototype is Zellweger syndrome)
  - Pompe disease
  - Congenital disorders of glycosylation
- Seizures
  - Nonketotic hyperglycinemia
  - Pyridoxine and pyridoxal phosphate deficiency
  - Isolated sulfite oxidase and molybdenum cofactor deficiency
- Delayed development
  - Many disorders, i.e., untreated PKU
- Ataxia
  - Congenital disorders of glycosylation syndrome (**Fig. 2**)
  - Abetalipoproteinemia
- Loss of consciousness/unexplained lethargy
  - Hyperammonemia
- Dystonia and other movement disorders
  - Glutaric acidemia type 1
  - Leigh's disease
  - Pterin cofactor deficiency
- Childhood dementia
  - Metachromatic leukodystrophy
- Spastic paraplegia/cerebral palsy-like picture
  - Arginase deficiency
- Strokes
  - MELAS
  - Homocystinuria
  - Fabry disease
- Muscle disease (myopathy/rhabdomyolysis)
  - Pompe disease
  - Carnitine palmitoyl transferase II
  - McArdle disease (glycogen storage type V)

### Renal Disease

Fabry disease can cause glomerular involvement and renal failure. Tubular function can be involved in mitochondrial disorders and galactosemia. Cystinosis can also impair kidney function.

### Dysmorphism/Multiple Congenital Malformations

Many disorders initially thought to be pure genetic syndromes have now been identified as having a metabolic basis.



**Figure 2** A 9-month-old male infant with inverted nipples and fat pads (Congenital disorders of glycosylation)



**Figure 3** Child with mucopolipidosis type II with coarse features and large tongue

For example, peroxisomal disorders generally are associated with dysmorphic features characterized by the Zellweger spectrum disorders (high forehead, flat occiput, large anterior fontanel, hypoplastic supraorbital ridges, epicanthal folds, broad nasal bridge, anteverted nostrils and micrognathia). Many of the CDG exhibit dysmorphic features (large ears, strabismus, and abnormal fat distribution, **Fig. 2**). Smith-Lemli-Opitz syndrome disorder of cholesterol metabolism causes ptosis, facial dysmorphism and the characteristic 2/3 toe syndactyly (**Figs 4A and B**). Mevalonic aciduria can also cause dysmorphic features with frontal bossing and failure to thrive.



**Figures 4A and B** Smith-Lemli-Opitz syndrome. (A) A young girl with hypotonia; (B) Syndactyly of 2/3 toe

Source: Reproduced with permission from Wiley Publications (Prasad C, Marles S, Prasad AN, et al. Smith-Lemli-Opitz syndrome: new mutation with a mild phenotype. *Am J Med Genet.* 2002;108:64-8).

### Skeletal/Skeletal Dysplasia

Morquio syndrome (type IV) has a predominant skeletal phenotype. Rhizomelic chondrodysplasia punctata (RCDP) is associated with short stature, rhizomelic shortening and stippling calcification. This is a peroxisomal disorder of plasmalogen biosynthesis. Homocystinuria causes marfanoid habitus with skeletal involvement (**Figs 5A to F**).

### Lung Disease

Interstitial lung opacities are seen in Niemann-Pick B and Gaucher disease. Pompe disease and other neuromuscular diseases can also affect lung function.

### Eye Involvement

Eye examination can provide clues to many IEM. Cataracts are seen in galactosemia and RCDP. Retinitis pigmentosa is a clue to mitochondrial disorders or abetalipoproteinemia. Corneal clouding may suggest Hurler syndrome. Macular cherry red spot (**Fig. 6**) is a characteristic feature of GM1 gangliosidosis and Tay-Sachs disease. Lens dislocation is a clue to homocystinuria (**Fig. 5**; also skeletal marfanoid phenotype) or molybdenum cofactor deficiency/isolated sulfite oxidase deficiency.

### Hearing

Recurrent ear infections are typically seen in MPS and hearing loss is also seen in biotinidase deficiency.

### Hair

*Menkes kinky hair disease* Pili torti hair abnormality is seen (X-linked recessive, **Figs 7A and B**). Alopecia is seen in untreated biotinidase deficiency.



**Figures 5A to F** Physical signs of homocystinuria. (A) Lens dislocation; (B) Marfanoid habitus; (C) Pectus excavatum; (D) Long fingers; (E) Pes cavus; (F) High arched palate





**Figure 6** Cherry red spot in the retina

### Endocrine Dysfunction

Congenital hypothyroidism and persistent hyperinsulinemic hypoglycemia in CDG; adrenal dysfunction and disorders of sexual development in congenital adrenal hyperplasia; and primary adrenal insufficiency in adrenoleukodystrophy.

### Hematological

Transcobalamin deficiency and gastric intrinsic factor deficiency can mimic leukemia. Thrombocytopenia and leukopenia is a clue to organic acidemia.

## INVESTIGATIONS

Investigations for IEM are summarized in **Tables 2 and 3**. We have also briefly summarized the investigations that need to be carried out at the time of death to ensure that appropriate samples are obtained which may be helpful in making a diagnosis (**Box 3**).

### BOX 3 Considerations regarding metabolic autopsy

- Notify pathology early
- Plasma, urine, bile, vitreous humor samples (can be used for acylcarnitine profile, DNA banking)
- Skin biopsy from well-perfused area (can isolate DNA)
- Permission for autopsy/multiple biopsies
- Flash-freeze liver
- Photograph and skeletal survey

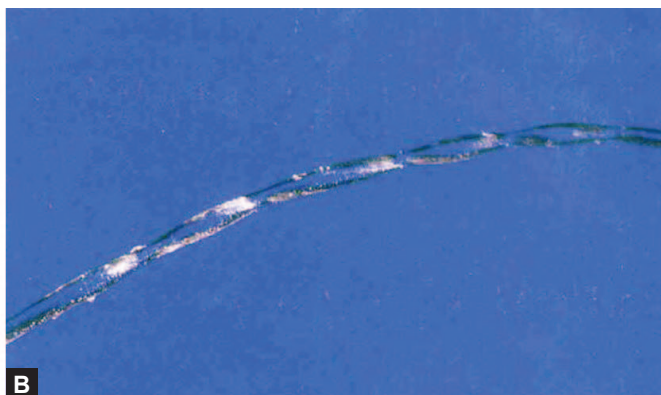
## THERAPIES FOR INBORN ERRORS OF METABOLISM

It is said that *one man's meat is another man's poison*. This is exemplified by many urea cycle patients who intuitively avoid protein as it causes them to be sick.

Therapy for IEM has to be individualized. A trained metabolic dietitian is an essential part of the team to help with the dietary modifications of the particular IEM. Once the diet is modified, there can be secondary effects on other systems such as the bone health, deficiencies of trace elements and minerals. Hence, regular monitoring and expertise of dietitian is essential for ensuring proper growth and development despite the modified diet. Important treatment modalities are listed below:

- **Dietary adjustment**
  - Substrate restriction, e.g., low phenylalanine formula in PKU (most well-studied)
  - Branched chain amino acids in MSUD
  - Galactose in galactosemia (difficult disorder to treat despite galactose restriction due to endogenous production)
- **Replacement of deficient product**
  - Thyroxine in congenital hypothyroidism
  - Biotin in biotinidase deficiency (very good prognosis if treated after NBS)
- **Vitamin supplementation—cofactors** (activation of dysfunctional protein)
  - Pyridoxine (vitamin B<sub>6</sub>) in homocystinuria
  - Thiamine in MSUD
- **Alternative pathway**
  - Carnitine to facilitate metabolic excretion of intermediate compounds in organic acidemias
  - Sodium benzoate and phenylacetate—urea cycle disorders
- **Enzyme replacement**

For example, in Gaucher disease (glucocerebrosidase). This has made a dramatic improvement in the clinical course of Gaucher disease. The enzyme therapy is given intravenously every two weeks. Other disorders for which enzyme replacement (ERT) is available are MPS I, II, IV, VI, Fabry disease. There are newer ERTs in the pipeline. So far none of the other ERTs have had as dramatic response as in Gaucher disease.
- **Protein replacement** Factor VIII replacement in hemophilia.
- **Hemodialysis/peritoneal dialysis** Removal of ammonia in urea cycle disorders. This is more effective than peritoneal dialysis.
- **Organ transplantation** Liver transplantation in OTC deficiency and other urea cycle disorders, organic acidemia [methylmalonic acidemia (MMA) and PA]. Combined liver and kidney transplant may have to be considered for MMA.



**Figures 7A and B** A young boy with Menkes kinky hair disease. (A) Gross appearance of hair; (B) Microscopic appearance showing Pili torti

**Table 2** Recommended laboratory investigations (examples of metabolic disorders are listed in parentheses)

Preliminary tests	Specialized tests
<ul style="list-style-type: none"> <li>Blood glucose</li> <li>Serum electrolytes</li> <li>Blood gases</li> <li>Calculate anion gap</li> <li>Ammonia (urea cycle disorders, organic acidemia)</li> <li>Plasma lactate</li> <li>Urine for ketones</li> <li>Uric acid (low in molybdenum cofactor deficiency)</li> <li>Complete blood count for transcobalamin deficiency</li> <li>Pancytopenia, neutropenia, thrombocytopenia</li> <li>Urine-reducing substances</li> </ul>	<ul style="list-style-type: none"> <li>Urine organic acids by gas chromatography-mass spectrometry (GC-MS, organic acidemia)</li> <li>Plasma amino acids (aminoacidopathies)</li> <li>Plasma carnitine (acyl and free)</li> <li>Plasma acylcarnitine profile (fatty acid oxidation disorder/organic acidemia)</li> <li>Skin fibroblasts to measure specific enzyme assays for specific disorders (storage disorders)</li> <li>DNA-based studies for molecular analysis</li> <li>Lactate/pyruvate ratio (pyruvate dehydrogenase/carboxylase/respiratory chain disorders)</li> <li>Cerebrospinal fluid lactate, amino acids</li> <li>Muscle biopsy for electron microscopy and respiratory chain analysis (mitochondrial disorders)</li> <li>Cholesterol (Smith-Lemli-Opitz syndrome)</li> <li>Very long-chain fatty acids (peroxisomal disorders)</li> <li>Urine GAA (disorders of creatine metabolism)</li> <li>Plasmalogens (rhizomelic chondrodysplasia punctata)</li> <li>Transferrin isoelectric focusing (congenital disorders of glycosylation)</li> <li>Homocysteine (homocystinuria)</li> <li>CK (metabolic myopathies)</li> <li>Cholesterol, triglycerides (glycogen storage disease)</li> </ul>

**Table 3** Other investigations that are performed in inborn errors of metabolism

Abdominal ultrasound	Rule out hepatosplenomegaly (storage disorders) Renal cysts (glutaric aciduria II)
Cardiac echo/MRI	Cardiomyopathy (Pompe disease), Pericardial effusion (CDG syndrome)
Cranial MRI/MRS	White matter changes in leukodystrophy Creatine peak absent in MRS in disorders of creatine metabolism Inverted lactate peak in mitochondrial disorders
Bone density	Low in many diet-related disorders
Neuropsychological testing	Many IEM (such as PKU monitoring)
Vision testing	Disorders with ophthalmological manifestations (homocystinuria)
Audiology	Disorders with hearing involvement (biotinidase deficiency)
EEG	Characteristic abnormalities in some IEM (triphasic waves in hyperammonemic encephalopathy)

Abbreviations: IEM, inborn errors of metabolism; EEG, electroencephalography; PKU, phenylketonuria; CDG, congenital disorders of glycosylation; MRS, magnetic resonance spectroscopy; MRI, magnetic resonance imaging.

- *Bone marrow transplantation, cord cell transplant* Lysosomal storage disorder—Krabbe disease
- *Gene therapy* Adenosine deaminase deficiency
- Substrate reduction, chaperone therapies (e.g., Miglustat for Niemann-Pick C disease)
- *Newer drugs*
  - Carbaglu (N-acetylglutamate synthase) for N-acetylglutamate synthase (NAGS) deficiency and carbamoyl phosphate synthetase (CPS) deficiency. It has also been used for acute hyperammonemia for MMA and PA
  - Kuvan (biopterin) cofactor for phenylalanine hydroxylase deficiency for PKU
  - Normosang (heme) infusion for acute intermittent porphyria

## PREVENTION

Early detection can make considerable difference in the prognosis of IEM. It has been almost 54 years since NBS was first instituted. In the last decade, due to the advent of tandem mass spectrometry, expanded NBS has become a mandatory public health strategy in most developed and some developing countries. The technology allows the inexpensive simultaneous detection of more than 30 different metabolic disorders in one single blood spot specimen with great accuracy and precision. The sensitivity and specificity of this method can be up to 99% and 99.995%, respectively for most amino acid disorders, organic acidemia, and fatty acid oxidation defects. Cost-effectiveness studies have confirmed that the savings achieved through the use of expanded NBS programs are significantly greater than the costs of implementation. NBS is discussed in detail in Chapter 3.19.



### IN A NUTSHELL

1. Genetically determined variability in biochemical processes may result in inborn errors of metabolism (IEM).
2. To understand the multisystem aspects and diagnostic strategies for the metabolic disorders.
3. To recognize the signs and symptoms suggestive of an IEM and formulate a logical diagnostic approach to determining when an IEM is suspected.
4. To describe the characteristics of different classes of metabolic syndromes.
5. To become familiar with the neonatal screening (criteria, advantages, pitfalls) for metabolic disorders.
6. To learn the principles of managing and treating some of the metabolic disorders, e.g., PKU and be aware of some of the newer therapies.
7. To recognize the importance of metabolic investigations in event of stillbirth, early neonatal death or in a case of sudden unexplained infant death (sudden infant death syndrome).
8. IEM have a genetic basis in most instances, so establishing a diagnosis will also help in genetic counseling, prenatal diagnosis and family carrier screening.

### MORE ON THIS TOPIC

Burton B. Inborn errors of metabolism in infancy: a guide to diagnosis. *Pediatrics*. 1998;102:69.  
 Dherai AJ. Inborn errors of metabolism and their status in India. *Clin Lab Med*. 2012;32:263-79.

*Indian Journal of Practical Pediatrics* 2010;2 (The entire issue is devoted to inborn errors of metabolism).

Levy HL. Newborn screening conditions: What we know, what we do not know, and how we will know it. *Genet Med*. 2010;12:S213-4.

Levy Paul A. Inborn errors of metabolism: part 1: overview. *Pediatr Rev*. 2009;30:131-7.

Mak CM, Lee HC, Chan AY, Lam CW. Inborn errors of metabolism and expanded newborn screening: review and update. *Crit Rev Clin Lab Sci*. 2013;50:142-62.

National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 1999. From: <http://www.ncbi.nlm.nih.gov/LocusLink>. Accessed August 1, 2014.

Online Mendelian Inheritance in Man, OMIM (TM). Center for Medical Genetics,

Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 1999. From: <http://www.ncbi.nlm.nih.gov/omim/>; and <http://www.biobase-international.com/product/hgmd>. Accessed August 1, 2014.

Saudubray JM, Charpentier C. Clinical phenotypes: diagnosis/algorithms. In: Scriver CR, Beaudet AL, Sly WS, Valle D (Eds). *The Metabolic and Molecular Bases of Inherited Disease*. 8<sup>th</sup> ed. New York: McGraw-Hill; 2001. pp. 1341-5.

Saudubray JM, Desguerre I, Sedel F, Charpentier C. A clinical approach to inherited metabolic diseases. In: Berghe GVD, Fernandes J, Walter JH, Saudubray JM (Eds). *Inborn Metabolic Diseases: Diagnosis and Treatment*. 4<sup>th</sup> ed. Germany: Springer; 2006. pp. 19-22.

Saudubray JM, Nassogne MC, de Lonlay P, Touati G. Clinical approach to inherited metabolic disorders in neonates: an overview. *Semin Neonatol*. 2002;7:3-15.

## Chapter 3.2

# Defects of Amino Acid Metabolism

Anil B Jalan, Ketki V Kudalkar

Aminoacidopathies is a group of rare and diverse inborn errors of metabolism which results in the accumulation of some amino acids or deficiency of one or more amino acids in the blood and/or urine, affecting about 1 in 1,000 humans worldwide. The majority of these disorders present in the neonatal period and most of them are inherited in autosomal recessive manner, having metabolic disturbances and neurologic manifestations. The range and severity of symptoms is hugely variable, ranging from asymptomatic to life-threatening metabolic decompensation at neonatal age, encompassing slow deterioration of mental capacities at later age. Even though some present at birth, presentation may be later in life. These disorders can be subdivided into organic acidurias, urea cycle defects, transport defects of urea cycle intermediates, and remaining aminoacidopathies.

Deficiencies of enzymes involved in amino acid metabolism frequently result in accumulation of toxic substances and subsequent organ damage. The organs most frequently affected are brain, liver and kidneys. Accumulation of a metabolite may lead to symptoms of toxicity, e.g., ammonia or deficiency of an essential metabolite, e.g., glucose may produce symptoms. This in turn depends on the type and severity of enzyme deficiency. It also depends partially on protein or amino acid intake or catabolism. Acute symptoms are often associated with catabolic states that lead to breakdown of endogenous proteins and release of large amounts of amino acids, whereas some disorders cause chronic neurological damage without acute decompensation.

Typical presenting features for aminoacidopathies are listed in **Box 1**.

### BOX 1 Typical presenting features of aminoacidopathies

- Acute coma/ataxia/encephalopathy
- Progressive neurological symptoms
- Multisystem disorder
- Unexplained acidosis
- Ketonuria
- Hyperammonemia
- Failure to thrive
- Vomiting/diarrhea.

## EVALUATION OF AMINOACIDOPATHIES

Amino acid profiling is routinely performed in plasma or serum, urine and sometimes even in cerebrospinal fluid (CSF). For majority of clinical situations, fasting plasma is preferred; however in severe metabolic disorders, random samples are also adequate. Routinely 22 or 24 amino acids are analyzed but a good amino acid analyzer can produce an aminoacidogram up to 30 or even more amino acids. A clinician should choose a method from the below, depending on the clinical situation and urgency. Cost may be an issue especially in developing countries.

For routine clinical purposes one of the following methods are used:

- a. **HPLC (High Performance Liquid Chromatography)** Quantitative analysis on plasma/serum, urine or CSF. Precolumn derivatization or postcolumn derivatization techniques are available. This is generally a lengthy procedure. Analysis time

can vary from 120–180 min. Depending on various instruments and methods.

- b. **UPLC/UHPLC (Ultra Performance Liquid Chromatography/ Ultra High Performance Liquid Chromatography)** This is a relatively more sophisticated form of HPLC with changes in hardware and software. The main advantage is faster techniques. Typical amino acid runs can be completed in 18–30 min instead of 120–180 min, quantitative method, and good for all the samples—plasma/serum, urine or CSF.
- c. **Ion Exchange Chromatography (Biochrome Analyzer)** This method is supposed to be gold standard for amino acid analysis, is quantitative with excellent results. 24–30 amino acids can be analyzed in any tissue—Plasma/Serum, urine or CSF. Run times are usually 120–180 min.
- d. **LC-MS/MS Tests** for 22–24 important amino acids can be performed both on plasma or urine. It provides quantitative analysis and is very fast. With a standard kit (EZphast), the total procedure time is usually 17 minutes.
- e. **Tandem Mass Spectrometry** It can analyze 10–12 important amino acids from dried blood spots, as a part of routine newborn screening. These results are rather semi-quantitative; however, run times are 60–120s. This is a good method for newborn screening, however, abnormal results need to be confirmed with quantitative analysis with any of the above procedures.

## Samples

Fasting EDTA or heparinized plasma is the preferred sample. After collection, sample should be immediately centrifuged and plasma should be stored frozen till analysis at  $-20^{\circ}\text{C}$ . Serum also is adequate for routine clinical analysis. In our experience urine amino acid does not provide much information as a primary test. However, in certain clinical situations, urine amino acids are very valuable, for example, lysinuric protein intolerance or where a clinician is interested in markers of bone loss or muscle wasting (e.g., hydroxyproline, hydroxylysine and cystine). A clinician must remember that a hemolysed sample will have lot of alterations in amino acids. The sample may show falsely high taurine, aspartic acid, ornithine, phosphoethanolamine and glycine (in our experience) and decreased arginine and cystine.

## Interpretation

Identification of aminoacidopathies by amino acid analysis is sometimes a difficult task. Identification of not only elevated but reduced amino acid levels also must be actively searched for. A practical guide is given below in **Table 1**. If results of amino acid analysis are nonconclusive, a repeat analysis in a different state of feeding (either fasting or post feed, especially protein load) may reveal subtle abnormalities. A typical pattern of abnormalities is more important than an isolated abnormality. For example, elevated leucine along with valine and isoleucine may suggest MSUD but alone it may suggest probably catabolic state.

Amino acid analysis in CSF also should be considered in all neonates and children presenting with seizures and unexplained neurological disorders. Interpretation will depend on the pattern of amino acid abnormalities (**Fig. 1**).

At present, dietary management is the mainstay of treatment for most aminoacidopathies. Dietary treatment aims to prevent accumulation of the substrates and associated metabolites to toxic levels, and to restore deficiencies of the enzymatic products. This can be accomplished by avoiding offending amino acids and substituting essential amino acids. Many a times simple low protein diet is helpful, e.g., glycine encephalopathy (NKHG).

## MAPLE SYRUP URINE DISEASE

In 1954, a family of four children was described where all affected newborns were described to have maple syrup urine disease (MSUD). Progressive disorder affected nervous system was fatal in each of them in the first weeks of life. MSUD is inherited in autosomal recessive manner and is caused by a deficiency in ability to metabolize the branched-chain amino acids, leucine, isoleucine and valine.

The branched chain  $\alpha$ -keto-acid dehydrogenase (BCKDH) complex is a multienzyme complex similar to pyruvate dehydrogenase complex. It carries out the decarboxylation of these branched chain amino acids. The enzyme complex consists of four subunits, including  $E_1\alpha$ ,  $E_1\beta$ ,  $E_2$  and  $E_3$ . MSUD results from mutations in any one of the *BCKDHA* ( $E_1\alpha$ ), *BCKDHB* ( $E_1\beta$ ), *DBT* ( $E_2$ ), and *DLD* ( $E_3$ ) genes. MSUD is estimated to occur in 1:100,000 newborns (Fig. 2).

### Clinical Symptoms

Maple syrup urine disease usually presents early in infancy with poor feeding, vomiting, lethargy and developmental delay.

If untreated, MSUD may lead to seizures, coma or even death. The most common form of MSUD (severe form) presents with progressive encephalopathy in the first days of life. Babies even though normal at birth soon begin to have feeding difficulties, at times with vomiting, slowly progressing to lethargy and coma within few days after protein feeds. Though metabolic acidosis is not very common, it is evident with increased anion gap and elevated branched chain amino acids in blood and urine. Hypoglycemia may occur and neurologic deterioration may be rapid. Cerebral edema results in encephalopathy. Alternating hyper- and hypotonia and often scissoring of legs or opisthotonos and boggy fontanel are also seen. Other less acute presentations (mild form) are associated with psychomotor retardation, fluctuating/progressive neurologic disease, and recurrent ketoacidotic decompensation. Neurological symptoms are evident in all forms of MSUD by 2 years at least.

### Diagnosis

The diagnosis of MSUD is based on measurement of plasma branched chain amino acids, *leucine*, *isoleucine* and *valine* along

**Table 1** Amino acid disorders and their diagnosis

Amino acids	Possible causes	Additional tests
1. Alanine (Increase)	Mitochondrial disorders Lactate/Pyruvate metabolism disorders Hyperammonemia syndrome	Ammonia, lactate, pyruvate Full plasma amino acids (If alanine elevation is detected on NBS) Urine orotic acid
2. Arginine (Increase)	Arginase deficiency Creatine deficiency Cystinuria Dibasic amino aciduria HHH syndrome Liver disease Lysinuric protein intolerance Ornithine aminotransferase deficiency Hyperalimentation	Plasma ammonia Plasma amino acids Urine amino acids Urine orotic acid
3. Arginine (Decrease)	Creatine deficiency HHH syndrome Ornithine aminotransferase deficiency (Gyrate atrophy)	MRI with MRS (Creatine peak), GAMT assay Fundus examination
4. Citrulline (Increase)	Argininosuccinic aciduria Citrullinemia type 1 Citrullinemia type 2 Lysinuric protein intolerance Liver disease Pyruvate carboxylase deficiency Hyperalimentation	Plasma ammonia Plasma amino acids Urine orotic acid Urine organic acids Blood lactate and pyruvate
5. Citrulline (Decrease)	P-SCS deficiency NAGS/CPS/OTC deficiency Respiratory chain defects Lysinuric protein intolerance	Plasma ammonia Plasma amino acids Urine orotic acid Urine organic acids Blood lactate and pyruvate
6. Cystine (Decrease)	Molybdenum cofactor deficiency Sulfite oxidase deficiency Homocystinuria	Urine sulfites, xanthine and hypoxanthine Urine/plasma sulfocysteine Serum homocysteine
7. Glutamine (Increase)	Hyperammonemia—Urea cycle defect	Serum ammonia Urinary orotic acid Plasma and urine amino acids
8. Glutamine (Decrease)	MSUD Glutamine synthase deficiency	Urine organic acids

Contd...

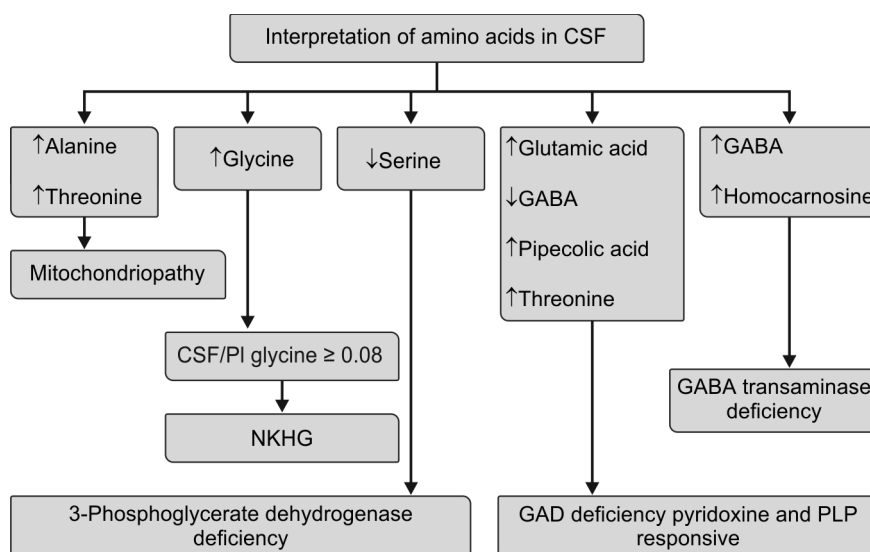
Contd...

<i>Amino acids</i>	<i>Possible causes</i>	<i>Additional tests</i>
9. Glycine (Increase)	Nonketotic hyperglycinemia	Plasma amino acids CSF amino acids (CSF/Pl gly) Urine organic acids
10. Glycine (Decrease)	Serine synthesis defect	CSF—Amino acids CSF—5 MTHF
11. Homocysteine (Total Hcy) (Increase)	Cobalamin disorders (C,D, E) Homocystinuria (CBD deficiency) Folate disorders MTHFR deficiency	Plasma amino acids Blood vitamin B <sub>12</sub> and folic acid CBS and MTHFR gene studies Coagulation profile
12. Homocysteine (Total Hcy) (Decrease)	Molybdenum cofactor deficiency Sulfite oxidase deficiency	Urine sulfites and purine/pyrimidines Urine/plasma sulfocysteine
13. Leucine	Maple syrup urine disease Hyperalimentation	Plasma amino acids Urine organic acids
14. Lysine (Decrease)	Creatine deficiency HHH syndrome	Urine amino acids—Homocitrulline
15. Methionine (Increase)	Homocystinuria Methyl-adenosyltransferase deficiency (MAT) Glycine N- methyltransferase deficiency Tyrosinemia type I Liver disease Hyperalimentation Prematurity	Plasma amino acids Plasma homocysteine Urine organic acids Urine succinylacetone
16. Methionine (Decrease)	Cobalamine disorders MTHFR deficiency	Serum homocysteine Urine organic acids
17. Ornithine (Increase)	Creatine deficiency HHH syndrome Ornithine aminotransferase deficiency (Gyrate atrophy)	Plasma ammonia Urine orotic acid MRI and MRS for creatine peak
18. Ornithine (Decrease)	P5CS deficiency	
19. Phenylalanine (Increase)	Phenylketonuria Biopterin synthesis defect Dihydrobiopterin reductase def Liver disease, hyperalimentation Prematurity	Plasma amino acids Urine pterin profile Blood DHPR activity
20. Proline (Increase)	Hyperprolinemia type II Hyperprolinemia type I Lactic acidosis, hyperalimentation	Plasma amino acids Urine organic acids
21. Proline (Decrease)	P5CS deficiency	
22. Serine (Decrease)	CBS : Cystathionine beta synthase deficiency Serine synthesis defect	Serum homocysteine CSF amino acids
23. Tyrosine (Increase)	Tyrosinemia type I (HT1) Tyrosinemia type II Tyrosinemia type III Transient tyrosinemia of the newborn, liver disease, Prematurity Hyperalimentation	Plasma amino acids Urine organic acids Urine succinyl acetone
24. Tyrosine (Decrease)	PKU and pterin disorders	Pterin studies in urine and DBS DHPR enzyme assay

with alloisoleucine and documenting elevated levels. In MSUD accumulation of these amino acids in very high levels occurs as they are not decarboxylated, the highest being leucine. Val/Phe, (Leu+Ile)/Phe and (Leu+Ile)/Ala ratios have also been informative in MSUD. The oxidative decarboxylation block in MSUD also results in accumulation of branched-chain keto acids, 2-oxoisocaproic acid from leucine, 2-oxo-3-methylvaleric acid from isoleucine and 2-oxoisovaleric acid from valine, which are detected in

high levels in urine of affected patients by gas chromatography-mass spectrometry (GC-MS). The deficiency of BCKDH enzyme complex activity can be measured in cultured fibroblasts. Antenatal diagnosis is possible by measurement of enzyme activity in chorionic villi cells or cultured amniocytes. However, molecular analysis of mutations in the *BCKDHA*, *BCKDHB*, *DBT* and *DLD* genes can provide a better method for prenatal diagnosis in families in which the mutation(s) is/are known (**Fig. 3**).





**Figure 1** Interpretation of amino acids in CSF

### Treatment

Aggressive intervention during acute crisis helps in reducing branched chain amino acid (BCAA) levels, especially hemodialysis is the fastest way of reducing BCAA levels in plasma. IV glucose and insulin may provide alternate energy that reduces protein catabolism and enhances anabolism. Long-term diet therapy involves restriction of protein intake and special formulas that are devoid of branched chain amino acids. In some patients, thiamine (10 mg/kg/day) trial may be considered depending upon response to therapy. Close monitoring of patients is essential to achieve optimal ranges of BCAA (Leu—100–250  $\mu\text{mol/L}$ , Ile—50–150  $\mu\text{mol/L}$  and Val—150–250  $\mu\text{mol/L}$ ). The prognosis depends on prompt and strict adherence to therapy.

### PHENYLKETONURIA (PKU)

The enzyme phenylalanine hydroxylase converts essential amino acid phenylalanine to tyrosine. Deficiency of phenylalanine hydroxylase causes PKU with severe central nervous system symptoms. PKU was the first neurogenetic disorder identified in 1934 by Fölling, the first successfully treated inborn error of metabolism (Bickel, 1953) and the disorder instrumental for the introduction of neonatal screening. It was Dr. Robert Guthrie who first developed a test for phenylalanine in dried blood spots for new born screening of phenylketonuria (PKU) and era of newborn screening began about 50 years back. Phenylalanine metabolism takes place in the cytosol. Enzyme phenylalanine hydroxylase converts phenylalanine to tyrosine. It requires tetrahydrobiopterin (BH4) as a cofactor. The deficiency of phenylalanine hydroxylase or tetrahydrobiopterin results in accumulation of phenylalanine which is transaminated to phenylpyruvate (**Fig. 4**).

### Clinical Symptoms

Affected children appear normal at birth or even in early neonatal period. Later they exhibit irritability, posturing, increased deep tendon reflexes, microcephaly, seizures and vomiting. If untreated the child may develop severe brain damage with intellectual disability, seizures and spasticity. Pigmentation of skin and hair may also be seen.

Phenylalanine is the major toxic metabolite in PKU. It accumulates in the blood and prevents transport of other long neutral amino acids (LNAA) across the blood brain barrier inhibiting the synthesis of neurotransmitters in the brain. This results in severe intellectual disability and white matter disease.

Untreated maternal PKU may result in high levels of phenylalanine in mothers which in turn crosses placenta and affects developing brain. Newborn may have neurological damage. To avoid such toxic and teratogenic effect of phenylalanine, mothers must receive proper dietary therapy and control of phenylalanine intake during pregnancy.

### Diagnosis

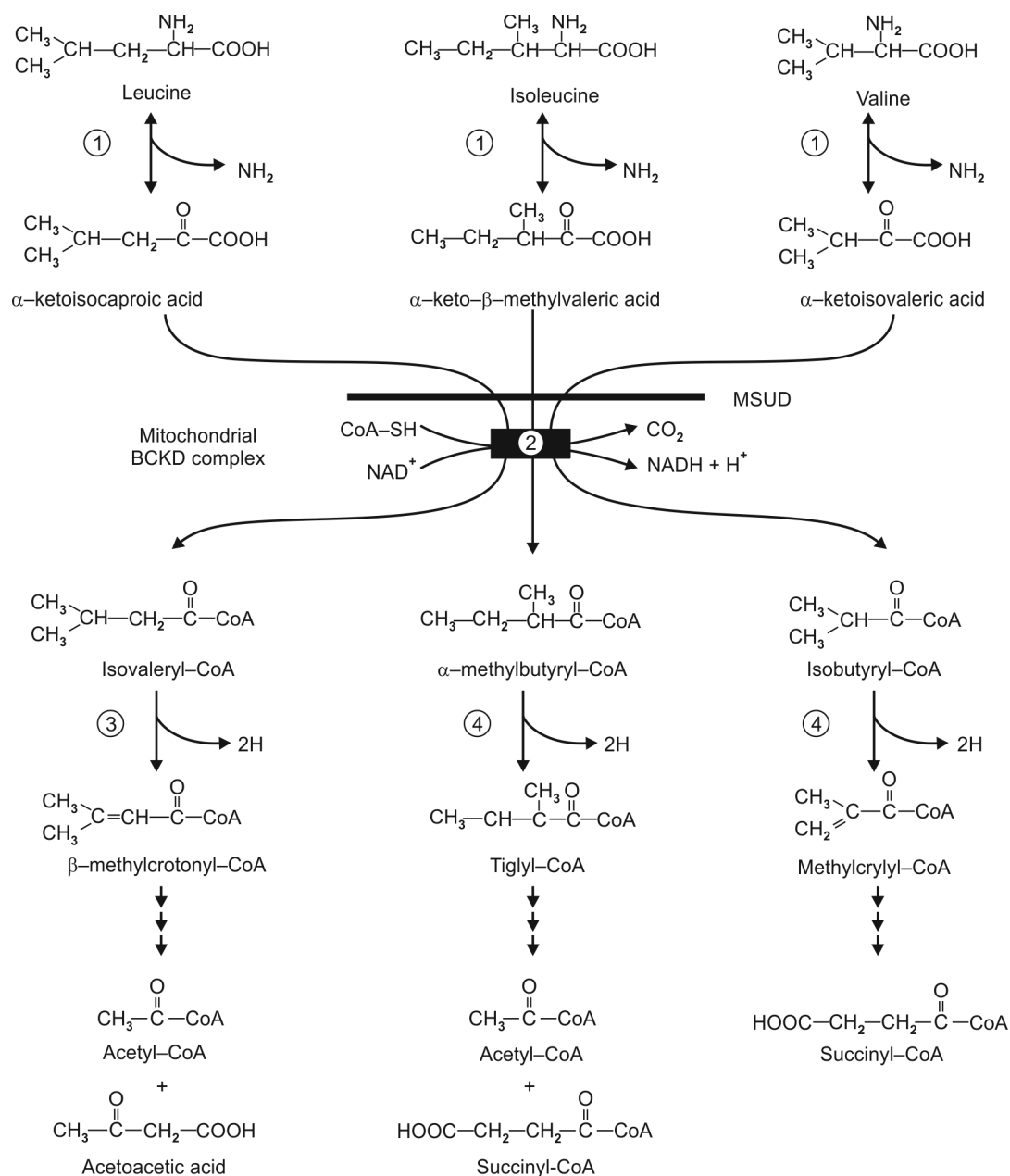
Screening for PKU began with Guthrie's bacterial assay. Now greater sensitivity has been achieved by implementation of TMS. An increased level of phenylalanine and increased phenylalanine/tyrosine ratio is suggestive of PKU. In classical PKU levels of phenylalanine are typically greater than 600  $\mu\text{mol/L}$ . Mild or tetrahydrobiopterin (BH4) responsive PKU show levels less than 600  $\mu\text{mol/L}$  typically and the levels improve after BH4 supplementation. All newborns with PKU should be screened for BH4 defects. Mutation analysis of PAH gene may allow prediction of severity and BH4 sensitivity.

### Treatment

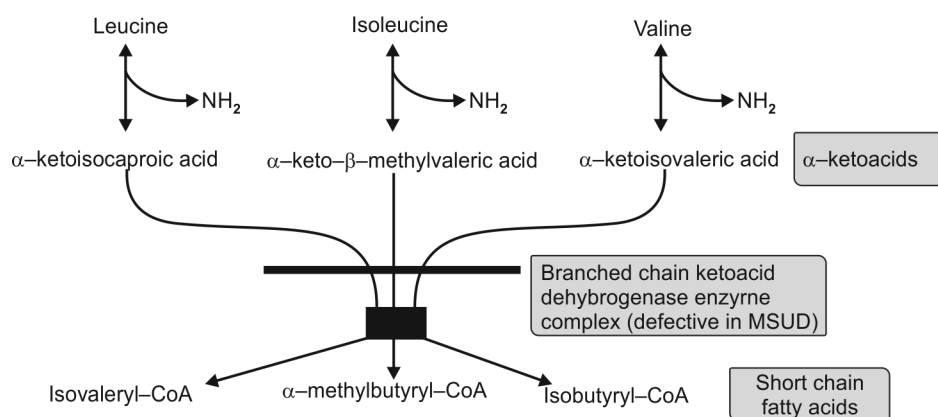
Children with PKU need to maintain phenylalanine levels controlled throughout their life. Special dietary PKU formulas and various phenylalanine restricted foods are available for PKU patients by various companies. Supplementation of essential amino acids and trace elements is necessary. BH4 supplementation should be tried in BH4 deficient patients. Monitoring of phenylalanine and tyrosine levels on a regular basis to follow dietary control is absolutely essential.

### TYROSINEMIA TYPE 1

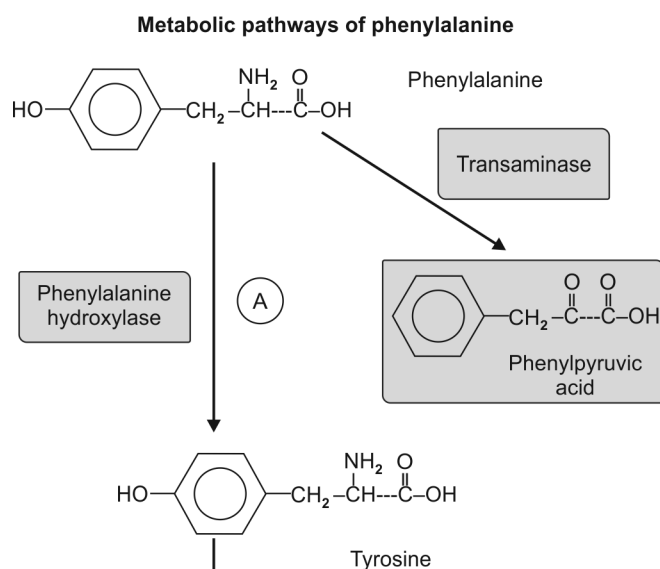
Tyrosinemia type I was described in 1957. It is an inborn error of tyrosine metabolism caused by the deficiency of fumarylacetoacetate hydrolase (FAH). It is estimated to occur in less than 1:100,000 livebirths worldwide but is more common in French



**Figure 2** Branched chain amino acids metabolism



**Figure 3** Maple syrup urine disease—metabolites



**Figure 4** Phenylalanine metabolism

Canadians (1 in 12,500). Deficiency of FAH causes accumulation of fumarylacetoacetate, succinyl acetoacetate and succinylacetone. These are highly toxic substances and cause inhibition of several enzymes including 4-hydroxyl phenyl pyruvate dioxygenase and aminolevulinate dehydratase and are carcinogenic (**Fig. 5**).

### Clinical Symptoms

Tyrosinemia type I acute or neonatal type may present in the first few months of life with severe failure to thrive, vomiting, hepatomegaly, liver dysfunction, bleeding, septicemia, hypoglycemia, metabolic acidosis and electrolyte disturbances due to renal tubulopathy (Fanconi syndrome). Progressive liver disease can result in cirrhosis of liver, hepatocellular failure or even death in undiagnosed patients. Patients may develop acute hepatocellular failure with ascites, jaundice and gastrointestinal bleeding. There is a high risk of developing hepatocellular carcinoma and hepatic nodules. Untreated patients usually die in infancy or early childhood.

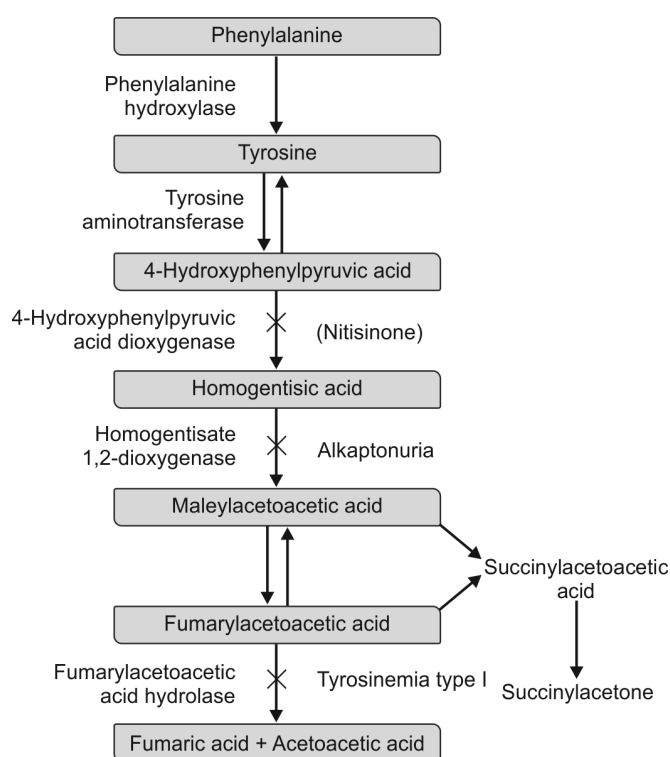
Chronic form of tyrosinemia type I presents with hepatomegaly, cirrhosis, growth retardation, rickets, hematoma, tubulopathy, neuropathy and neurological crises (due to porphyrins).

### Diagnosis

Presence of succinylacetone in urine or blood is diagnostic of tyrosinemia type I. Elevated levels of 4-hydroxyphenyl derivatives may also be seen in urine by GC-MS. Elevations of plasma tyrosine and methionine and occasionally generalized amino acidemia are seen in tyrosinemia type I. Alpha fetoprotein is elevated in serum and may serve as a marker for hepatocellular carcinoma/cirrhosis. Leukocytes, erythrocytes and liver tissues are deficient in FAH activity. Quantitative estimation of succinylacetone in amniotic fluid or FAH enzyme activity in chorionic villi cells may be used for prenatal diagnosis. But in our experience molecular diagnosis is the best method.

### Treatment

Patients with tyrosinemia type I must be treated aggressively with dietary restriction of tyrosine and phenylalanine along with administration of nitisinone (NTBC) [2(2-nitro-4-trifluoromethylbenzoyl)-1, 3-cyclohexanedione] in the dose of 1–2 mg/kg/day. This drug inhibits 4-hydroxyphenylpyruvate dioxygenase and blocks the accumulation of toxic metabolites. However, an increase



**Figure 5** Tyrosine metabolism

in tyrosine levels may be seen after administration of NTBC. Liver transplantation is another option as it provides normal FAH activity.

### TYROSINEMIA TYPE II AND TYROSINEMIA TYPE III

High tyrosine levels in blood may also be seen in other conditions like, transient tyrosinemia of the newborns, galactosemia, fructose intolerance, neonatal hepatitis, liver disorders, respiratory chain defects, bile acid synthesis disorders, etc.

Tyrosinemia type II is asymptomatic in the neonates but may cause hyperkeratosis of skin (soles and palms), painful corneal lesions (lacrimation, photophobia, scars) and mild intellectual disability. It is caused by the deficiency of cytosolic tyrosine amino transferase enzyme and diagnosed by increased levels of tyrosine and phenylalanine in blood and 4-hydroxyphenylacetate and 4-hydroxyphenylpyruvate in urine. Treatment for tyrosinemia type II is restriction of phenylalanine and tyrosine.

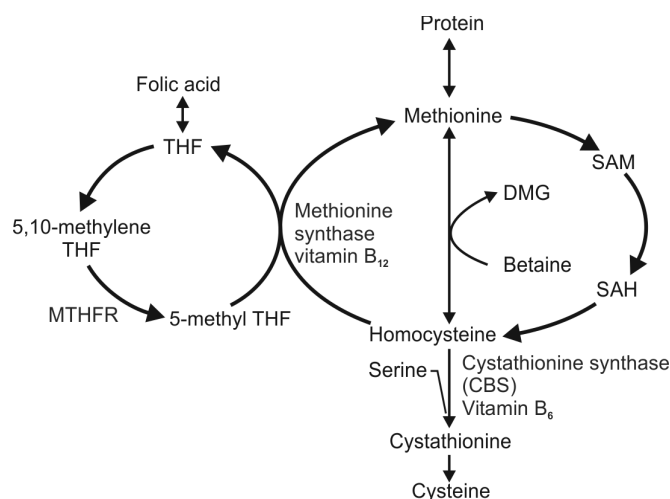
Tyrosinemia type III is caused by a deficient 4-hydroxyphenylpyruvate dioxygenase activity. However, the clinical relevance is uncertain and the disease may be benign.

### HOMOCYSTINURIA

Classic homocystinuria is a metabolic disorder of sulfur metabolism, caused by CBS (cystathionine-β-synthase) deficiency and inherited in autosomal recessive manner. There are two main phenotypes: a milder pyridoxine-responsive form, and a more severe pyridoxine-nonresponsive form. Pyridoxine works as a cofactor for the CBS enzyme, and aids in the conversion of homocysteine to cysteine (**Fig. 6**).

### Clinical Symptoms

Untreated classical homocystinuria (CBS deficiency) usually manifests in the first or second decade of life. Most common presentation is myopia and ectopia lentis. Some children also



**Figure 6** Homocysteine and methionine metabolism

suffer from mental retardation, marfanoid habitus (skeletal anomalies resembling Marfan syndrome), and sometimes thromboembolic events. However, in our experience, this is not a common manifestation. Milder variant of homocystinuria has also been reported characterized by increased plasma homocysteine and increased risk for thrombotic events in young adulthood, but without the other marfanoid features or ocular, or nervous system manifestations.

### Diagnosis

Increased levels of methionine, homocysteine ( $>150 \mu\text{mol/L}$ ), reduced cysteine and positive nitroprusside test are diagnostic of classic homocystinuria. Mutations in the CBS gene can be identified for the confirmation of the diagnosis.

### Treatment

For pyridoxine-dependent homocystinuria treatment is pyridoxine (50–100 mg/day). For nonresponsive patient's treatment involves strict methionine restriction along with anhydrous betaine (Tri Methyl Glycine—TMG) (100 mg/kg/day), hydroxycobalamin (1 mg/day), vitamin C (100 mg/day).

### NONKETOTIC HYPERGLYCINEMIA

Nonketotic hyperglycinemia (NKHG) is also known as glycine encephalopathy. It is an inherited metabolic defect with abnormally high blood and CSF glycine levels. The enzyme system for cleavage of glycine (glycine cleavage system; GCS) which is confined to the mitochondria, is composed of 4 protein components: **P** protein (GLDC) (a pyridoxal phosphate-dependent glycine decarboxylase); **H** protein (GCSH) (a lipoic acid-containing protein); **T** protein (AMT) (a tetrahydrofolate-requiring enzyme); and **L** protein (a lipoamide dehydrogenase). Mutations in the P, T and H proteins cause glycine encephalopathy.

### Clinical Symptoms

Almost 85% of glycine encephalopathies present in the neonatal period as a severe form. Overall, 20% of all children presenting as either neonates or infants have a less severe presentation. Atypical form or milder form is not so common. The severe neonatal form of encephalopathy presents in the first few hours to days of life. Progressive lethargy, hypotonia and myoclonic jerks are common presenting features; soon babies develop apnea and require ventilator support. Death is quite common in early neonatal period. Those who survive develop profound

intellectual disability and intractable seizures. The late onset infantile form is characterized by hypotonia, developmental delay, progressive neurological symptoms and seizures. The atypical forms may have milder disease, with onset varying from late infancy to adulthood, to even rapidly progressing severe disease of late onset.

### Diagnosis

Elevated glycine concentration in blood and CSF is the hallmark of the disease. An increase in CSF glycine concentration along with an increased CSF-to-plasma glycine ratio  $> 0.08$  (0.02–0.08) suggests the diagnosis. Enzymatic confirmation is possible by assay of glycine cleavage system (GCS) enzyme activity in liver. Mutations in T, P and H proteins can be identified as the cause of glycine encephalopathy.

**Newborn Screening** Tandem mass spectrometry is not a very good method to detect glycine encephalopathy in newborn screening. Many a times symptoms appear even before the results arrive.

### Treatment

There is no specific therapy for severe glycine encephalopathy. Early treatment with sodium benzoate to reduce plasma glycine concentration in the dose of 250–500 mg/kg/day and NMDA receptor blockers like dextromethorphan in the dose of 5–20 mg/kg/day may have better outcome than those treated late or untreated. Other supporting therapy like antiepileptic drugs, especially benzodiazepine group and/or ketogenic diet for seizure control is needed. For feeding nasogastric (NG) tube or gastrostomy (G button) may also be required. Physical therapy and treatment for gastroesophageal reflux may also be necessary. Folinic acid (15 mg/day) supplementation is also helpful.

### GYRATE ATROPHY OF CHOROID AND RETINA

Gyrate atrophy of the choroid and retina is caused by deficiency of ornithine aminotransferase. It is a triad of progressive chorioretinal degeneration, early cataract formation, and type II muscle fiber atrophy. It has been postulated that hyperornithinemia-induced deficiency of high-energy creatine phosphate leads to changes in skeletal muscle, as well as the ocular changes.

### Clinical Symptoms

It is manifested by chorioretinal atrophy and progressive constriction of the visual fields, which leads to blindness at the latest during the sixth decade of life. Patients generally have normal intelligence. By the end of second decade most of the patients have posterior subcapsular cataracts. Manifestations include myopia (in childhood), and impaired night vision progressing to blindness. Fundoscopy shows retinopathy (gyrate atrophy, increasing from the periphery). Atrophy of type II muscle fibers although asymptomatic in the beginning progresses slowly to complete loss of type II muscle fibers.

### Diagnosis

Ornithine levels in plasma, urine, CSF and aqueous humor are 10–20 times higher than normal. Hyperammonemia is uncommon (except occasionally in neonates). It is also associated with milder degree of phosphocreatine deficiency.

### Treatment

Dietary arginine is the main source of ornithine. Therefore, arginine restricted diet appears to be of therapeutic importance. Consider pyridoxine (40–200–600 mg/day), creatine monophosphate (up to 2 g/kg/day).



## DISORDERS OF AMINO ACIDS TRANSPORT

Process of transport of amino acids from intestine and from renal tubules back to circulation is energy dependent. For transport, enzymes are not required. They require special transport proteins embedded in cellular or intracellular organelle membranes. Thus, mutated proteins cause loss of certain amino acids in urine which are dependent on such transport system and lead to a specific disorders, e.g., cystinuria, lysinuric protein intolerance, Hartnup disease, etc.

### Lysinuric Protein Intolerance (LPI)

Defective cationic amino acid transport at the basolateral membrane of epithelial cells in kidney and intestine causes LPI. Characteristic metabolic abnormalities associated are increased renal excretion of amino acids, reduced amino acid absorption from intestine, and orotic aciduria. The gene involved in LPI is the amino acid transporter gene *SLC7A7*.

#### Clinical Symptoms

Clinical symptoms in LPI include diarrhea, vomiting and severe failure to thrive, hepatomegaly, cirrhosis, interstitial pneumonia, osteoporosis, renal failure, hemolysis and leukopenia. Symptoms are worsened by high protein intake and relieved by low protein diet. At times, LPI is complicated with HLH (hemophagocytic lympho-histiocytosis) syndrome. Some patients are reported to have symptoms like SLE (systemic lupus erythematosus).

#### Diagnosis

Low blood urea and hyperammonemia, along with increased LDH and ferritin is often observed. An increased urinary excretion of ornithine, arginine and lysine is observed but cystine excretion is normal. Plasma levels of these amino acids are low and especially arginine is significantly low affecting urea genesis, thus causing hyperammonemia.

#### Treatment

Low protein diet with citrulline supplementation is the therapy. It results in substantial increase in protein tolerance along with acceleration of linear growth and improvement in bone mass. Immunological abnormalities need special attention in this disorder.

### Cystinuria

Cystinuria is usually inherited as an autosomal recessive disorder but both recessive and dominant inheritances are suggested. There is a basic defect in the transport of cystine and dibasic amino acids lysine, ornithine, and arginine. Epithelium of proximal renal tubule and gastrointestinal tract are affected. Cysteine is not reabsorbed properly and it is also insoluble in water, resulting in formation of crystals and calculi. This in turn results in obstructive uropathy, pyelonephritis and renal failure. A classification has been proposed by Dello Strologo *et al.* (2002) based on the defective genes:

1. Type A—*SLC3A1* gene
2. Type B—*SLC7A9* gene
3. Type AB—*SLC3A1* and *SLC7A9* genes

#### Diagnosis

Onset is usually in the first or second decade. Besides nephrolithiasis, urinary infections are also common and may contribute to

renal failure. Type A (*SLC3A1* heterozygote) presents with excretion of large amounts of urinary amino acids, cystine, lysine, arginine and ornithine. Type B (*SLC7A9* heterozygotes) is characterized by moderate degree of amino aciduria, mainly cystine and lysine, and may occasionally form cystine stones.

#### Treatment

Treatment involves high fluid intake (> 5 L/day), alkalinization of the urine and penicillamine (1–2 g/day). Penicillamine is usually well tolerated without many side effects in these patients.

### Hartnup Disease

This autosomal recessive disorder was first described by Baron *et al.* (1956) and is caused by mutation in *SLC9A19* gene. It is often asymptomatic but may sometimes present with a pellagra-like light-sensitive rash; cerebellar ataxia; emotional instability; and aminoaciduria. Two forms were suggested by Scriver *et al.* (1985).

1. *Classic form* The defect is expressed in both intestine and kidney
2. *Variant form* It is expressed only in kidney.

#### Management

Increased excretion of neutral amino acids in urine (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, glutamine and asparagine) is associated with normal-low neutral amino acids in plasma. Treatment involves nicotinamide administration (50–300 mg/day) and sun-protection.

### IN A NUTSHELL

1. Aminoacidopathies are the most common inborn errors of metabolism detected in India and hence they should always be kept in mind while screening of inborn errors of metabolisms.
2. Presentation of aminoacidopathies could be variable, involving purely neurological or hepatic or combined symptoms. They may also present with failure to thrive and rickets.
3. Plasma or serum amino acid screening should be the first choice and not only urine. However, a combination of plasma and urine amino acids gives a better understanding of the pathology.
4. Collection of the sample, timing in relation to feeds, transportation in appropriate tubes and at appropriate temperatures are the preanalytical factors that can affect results and interpretation.
5. Use of the best available quantitative estimation method and interpretation in relation to the age of the patient by an experienced metabolic physician cannot be overemphasized.
6. Some conditions are episodic (e.g., MSUD) and repeated sampling and testing may be required if clinical suspicion is very high.
7. Elimination of offending amino acids or supplementing the essential amino acids or both may form the corner-stone of the therapy.

### MORE ON THIS TOPIC

Barnby E. Tyrosinemia type 1: an overview of nursing care. *Pediatr Nurs.* 2014;40:61-8, 90.

- Blau N, van Spronsen FJ, Levy HL. Phenylketonuria. *Lancet*. 2010;23:376(9750):1417-27.
- Cakir B, Teksam M, Kosehan D, et al. Inborn errors of metabolism presenting in childhood. *J Neuroimaging*. 2011;21(2):e117-33.
- Casey L. Caring for children with phenylketonuria. *Can Fam Physician*. 2013;59(8):837-40.
- D'Alessandro G, Tagariello T, Piana G. Oral and craniofacial findings in a patient with methylmalonic aciduria and homocystinuria: review and a case report. *Minerva Stomatol*. 2010;59:129-37.
- de Koning TJ. Amino acid synthesis deficiencies. *Handb Clin Neurol*. 2013;113:1775-83.
- Hoffmann GF, Kölker S. Defects in amino acid catabolism and the urea cycle. *Handb Clin Neurol*. 2013;113:1755-73.
- Lee WT. Disorders of amino acid metabolism associated with epilepsy. *Brain Dev*. 2011;33:745-52.
- Mak CM, Lee HC, Chan AY, Lam CW. Inborn errors of metabolism and expanded newborn screening: review and update. *Crit Rev Clin Lab Sci*. 2013;50(6):142-62.
- Mulligan JL. Neonatal nonketotic hyperglycinemia: a case study and review of management for the advanced practice nurse. *Neonatal Netw*. 2013;32:95-103.
- Walter JH, Jahnke N, Remington T. Newborn screening for homocystinuria. *Cochrane Database Syst Rev*. 2013;8:CD008840.
- Yazici N, Sarılioğlu F, Alkan O, Kayaselçuk F, Erol I. Glutaric aciduria type II [corrected] and brain tumors: a case report and review of the literature. *J Pediatr Hematol Oncol*. 2009;31:865-9.

## Chapter 3.3

# Urea Cycle Disorders

Sunita Bijarnia-Mahay

The urea cycle, first described by Krebs and Henseleit in 1932, is an extremely important enzymatic process in humans and terrestrial animals as it is the only pathway for detoxification of ammonia, the toxic product of breakdown of protein and other nitrogen containing molecules. Disorders that directly or indirectly affect the urea cycle disrupt the detoxification process, and lead to hyperammonemia with consequent toxic brain injury and death. Thus, it is important to recognize these disorders early for any possible intervention and treatment.

The urea cycle is exclusively present in the hepatocytes, distributed between the mitochondrial matrix and the cytosol. The urea cycle enzymes are activated only after either excess nitrogen load (high protein diet) or excess breakdown of protein within the body. The five catalytic enzymes and three other proteins taking part for smooth functioning of the urea cycle are described in the chapter.

## EPIDEMIOLOGY

The worldwide incidence of urea cycle disorders (UCD) is approximately 1 in 25,000–30,000 livebirths. While these disorders are commonly encountered in most of the tertiary care centers in India, and recognized because of hyperammonemia, their exact prevalence is not known.

Worldwide, ornithine transcarbamylase (OTC) deficiency is the most common defect (1:15,000), but in our experience in India, citrullinemia type 1 is by far the most common among neonatal classical presentations. This is followed by children with OTC and argininosuccinate lyase (ASL) deficiency. It is possible that a lot of OTC deficiency patients, especially girls are being missed out. Deficiency of carbamoyl phosphate synthetase (CPS1) and N-acetylglutamate synthase (NAGS) have not yet been diagnosed in the Indian sub-continent. This may be due to the unavailability of gene studies for these disorders.

## ETIOLOGY

All the urea cycle enzyme defects are genetically determined, caused by mutations in genes coding for enzymes, cofactor producer or transporter proteins of the urea production pathway. All UCDs are autosomal recessively inherited, except for OTC which is inherited in an X-linked pattern. OTC deficiency may manifest in females frequently (in up to 15% cases), although with less severity than males. The symptoms in a female carrier depend on the degree of skewed inactivation of the X chromosome.

## PATHOGENESIS

### The Urea Cycle

Ammonia is produced by deamination of amino acids in liver, other tissues as well as from gut bacteria. Whatever its source, the ammonia reaching the liver is immediately used to form urea. The urea cycle begins within the mitochondrial matrix of hepatocytes by formation of carbamoyl phosphate by a combination of ammonia with bicarbonate requiring two molecules of ATP, catalyzed by enzyme, CPS1 (**Fig. 1**). The enzyme CPS1 requires N-acetylglutamate for its activation, which itself is synthesized from acetyl CoA and glutamate by enzyme, NAGS. Thus, for initiation of the urea cycle, both CPS1 and NAGS are required (as a cofactor). Hyperammonemia is a direct effect of either deficiency of these

two enzymes, or indirect effect caused by suppression of NAGS as in many of the organic acidemia.

Carbamoyl phosphate then condenses with ornithine and forms citrulline in presence of enzyme, OTC. Ornithine enters the mitochondria by the ornithine transporter (ORNT). Disorders at these levels are caused either by deficiency of the enzyme OTC, or the transporter defect, ORNT. Citrulline is then transported out of the mitochondrial matrix into the cytosol for proceeding with the cytosolic component of the urea cycle (**Fig. 1**).

Alternate mechanisms of detoxification of ammonia are utilized in treatment of hyperammonemia. Conjugation of sodium benzoate with glycine to form hippurate, and conjugation of phenylbutyrate (converted to phenylacetate) with glutamine generate phenylacetylglutamine. Both these compounds are nontoxic and excreted in the urine, thus enabling removal of waste nitrogen from body.

## Mechanism of Central Nervous System Toxicity in Hyperammonemia

The main reason for sickness in urea cycle enzyme defects is the progressive accumulation of toxic levels of ammonia. Thus, the clinical presentation is primarily neurologic, whether it is in neonatal period or later in life. Hyperammonemia is toxic to the brain both in the acute severe form as well as in chronic elevated form.

The acute symptoms are caused by progressive cerebral edema because of elevated ammonia. At the cellular level, high ammonia causes astrocyte swelling and loss of neuronal function. Secondary metabolic derangements include elevation of glutamine, a buffer for excess nitrogen, causing osmotic brain edema triggering apoptosis, arginine deficiency causing a decrease in nitrous oxide, and creatine synthesis, further leading to neuronal damage.

Chronically, hyperammonemia can lead to progressive cortical atrophy, lesions in the basal ganglia, delayed myelination and cystic changes—all leading to developmental delay, seizures and progressive cognitive impairment.

The extent of central nervous system damage depends on both severity and duration of hyperammonemia. Newborn and infantile brains are the most vulnerable to irreversible neurological damage. The prognosis is bad even with treatment of hyperammonemia in these ages.

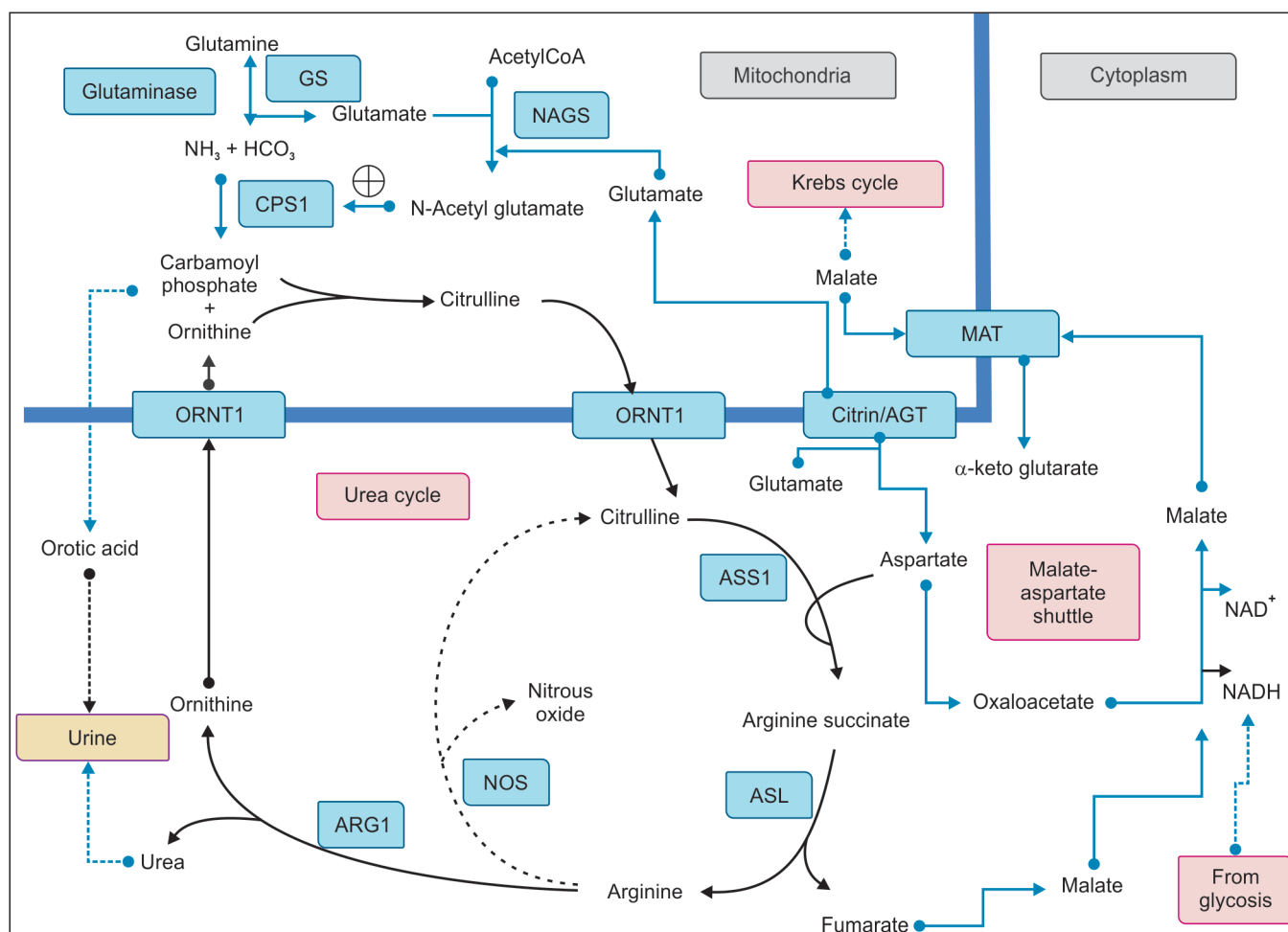
## CLINICAL PRESENTATION

The severity of enzyme deficiency is the key to the clinical severity. Severe deficiency or total absence of enzyme activity leads to classical neonatal presentation with hyperammonemia with ensuing coma and death, if untreated. This presentation is classical for severe deficiency of any of the first four enzymes of urea cycle (CPS1, OTC, NAGS, and ASL, i.e., up to formation of arginine). Less severe deficiency may result in episodic presentation later in life because of hyperammonemia in acute stressful conditions such as intercurrent illnesses and fasting. The deficiency of the fifth enzyme, arginase 1 (ARG1), and two transporters, ornithine and aspartate transporter leads to different clinical presentations. Only the common defects are discussed in this chapter.

## Clinical Presentation of Deficiency of the Initial Four Enzymes of the Urea Cycle and One Cofactor Producer

### Neonatal Classical Presentation

The neonates appear normal at birth and present within the first week, mostly within first 48–72 hours of life with progressive lethargy, and refusal to feed. This coincides with increase in oral



**Figure 1** The urea cycle with its links with the other pathways—nitrous oxide synthesis, malate-aspartate shuttle, glycolysis and Krebs cycle  
 Abbreviations: GS, glutamine synthase; NAGS, N-acetyl glutamate synthetase; CPS1, carbamoyl phosphate synthetase 1; ORNT1, ornithine transporter 1; AGT, aspartate glutamate transporter, also called citrin; MAT, malate  $\alpha$ -ketoglutarate transporter; ASS, argininosuccinate synthetase; ASL, argininosuccinate lyase; ARG1, arginase 1; NOS, nitrous oxide synthetase; NADH, nicotinamide adenine dinucleotide; Black arrows, urea cycle; Blue arrows, linked pathways; Dotted arrows, not showing complete pathways, only directing toward them.

intake of protein, as well as with ongoing catabolism and stress of birth. As stage advances, the babies may have irritability, vomiting, tachypnea (because of cerebral hyperventilation), and seizures in 50%, as a sign of neurotoxicity. There are no other metabolic derangements initially, apart from hyperammonemia. Later, there can be apnea owing to reduced respiratory drive, metabolic acidosis (especially in argininosuccinic aciduria or ASL deficiency), hypoglycemia (neurotoxicity), hypothermia and lactic acidemia as encephalopathy deepens. Progressive coma and death ensues, if untreated, accompanied by brain stem herniation.

### Delayed Onset

The affected individuals have a varied disease-free or crisis-free period, ranging from months to years, depending on the enzyme level and circumstances leading to hyperammonemia. The diagnosis is most often delayed as minor hyperammonemic episodes go unnoticed, and produce a cumulative effect on the neurological development of the child. Sometimes, children can be asymptomatic until a trigger sets in hyperammonemia, like drugs (Valproate), acute severe infections, starvation or any catabolic state. This can happen any time during the lifetime of the individual. Children may also present with physical failure to thrive with liver dysfunction, especially in citrullinemia type 1 or 2 and ASL

deficiency. Some children show self-restriction of protein in diet.

Particularly for ASL deficiency, manifestations that appear to be unrelated to the severity or duration of hyperammonemic episodes include: (1) neurocognitive deficiencies (attention deficit hyperactivity disorder, developmental disability, seizures, and learning disability); (2) liver disease (hepatitis, cirrhosis); (3) trichorrhexis nodosa (coarse brittle hair that breaks easily); and (4) systemic hypertension.

Deficiency of OTC in females results in clinical manifestations in about 15% girls. It has now been recognized that carrier females may have deficiencies in executive function, even when they may never have had symptoms of overt hyperammonemia.

## Clinical Presentation for Other Enzyme and Transporter Defects

### Arginase Deficiency

Clinical presentation in children with arginase deficiency is not typically because of hyperammonemia, although they can occur in severe episodes leading to death. In infancy, there may be irritability and failure to thrive. This is followed by development of spasticity, plateauing of cognitive development, and subsequent loss of developmental milestones. The age of onset and symptoms



vary with degree of enzyme deficiency. As the symptoms advance, the children have progressive spasticity leading to complete loss of ambulation, autonomic dysfunction with loss of bowel/bladder control and severe cognitive impairment.

### Citrin Deficiency (Aspartate Glutamate Transporter Defect)

Citrin deficiency is unique because of its varied clinical presentation at different ages. It leads to disruption of not only the urea cycle but also other energy producing pathways like glycolysis and Krebs cycle. Clinically, it can manifest in newborns as neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD), in older children as failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD), and in adults as recurrent hyperammonemia with neuropsychiatric symptoms in citrullinemia type II. The neonatal form, NICCD manifests with neonatal intrahepatic cholestasis, characterized by metabolic derangements like hypoglycemia, hyperammonemia, hemolytic anemia and cataracts. The disease remits spontaneously by 12 months of age after which body starts to self-control the diet. Often citrin deficiency is characterized by fondness for protein-rich and/or lipid-rich foods and aversion to carbohydrate-rich foods. Although citrin deficiency is most often described in oriental population, but it has increasingly been reported from other parts of the world.

## DIAGNOSIS AND APPROACH

The diagnosis of UCD starts a high index of suspicion—in every sick baby or child! The family history is very important as it may provide vital clues, especially in X-linked pedigree pattern or presence of consanguinity and previous neonatal deaths. With this background and high index of suspicion, the only important investigation in a child presenting with clinical symptoms described above is a plasma ammonia level.

Precautions taken for sample collection for plasma ammonia: There are practical issues with collection of blood for plasma ammonia levels. Ideally, this should be taken as a free-flowing blood sample and transported to the laboratory within minutes (ideally < 15 minutes), and on ice so that the spontaneous production of ammonia from deamination of glutamine in red blood cells is reduced to a minimum. Thus, the facilities for testing ammonia should be present in every major hospital, and there should be a system of transporting the blood drawn immediately on ice to the concerned laboratory.

If child is sick, clinicians must start therapy on grounds of suspicion alone and not wait for ammonia levels to come. It must be emphasized here that neonates typically have higher ammonia levels normally, thus the normal range for ammonia in plasma for a term neonate is less than 110  $\mu\text{mol/L}$  (in preterms the normal level is < 150  $\mu\text{mol/L}$ ), and less than 80 for infant under 1 year, reaching the adult range of less than 35  $\mu\text{mol/L}$  only after infancy. In general, plasma ammonia level more than 150 in neonates and infants and more than 100  $\mu\text{mol/L}$  in older age is to be considered significant to warrant further action. Additionally, indirect evidence of hyperammonemia can be detected on neuroimaging with MRI scans showing features of cerebral edema.

Apart from ammonia, the other relevant tests to be done include arterial blood gas, anion gap, blood lactate, acylcarnitine (by tandem mass spectrometry), plasma and urine amino acids, and urine organic acid analysis (specifically for orotate).

An algorithm for approach to hyperammonemia is provided in **Flow chart 1**. Typical urea cycle defect children will have normal glucose, electrolytes and lactate. The pH and  $\text{CO}_2$  varies with stage of neurotoxicity and cerebral edema. Once the results of these tests are available, one can follow the algorithm described to come to a

diagnosis. Once clinically suspected and biochemically diagnosed, a definitive diagnosis of a urea cycle defect depends on either molecular genetic testing or measurement of enzyme activity. Molecular genetic testing is possible for all urea cycle defects (**Table 1**).

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis for UCD is mainly conditions that give rise to hyperammonemia which are listed in the **Table 2**. A quick guide to bedside diagnosis is provided in **Table 3**, based on basic investigations. Other than hyperammonemia, disorders like citrullinemia type 1, citrin deficiency and argininosuccinic aciduria present with liver dysfunction, which need to be differentiated from other inherited or acquired causes of cholestasis and liver disease. Arginase deficiency and hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome often present with spasticity, thus making it difficult to differentiate from other causes of spasticity like spastic diplegia as sequelae of perinatal asphyxia or hereditary spastic paraparesis.

## MANAGEMENT

Immediate treatment is to be initiated in hyperammonemia to prevent and minimize the drastic neurological consequences. Four principle aims of management are:

1. Immediate ammonia detoxification from body fluids
2. Inhibition of production of ammonia further in body
3. Providing hemodynamic stability, by correction of fluid or electrolyte and acid-base imbalance in the body
4. Treatment of underlying cause of acute deterioration—sepsis or trauma, etc. which triggered the metabolic decompensation.

### Immediate Treatment

Emergency management of acute presentation is summarized in **Box 1**. The most important and most urgent of all is a rapid correction of ammonia. The decision to start therapy is purely clinical, but generally, any ammonia more than 150  $\mu\text{mol/L}$ , especially in a sick neonate/child or adult should be taken seriously and treated immediately.

In view of the rarity of presentation, treatment must be coordinated by a metabolic center with experience in UCD, and whenever possible, shifted to a tertiary care center with intensive care unit (ICU) facilities. Immediate steps to be taken before shifting to higher center are:

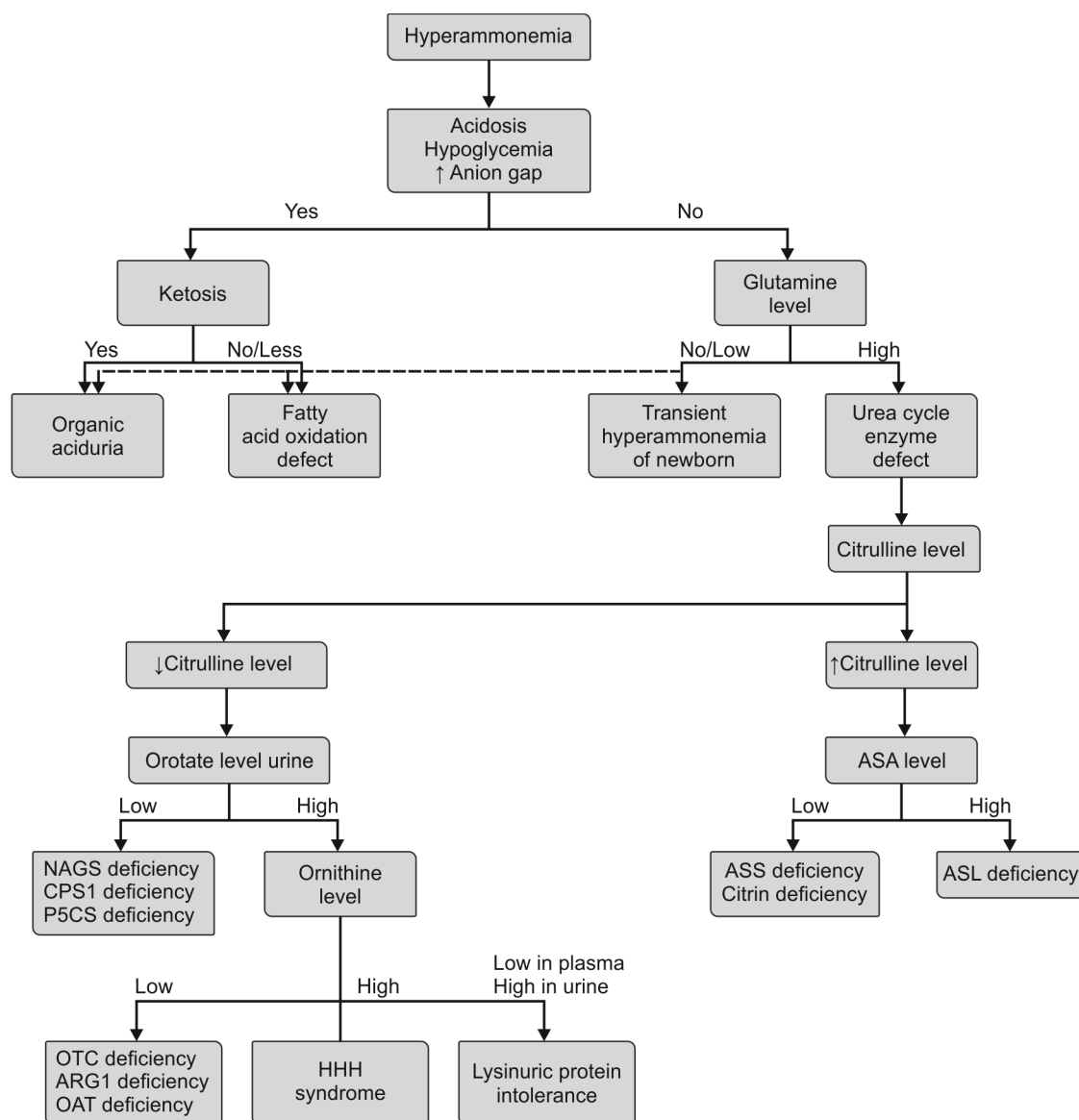
- Stop all oral intake of protein (but only for 24 hours, followed by gradual introduction of small amounts)
- Start intravenous (IV) 10% glucose infusion
- Initiation of first-line medications—ammonia scavengers like oral sodium benzoate powder
- Collection of blood and urine samples for diagnostic purposes and appropriately transporting to laboratory concerned.

Specific testing should go hand-in-hand with initiation of therapeutic measures so that a quick and accurate diagnosis is achieved in minimum possible time. Once at tertiary care center, the treatment of acute severe hyperammonemia should be as follows as per the principle aims listed above.

### Ammonia Detoxification

The child should be started on ammonia scavengers if not started by that time, and a decision for hemodiafiltration taken depending upon the ammonia level on arrival (indications: ammonia > 500  $\mu\text{mol/L}$  or rapidly rising).

**Sodium benzoate** It is the only medicine that is freely available as oral preparation/powder in India and this should be used as soon as hyperammonemia is detected. Dose of oral sodium benzoate

**Flow chart 1** The algorithm showing approach to diagnosis of urea cycle disorder based on biochemical tests

Abbreviations: NAGSD, N-acetyl glutamate synthetase deficiency; CPS1D, carbamoyl phosphate synthetase 1 deficiency; OTCD, ornithine transcarbamoylase deficiency; ARGD, arginase deficiency; OATD, ornithine aminotransferase deficiency; HHH, hyperammonemia-hyperornithinemia-homocitrullinemia; ASS1D, argininosuccinate synthetase 1 deficiency; ASLD, argininosuccinate lyase deficiency; LPI, lysinuric protein intolerance.

is 250 mg/kg/day, divided at 6–8 hourly intervals. This may be increased up to 500 mg/kg/day if required. Ideally, in a sick child, intravenous bolus infusions of sodium benzoate should be given at similar doses at 6-hourly intervals.

**Sodium phenylbutyrate/sodium phenylacetate** Phenylbutyrate is a precursor of phenylacetate and more palatable than phenylacetate. Available outside India as tablets, given in doses similar to sodium benzoate of 250–500 mg/kg/day divided in 3 or 4 doses. In developed countries, a combination of IV sodium benzoate and sodium phenylacetate (Ammonul®) or with sodium phenylbutyrate (Ammonaps®) is available.

**Arginine and citrulline** Arginine and citrulline are used to promote waster nitrogen excretion. Arginine helps in maximizing ammonia excretion through urea formation. It is also an amino acid that becomes essential especially when urea cycle is not functioning. Thus, it needs to be supplemented to avoid deficiency of arginine

affecting nitrous oxide and creatine synthesis. Dose for arginine in acute emergency (as intravenous) is 360 mg/kg in 2 hours followed by 180–360 mg/kg/day, depending on type of UCD, divided in intervals of 6–8 hours. Arginine is only available as sachets in India containing powdered form. Oral dose of arginine is the same as IV doses per day. Arginine should not be used in arginemia and is not effective in OTC deficiency. Citrulline is not easily available and, therefore, not given.

**N-carbamoylglutamate (Carbaglu®)** This product is extremely helpful in NAGS deficiency as it mimics N-acetylglutamate and helps activation of the CPS1 enzyme to start the urea cycle. Carbamoyl glutamate can also be used in hyperammonemia in organic aciduria, as there is secondary inhibition of NAGS by organic acids. Dose is 100 mg/kg orally/24 hours in three divided doses. The use of this drug is limited due to its high cost and nonavailability here in India.

**Table 1** Diagnostic features and genes related with urea cycle disorders

Disorder	Gene	Inheritance pattern	Plasma amino acid concentrations	Urinary orotic acid levels	Diagnostic modality
N-acetyl glutamate dehydrogenase deficiency (NAGS deficiency)	NAGS	AR	↑↕ Glutamine ↑ Alanine	Normal	Enzyme assay (liver) or gene study
Carbamoyl phosphate synthetase deficiency (CPS1 deficiency)	CPS1	AR	↑ Glutamine ↑ Alanine ↓ Citrulline ↓ Arginine	Normal	Enzyme assay (liver) or gene study
Ornithine transcarbamoylase deficiency (OTC deficiency)	OTC	X-linked	↑ Glutamine ↑ Alanine ↓ Citrulline ↓ Arginine	↑↑	Enzyme assay (liver) or gene study
Argininosuccinate synthetase deficiency (ASS deficiency or citrullinemia type 1)	ASS1	AR	↑ Glutamine ↑ Alanine ↑↑ Citrulline ↓ Arginine	↑	Enzyme assay (liver, skin fibroblasts) or gene study
Argininosuccinate lyase deficiency (ASL deficiency or argininosuccinic aciduria, ASA)	ASL	AR	↑ Glutamine ↑ Alanine ↑ Citrulline ↑↑ Arginino-succinate ↓ Arginine	↑	Enzyme assay (liver/skin fibroblasts/RBCs) or gene study
Arginase deficiency (hyperarginemia)	ARG1	AR	↑ Arginine	↑	Enzyme assay (liver/RBCs) or gene study
Aspartate-glutamate carrier deficiency (citrin deficiency, citrullinemia type 2, NICCD in neonates)	SLC25A13	AR	↑ Glutamine ↑ Alanine ↑/N Citrulline ↓ Arginine	↑	Gene study
Ornithine transporter deficiency (HHH syndrome)	SLC25A15	AR	↑ Ornithine ↑ Homocitrulline in urine	↑	Gene study

Abbreviations: AR, autosomal recessive; HHH, hyperornithinemia-hyperammonemia-homocitrullinuria; NICCD, neonatal intrahepatic cholestasis caused by citrin deficiency.

**Table 2** Causes of hyperammonemia

Inherited deficiency of enzymes of urea cycle	N-acetyl glutamate synthetase deficiency Carbamoyl phosphate synthetase deficiency Ornithine transcarbamoylase deficiency Argininosuccinate synthase deficiency (citrullinemia type 1) Argininosuccinate lyase deficiency (argininosuccinic aciduria) Arginase deficiency (argininemia)
Inherited defect of transporters affecting the urea cycle intermediates	Ornithine transporter (HHH syndrome) Dibasic amino acid transporter (lysinuric protein intolerance) Citrin or aspartate—glutamate transporter (citrullinemia type 2)
Inherited deficiency of enzymes of other metabolic pathways	Organic aciduria (propionic acidemia, MMA and others) Disorders of fatty acid oxidation (MCADD, primary carnitine deficiency, etc.) Hyperinsulinism/hyperammonemia syndrome Ornithine aminotransferase deficiency (neonatal form) Mitochondrial respiratory chain defects Pyruvate dehydrogenase deficiency Pyruvate carboxylase deficiency (neonatal form)
Acquired causes	Liver failure/impairment Any severe systemic illness in neonate Gastrointestinal bacterial overgrowth Urinary tract infections Drugs: e.g., valproate, chemotherapy Total parenteral nutrition Reye's syndrome
Other causes	Artificial preanalytical increase: Poor specimen quality/hemolysis Difficult venipuncture Skin contamination Contaminated tube Delayed analysis and inappropriate transport to lab without ice Transient hyperammonemia of the newborn Portosystemic shunt

Abbreviations: HHH, hyperornithinemia-hyperammonemia-homocitrullinuria; MCADD, Medium-chain acyl-CoA dehydrogenase deficiency; MMA, methylmalonic acidemia.

**Table 3** Differential diagnosis of urea cycle disorders using baseline investigations

Parameter	Urea cycle disorder	Organic aciduria	Carnitine/fatty acid oxidation disorder	Mitochondrial disorders (Pyruvate carboxylase/dehydrogenase/respiratory chain disorders)	Hyperinsulinism/hyperammonemia syndrome	Transient hyperammonemia of newborn
Ammonia	++/++++	++/+++	++	++	++	++++
Acidosis	+/-	+	+/-	+	-	-
Ketosis	-	++	-	N/++	-	-
Lactate	N	N/++	N/++	++/+++	N	N
Glucose	N	N/↓	↓	N/↓	↓	N
AST/ALT	N/D	N	N/D	N/D	N	N
WBC/RBC	N	N/↓	N	N	N	N

Ammonia: + (< 200 μmol/L), ++ (200–600), +++ (> 600), ++++ (> 1,500)

Abbreviations: N, normal; D, deranged; ↓, low.

### BOX 1 Emergency treatment of severe acute hyperammonemia

1. Basic life support and supportive treatment, e.g., ventilation (particularly prior to transfer) treatment of sepsis, seizures, etc.
2. Stop protein intake
3. Provide high-energy intake
  - Orally (if accepting): 10–25% sugar or juice, protein-free formula (special dietary formula)
  - Intravenous: 10% glucose by peripheral infusion, or 10–25% glucose by central venous line, IV intralipid infusion 2–4 g/kg/24 hours
4. Ammonia detoxification
  - Sodium benzoate up to 500 mg/kg/day—oral or IV
  - Sodium phenylbutyrate up to 600 mg/kg/day
  - L-arginine 50 up to 600 mg/kg/day depending upon disorder (contraindicated in arginase deficiency)
5. Dialysis (hemodialysis, hemodiafiltration or hemofiltration)
  - Start immediately if plasma ammonia more than 500 μmol/L or if ammonia does not fall with the above measures
  - Peritoneal dialysis in neonate.

**Dialysis** In acutely sick babies and children with rapidly increasing or very high levels (> 500 μmol/L) of ammonia, this invasive but very effective procedure of extracorporeal detoxification is employed. Hemodialysis is superior to all other forms of dialysis, resulting in more than 50% reduction in ammonia levels within hours. Continuous high-volume venovenous hemodiafiltration (CVVH) can be used very effectively due to its availability in most advanced ICUs in India.

### Inhibition of Ammonia Production

**Increase calorie supplementation to offset catabolism and protein breakdown** Provide 10–20% glucose infusion and add insulin if hyperglycemia occurs. IV lipids infusion @ 2–3 g/kg/24 hours is also helpful.

**Stop all natural protein intake (in diet) to reduce the ammonia production initially** The duration of *nil protein* intake should not exceed 24–36 hours as it causes tissue breakdown to meet protein demands. Thereafter little amount of protein is initiated either orally or parenterally, and titrated up to maintain anabolism as well as to keep the ammonia levels down.

### Correction of Fluid and Electrolyte/Acid-Base Disturbance

In the acute state, there is often dehydration because of vomiting and reduced oral acceptance, which needs immediate attention. Electrolytes need to be monitored as the drugs used for ammonia detoxification themselves have sodium (1 g of

sodium benzoate contains 7 mmol of Na<sup>+</sup>; thus, the sodium intake needs to be monitored). Respiratory alkalosis accompanying hyperammonemia does not need correction most of the time.

### Treatment of Underlying or Triggering Factors

A full diagnostic work-up and prompt and aggressive treatment should be initiated to combat the underlying cause, which in most cases is an infection especially in older infants and children.

### Long-term Management

#### Dietary Management

The basis of dietary management is to prevent production of ammonia. This is achieved by keeping the protein intake to the lowest required level, which is enough to sustain linear growth and carry out all the cellular functions appropriately. Thus, if the body is maintained in positive nitrogen balance (protein synthesis greater than protein breakdown), the ammonia will not be generated and urea cycle may not be initiated. The protein requirement can be ascertained on the basis of age, weight and physical health of an individual. The minimum dietary protein requirement can be met in a vegetarian diet, but this may be deficient in calories and vitamin/minerals and trace elements. Thus, extra carbohydrate or fats, vitamins and other trace element supplements need supplementation. Special diets, containing essential amino acids are available that take care of the requirement of quality protein and vitamin/trace elements.

#### Drug Therapy

The same ammonia scavenging medications (generally sodium benzoate and arginine) need to be continued, with regular monitoring of ammonia levels. The doses vary with every child's requirement and should be modified according to ammonia levels from time to time.

### Management of Acute Intercurrent Illnesses/Other Stressful Situations—Emergency Protocols for Home and Hospital

Any acute illness like viral fever or sore throat is an added stress on the body, with increased demand for energy leading to a catabolic state if oral intake is poor. In order to circumvent this stress, the body needs extra energy with no extra protein intake to reduce production of more ammonia. Thus, a careful balance of reduced protein intake coupled with extra calories in the diet is required for a few days. This can be managed safely at home, for minor illnesses. The family should be informed of danger signs when the child requires hospital management. Thus, protocols for both



home management (*sick day regime*) and hospital emergency department should be provided to the family.

### Monitoring for Growth and Development

Regular assessment of growth and development is required to assess appropriateness of dietary protein and energy intake of patient. In addition, few blood parameters, such as hemoglobin, albumin and pre-albumin levels, vitamins and amino acid levels, should be checked regularly to assess growth and efficacy and adequacy of maintenance therapy. Ammonia should be monitored more frequently both in normal state as well as during times of acute illness.

### Supportive Treatment

As most of the children are diagnosed with UCD after an acute illness, it is usual to find various degrees of neurological sequelae and developmental delay in these children. A multidisciplinary approach is recommended which would take care of the child's all round development. Anticonvulsants may be required for seizures, but valproate therapy should be avoided as valproate itself can cause hyperammonemia.

### Liver Transplantation as an Option for Long-term Cure

Over the last two decades, reasonable evidence has gathered that liver transplantation is the only modality that provides a definitive cure to patients of UCD. Long-term (5-year) survivals are now close to 90% with minimum morbidity, if offered at a time when the child has not had many neurological insults. The quality of life improves as child is allowed a limitless diet of choice, and reduction in hospital admissions. However, lifelong immunosuppressant therapy is required which may be a deterrent for few patients, along with the exorbitant cost of a liver transplant.

### OUTCOME

Irrespective of the treatment, the outcome of acute severe neonatal presentation of UCD remains poor. Only a few neonates who are picked up early before elevation of ammonia to toxic levels, and siblings of affected children do well with timely initiation of appropriate therapy. Outcome of children presenting later is better, provided the hyperammonemic episodes are briskly and effectively managed and continued in the long-term.

### PREVENTION

As all the UCDs are inherited, prenatal diagnosis is feasible and available in India, and is recommended to all couples that have had a child with UCD. Relatives at risk also can be screened for carrier status by gene studies followed by appropriate genetic counseling

regarding risk to their offsprings. Prenatal diagnosis is carried out using mutation analysis (only in cases where the causative mutation is known) after chorionic villus sampling at 11–13 weeks of pregnancy.

### MORE ON THIS TOPIC

- Cox MM, Nelson DL. Amino acid oxidation and the production of urea. *Lehninger Principles of Biochemistry*. 5<sup>th</sup> ed. New York: Freeman & Co. 2008.
- Häberle J, Boddaert N, Burlina A, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders. *Orphanet J Rare Dis*. 2012;7:32.
- Lanpher BC, Gropman A, Chapman KA, et al. Urea Cycle Disorders Overview. From: <http://www.ncbi.nlm.nih.gov/books/NBK1217/>. Accessed August 1, 2014.
- Summar ML. Urea cycle disorders. In: Sarafoglou K, Hoffmann GF, Roth KS (Eds). *Pediatric Endocrinology and Inborn Errors of Metabolism*. New York: McGraw Hill; 2009. pp. 141–52.
- UK National Metabolic Biochemistry Network Guidelines for the Investigation of Hyperammonemia. From: [MetBio-Guideline-UMUF338839-23-07-2013.pdf](http://www.metbio-guideline-umuf338839-23-07-2013.pdf).
- Wijburg FA, Nassogne MC. Disorders of the urea cycle and related enzymes. In: Saudubray JM, Van den Berghe G, Walter JH (Eds). *Inborn Metabolic Diseases—Diagnosis And Treatment*. 5<sup>th</sup> ed. Heidelberg: Springer; 2012. pp. 297–310.

### IN A NUTSHELL

1. Urea cycle is the only metabolic pathway utilized for detoxification of ammonia and disposal of nitrogen waste.
2. Disruption of this cycle or urea genesis, either directly or indirectly, leads to progressive accumulation of toxic ammonia in the body.
3. Hyperammonemia is an absolute emergency condition as if not detected promptly; it can lead to progressive neuronal damage and death.
4. Very high index of suspicion should be kept and ammonia levels should be checked in any sick neonate or child who presents with neurological symptoms.
5. Treatment of UCD is based on low-protein diet as well as drugs to provide alternate pathway for waste nitrogen disposal (sodium benzoate, sodium phenylbutyrate).
6. Some new innovative therapies are available now, like carbamoyl glutamate for children with NAGS deficiency, and liver transplantation as a one-time treatment.
7. Urea cycle disorders are genetic in origin; each being inherited either in autosomal recessive or X-linked manner. More severe genetic defects lead to presentation as early as few days of life, and some may present even in adulthood.
8. Genetic testing and prenatal diagnosis is available for all the UCDs.

## Chapter 3.4

# Organic Acidemias

Neerja Gupta

Organic acidemias refer to an inborn error of metabolism (IEM) characterized by urinary excretion of the nonamino organic acids. The clinical presentation is often nonspecific, highly variable and requires high index of suspicion by pediatricians and neonatologists. Classically, patients with severe forms will present acutely in the neonatal period, as a sepsis like illness with encephalopathy, vomiting, poor feeding, seizures or lethargy after an initial asymptomatic period. Children with milder forms manifest over a long period of time but sometimes with acute episodes.

Exact prevalence of organic acidemia is not known due to lack of newborn screening program. In author's experience and based upon other Indian studies, organic acidemias appear to be one of the most common IEMs in India.

## PATHOGENESIS

Organic acidemia is a broad term where deficiency of specific enzyme in amino acid metabolism, mitochondrial disorders,  $\beta$ -oxidation of fatty acids or carbohydrate metabolism results in abnormal urinary excretion of organic acids. Most organic acids are carboxylic acids derivatives and are the byproducts of several metabolic pathways (**Fig. 1**). Organic acids are generated as a result of first transamination step and second dehydrogenation step of amino acid catabolism. Most organic acidemias are due to a downstream defect in the catabolism of branched-chain amino acids (BCAA). Any block in their breakdown leads to the accumulation of organic acids in the cell and its elevation in plasma and urine. These accumulated organic acids are either toxic themselves or metabolized to other toxic byproducts affecting function of various major organs. Organic acidemias are characterized by the presence of metabolic acidosis with increased anion gap in combination with hyperammonemia, hypoglycemia, hypocalcemia, ketosis or lactic acidosis.

Most of the affected babies are delivered as healthy term babies as during pregnancy placenta acts as a dialyzer for removing the accumulated toxic metabolites. After birth, the combination of initial catabolic state and initiation of feeds result in precipitation of clinical symptoms. These episodes of metabolic decompensation are precipitated by catabolic states, such as fasting, infections and fever. Diagnosis is possible by using gas chromatography-mass spectrometry (GCMS) as it can detect the typical urinary organic acids profile seen in various organic acidurias. Majority of these disorders have autosomal recessive inheritance. Based upon the deficiency of enzyme, the common organic acidemias are maple syrup urine disease (MSUD), propionic acidemia (PA) and methylmalonic acidemia (MMA), glutaric acidemia type 1 (GA-1) and isovaleric acidemia (IVA). Other rare disorders are biotin-unresponsive 3-methylcrotonyl-CoA carboxylase

deficiency, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency, mitochondrial acetoacetyl-CoA thiolase deficiency (3-ketothiolase deficiency) and 3-methylglutaconic acidurias. **Figure 2** shows the pathway of BCAA catabolism leading to various organic acidemia.

## CLINICAL FEATURES

Typical presentation includes neonates with vomiting, poor oral acceptance, lethargy, tone abnormalities or seizures rapidly progressing to encephalopathy at around 7–10 days of life. Presence of a positive family history, consanguinity, history of previous neonatal death with similar illness provides an important clue to the diagnosis. Although physical examination of babies with organic acidemia is unremarkable, yet there are certain clues (**Table 1**) that can point toward a specific diagnosis. Accumulation of organic acid can give rise to a peculiar odor of the urine or sweat.

Older children present with failure to thrive, developmental delay with or without convulsions, regression, static or progressive dystonia, or choreoathetoid movements. They may also present with acute decompensation precipitated by starvation or intercurrent illness.

## INVESTIGATIONS

### Basic Metabolic Screen

Measurement of blood glucose, electrolytes, pH for acidosis, lactate levels, ammonia levels and urinary ketones give a fair clue toward underlying organic acidemia. Salient features of most organic acidemias are discussed further:

- **Metabolic acidosis** Accumulation of organic anions, lactate or ketones result in metabolic acidosis with increased anion gap ( $>20$  mmol/L).
- **Lactic acidosis** Normal blood lactate levels 0.5–1 mmol/L; abnormal greater than 2 mmol/L.
- **Ketosis** Presence of ketones in a sick newborn is an alarming sign as neonates normally do not produce any ketones. A simple bedside positive urinary dipstick test for ketones (acetoacetic acid and acetone) in a sick baby presenting with acute encephalopathy gives a clue toward the diagnosis of organic acidemia and should be promptly followed by GCMS.
- **Hyperammonemia**

There may be associated abnormal liver function test, hypo- or hyperglycemia, hypocalcemia, thrombocytopenia or neutropenia. The basic approach to a child with organic acidemia is shown in **Flow chart 1**.

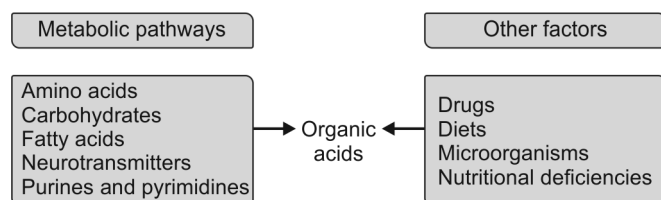
### Specific Diagnosis

This is possible through the combination of blood acylcarnitine by tandem mass spectrometry (TMS) or plasma amino acid profile and urine organic acid profile by GCMS. GCMS is helpful in identifying the unmeasured organic anions,  $\beta$ -hydroxybutyrate and acetoacetic acid. While ordering these special tests, it is mandatory to include full details about the diet, fluids and drugs provided to the patient. Sample should be rapidly transported to the laboratory. In case blood transfusion is anticipated, a pretransfusion sample should be obtained.

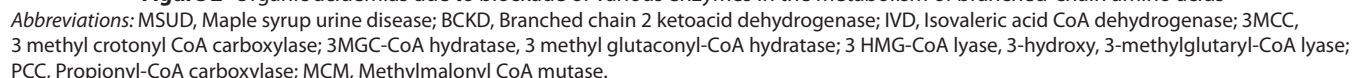
Specific enzyme assay or DNA testing provides further confirmation. These studies are basically helpful for the prenatal diagnosis in future pregnancies.

## MANAGEMENT

Management of a child presenting with organic acidemia is done in two phases: (i) initial acute management, (ii) ongoing long-term management.

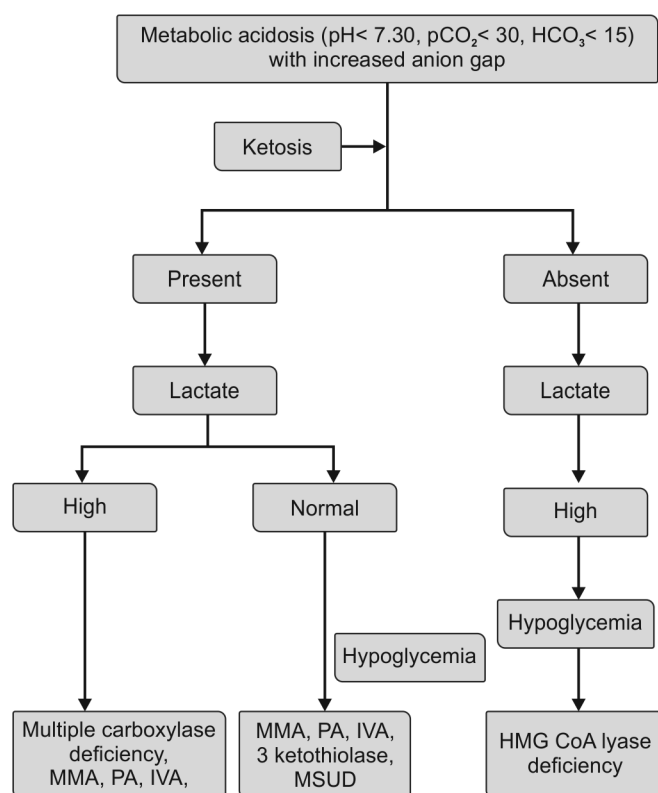


**Figure 1** Factors responsible for organic acid origin



**Abbreviations:** MMA, methylmalonic acidemia; PA, propionic acidemia; IVA; isovaleric acidemia; GA-1, glutaric acidemia type 1; MSUD, maple syrup urine disease.

Any child with acute presentation should be first stabilized and assessed for any circulatory and ventilatory support. Majority of these patients require maintenance of hydration, and correction of metabolic acidosis, hypoglycemia, dyselectrolytemia and hypocalcemia as guided by the initial screening investigations. Such patients frequently suffer from infections that can result in persistent catabolism and therapeutic failure. Major steps of initial management include maintenance of intravenous line and collection of various samples (**Table 2**). Hydration and anabolic state is maintained using 5–10% intravenous dextrose in 0.2% of NaCl at 1.25–1.5 times calculated maintenance. KCl is added once the adequate urinary output is established. The caloric intake of up to 100–120 kcal/kg/day can be given. Protein is eliminated from diet. Some experts recommend use of insulin to promote anabolic state. Within 1–2 days of initial management, low protein diet is introduced gradually over a period of 2–3 days to prevent catabolic state due to acute protein malnutrition and to promote adequate growth. Patients with severe metabolic acidosis and hyperammonemia usually require hemodialysis which is more efficient than peritoneal dialysis. Carnitine therapy is given to compensate for secondary carnitine deficiency which is often seen in such patients due to urinary excretion of carnitine-bound organic acids. *Supportive care* includes artificial ventilation for respiratory insufficiency, treatment of raised intracranial tension and cerebral edema, antibiotics for associated infections and anticonvulsants for seizures.

**Flow chart 1** Outline for the approach to different organic acidemia**Table 2** Basic metabolic investigations in an acutely sick baby

Test (normal range)	Remarks
Serum ammonia	
• Neonates	• Rapidly flowing fasting blood (uncuffed venous or arterial)
– Healthy: < 110 $\mu\text{mol/L}$	• Sample is transported on ice
– Sick: up to 180 $\mu\text{mol/L}$	• The test should be done within 1 hour, so prior notification to the laboratory is desirable
– Suspect IEM: > 200 $\mu\text{mol/L}$	• Artefactual elevations are common
• After the neonatal period	
– Normal: 50–80 $\mu\text{mol/L}$	
– Suspect IEM: > 100 $\mu\text{mol/L}$	
Lactate	
• Blood: < 2.4 mmol/L	• Should be sent immediately to the lab for analysis
• CSF: < 2.0 mmol/L	• Artefactual elevations are common
Blood gas for pH and anion gap (normal anion gap = 15–20 mmol/L)	Increased in organic acidemia
Blood glucose	
Urinary ketones	
Others	
• Blood count, liver function test, renal function test	

Abbreviations: IEM, Inborn errors of metabolism; CSF, cerebrospinal fluid.

### Long-term Treatment

Long-term management includes maintenance of adequate metabolic control with periodic biochemical monitoring. A metabolic dietician has a vital role in providing age-specific adequately protein-restricted diets. Calcium supplements and specific vitamin therapy are given depending upon the type of specific defect.

## SPECIFIC DISORDERS

### Maple Syrup Urine Disease

Maple syrup urine disease is classified both as organic acidemia and aminoacidopathy. It is caused by the deficiency of the branched-chain  $\alpha$ -keto acid dehydrogenase complex, a common enzyme involved in the second enzymatic step in the degradative pathway of the BCAAs—leucine, isoleucine and valine.

#### Genetics

Maple syrup urine disease is a rare autosomal recessive metabolic disorder with an incidence of approximately 1:200,000 livebirths. Three genes are responsible for MSUD—(i) *BCKDHA*, encoding branched-chain keto acid (BCKA) decarboxylase (E1)  $\alpha$ -subunit (MSUD type 1A); (ii) *BCKDHB*, encoding BCKA decarboxylase (E1)  $\beta$ -subunit (MSUD type 1B); and (iii) *DBT*, encoding dihydrolipoyl transacylase (E2) subunit (MSUD type 2).

#### Clinical Features

The clinical phenotype depends upon the residual enzyme activity with classical and severe phenotype being associated with deficient activity (< 2%) and milder or intermittent phenotypes with partial enzyme activity (3–40%). Classically such patients have neonatal presentation mostly after 3–5 days of life and present with poor feeding, irritability followed by progressive encephalopathy with lethargy, respiratory abnormalities, opisthotonus, stereotypic limb movements, such as *fencing and bicycling* and finally coma and central respiratory failure. Milder forms present with poor feeding and growth along with developmental delay. They may have encephalopathy like episodes during illness. Intermittent forms have mild to severe episodic illness precipitated by any catabolic state. The severity of the neurological involvement and encephalopathy is directly related to the leucine concentration and requires careful monitoring.

#### Diagnosis

Most babies present with typical clinical features and ketonuria is often precipitated by a catabolic event. Hypoglycemia and mild hyperammonemia may be seen uncommonly in such patients.

Diagnosis is made by detection of BCKAs and  $\alpha$ -hydroxyl acids in urine by following biochemical methods:

- **Dinitrophenylhydrazine (DNPH) test** Equal volumes of urine and DNPH reagent are mixed and color change is observed after 10 minutes. A positive test is indicated by the presence of yellow-white precipitate. It is a good bedside test.
- GCMS for BCKAs and hydroxyacids.
- Plasma amino acids show elevated levels of all BCAAs especially leucine.
- Enzyme activity measurement in different cells.
- DNA testing for three genes: (i) *BCKDHA*; (ii) *BCKDHB*; and (iii) *DBT*.

#### Treatment

Acute phase management for metabolic decompensation includes lowering down the toxic concentration of leucine and reversal of acute metabolic decompensation by exogenous removal of toxins with either hemodialysis or hemofiltration. This rapidly lowers the levels of leucine. Levels of valine, isoleucine also fall below the normal level. To stimulate the adequate protein synthesis, such patients require oral BCAAs free formula along with adequate calories and supplementation with isoleucine and valine during recovery. A careful monitoring of plasma BCAA, especially leucine is needed to ensure adequate metabolic control.

Long-term management requires strict and carefully monitored diet and includes combination of measured proportion of natural



protein (BCAA containing food) and BCAA-free special diet. The goal is to achieve postprandial plasma concentration of leucine (80–200  $\mu\text{mol/L}$ ), isoleucine (40–90  $\mu\text{mol/L}$ ) and valine (200–425  $\mu\text{mol/L}$ ), normal or near normal values. The dietary adjustment is usually based upon plasma leucine concentration (being most toxic) to maintain a plasma leucine-to-valine concentration ratio (mol:mol) of half (0.5) or less and a leucine-to-isoleucine ratio of about 2.0. This requires judicious supplementation with isoleucine and valine. Unlike other organic acidemias, carnitine supplementation is not required as no abnormal acylcarnitine is formed. Supplementation with thiamine (50–100 mg twice a day) may be helpful in thiamine responsive forms. Liver transplantation results in increased enzymatic activity, avoidance of BCAA-free special diet and metabolic decompensation during catabolic states.

### Propionic Acidemia and Methylmalonic Acidemia

Propionic and methylmalonic acids are formed from the catabolism of BCAAs, like isoleucine and valine, odd-chain fatty acids and cholesterol. They are ultimately converted to succinyl CoA which feeds into the Krebs cycle. Defects in any of the steps below result in the accumulation of toxic precursors.

#### Genetics

Propionic acidemia (PA) and methylmalonic acidemia (MMA) are autosomal recessive disorders. PA results from mutations in propionyl CoA carboxylase alpha (PCCA) or propionyl CoA carboxylase beta (PCCB) gene encoding  $\alpha$  and  $\beta$  units of propionyl CoA carboxylase (PCC) enzyme. Incidence of PA is less than 1 in 100,000.

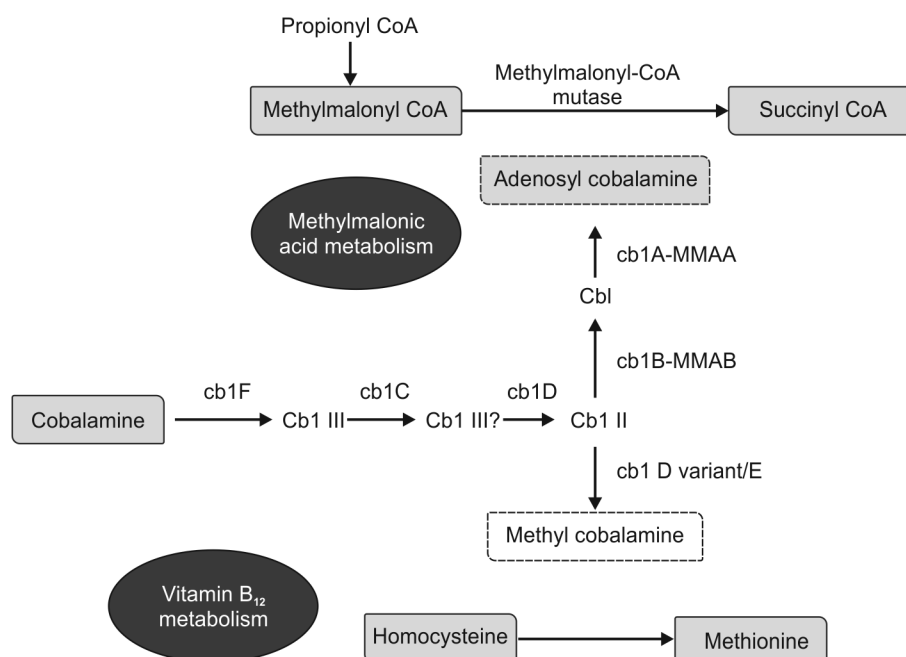
Methylmalonic acidemia is caused either by mutations in *MUT* gene encoding methylmalonyl-CoA mutase (MCM) enzyme or by genetic defects in the genes required for its cofactor. In approximately 50–65%, mutations in *MUT* gene cause MMA, the remaining patients have various cobalamin variants. MMA is relatively more common than PA with an incidence of 1 in 50,000.

### Pathophysiology

As shown in the **Figure 2**, PA is caused by a deficiency of the mitochondrial enzyme PCC, a biotin-dependent enzyme. In the absence of PCC activity, intermediary products such as propionylcarnitine, 3OH-propionate and methylcitrate accumulate.

Methylmalonic acidemia occurs either due to the deficiency of adenosylcobalamin-dependent MCM or due to deficiency of enzymes interfering with the transport and metabolism of its cofactor, adenosylcobalamin. Deficiency in either of these two enzymes results in greatly increased levels of methylmalonic acid in plasma and urine. As propionyl CoA carboxylation is reversible, propionate metabolites also accumulate and can be seen in plasma or urine of patients with MMA. Depending upon the level of enzyme activity, whether completely or partially absent, these are classified as *mut*<sup>0</sup> or *mut*<sup>-</sup>. Defect in MCM cofactor adenosylcobalamin synthesized from vitamin B<sub>12</sub> can occur due to mitochondrial cobalamin reductase deficiency (*cb1A*) and mitochondrial cobalamin adenosyltransferase deficiency (*cb1B*). Both MMA and homocystinuria can occur due to defects in adenosyl and methylcobalamin synthesis and are classified as cobalamin *cb1C*, *cb1D* and *cb1F*. In all these disorders, the levels of plasma vitamin B<sub>12</sub> are normal. The other cause of increased urine and plasma methylmalonic acid is vitamin B<sub>12</sub> deficiency secondary to dietary deficiency and seen exclusively in breastfed infants of vegan mothers. In vitamin B<sub>12</sub> deficiency, the deficient plasma levels of vitamin B<sub>12</sub> are seen in combination with MMA.

**Figure 3** depicts the linkage between various intracellular metabolic pathways involving vitamin B<sub>12</sub>, homocysteine, catabolism of isoleucine and Krebs cycle. Based upon the plasma concentration of MMA, homocysteine and vitamin B<sub>12</sub> levels, the type of defect can be characterized. Accumulation of secondary metabolites in both PA and MMA leads to inhibitory effect on various pathways causing hypoglycemia, elevated plasma lactate, hyperammonemia and hyperglycinemia.



**Figure 3** Close linkage between vitamin B<sub>12</sub> and methylmalonic acid metabolism

## Clinical Features

Most babies with severe forms of PA and MMA have similar clinical presentations and present with metabolic acidosis, ketosis, hypoglycemia, vomiting, hypotonia and lethargy during neonatal period. During late infancy, they present with failure to thrive, intermittent decompensation associated with illness or fasting, Reye syndrome like illness, seizures, and metabolic derangements like hypoglycemia. Milder forms can have developmental delay, chronic progressive neurological disease, ataxia, metabolic stroke, extrapyramidal signs. About 25–50% of patients with PA have dilated or hypertrophic cardiomyopathy and can also have conduction abnormalities. Patients with PA or MMA may have subtle facial dysmorphism like triangular mouth, broad nasal bridge, epicanthic folds and smooth philtrum.

## Diagnostic Tests

### Propionic acidemia

- Urine organic acid analysis by GCMS shows presence of 3OH-propionate, methylcitrate, propionylglycine and tiglyglycine.
- Blood acylcarnitine analysis shows increased propionylcarnitine (C3), low free carnitine due to secondary carnitine deficiency.
- Enzyme assay of 14C-propionate incorporation into cultured fibroblasts or PCC in cultured fibroblasts or leukocytes confirms the diagnosis.
- DNA analysis for PCCA and PCCB gene analysis.

### Methylmalonic acidemia

- Urine organic acid analysis shows presence of methylmalonate, 3OH-propionate and methylcitrate.
- Blood acylcarnitine analysis shows raised propionylcarnitine (C3) but low free carnitine levels as seen in PA.
- Complementation analysis, though not routinely available in India, is helpful in determining the affected gene.
- DNA analysis for various genetic defects can be done. Prenatal diagnosis is possible by analyzing the previously identified genetic defect in the fetus. In case mutation is not known, direct measurement of metabolites in amniotic fluid can also be performed.

## Treatment

**Acute management** Stop protein intake. Promote anabolism by providing glucose and insulin. Correct metabolic acidosis. Administer sodium benzoate to remove ammonia and/or L carnitine to remove propionic acid.

**Long-term treatment** Goal is to reduce the levels of toxic intermediary metabolites, i.e., methylmalonic acid and propionic acid. This can be achieved by natural protein restriction (1–1.5 g/kg/day) that provides at least minimum amount of protein and essential amino acids to ensure normal growth. The diet has to be individualized depending upon the patient's nutritional status, metabolic control and age. One should avoid fasting and restrict protein during intercurrent illness that promotes catabolism. In cases of isolated MMA, provide diet restricted in BCAAs, odd-chain fatty acids and polyunsaturated fatty acids. Patients with combined MMA and homocystinuria require a diet restricted both in BCAA and methionine and threonine. Biochemical monitoring to ascertain MMA levels is frequently required.

### Drugs

- L-Carnitine (100 mg/kg/day)
- Metronidazole for reduction of intestinal production of propionic acid. It is given at 10–20 mg/kg/day orally as a single dose for 10 consecutive days every month.
- Betaine may also be given in the presence of homocystinuria. It acts as a methyl donor and reduces the homocysteine concentration converting homocysteine to methionine. It is given at 100 mg/kg/day orally, divided into two doses given every 12 hours.

- **Injection hydroxycobalamin** Patients with partial defects in adenosylcobalamin synthesis sometimes respond to supraphysiological doses of injection hydroxycobalamin 1,000–2,000 µg/day for about 5–10 days. Repeat urine organic acid analysis shows decrease in the intermediary metabolites confirming the responsiveness to vitamin B<sub>12</sub>. Most vitamin B<sub>12</sub> responsive patients require mild protein restriction with either daily oral vitamin B<sub>12</sub> or weekly 1,000–2,000 µg parenteral and folate supplements (15 µg/kg).

## Prognosis

Patients who are vitamin B<sub>12</sub> responsive MMA have milder disease and relatively good prognosis. Otherwise overall prognosis of MMA and PA is poor. Most of the patients with acute presentation either die during neonatal period or during any episode of decompensation. Despite good metabolic control, survivors develop developmental delay, metabolic strokes and learning difficulties. Toxic effects of MMA cause renal tubular acidosis and tubule interstitial nephritis. Renal disease and optic atrophy are late complications of MMA.

Despite treatment, patients with PA develop developmental delay, neurocognitive decline, seizures, movement disorders, osteoporosis, cardiomyopathy and pancreatitis. Recurrent pancreatitis is a common complication. Liver or combined liver-renal transplantation may be an option in certain patients with severe and recurrent metabolic decompensation. It averts the metabolic decompensation and can reverse the cardiomyopathy in PA.

## Glutaric Acidemia Type 1

Glutaric aciduria type 1 is probably the second common organic acidemia in India, the most common being MMA. The estimated worldwide frequency of GA 1 varies from 1 in 30,000 to 1 in 100,000 newborns in different population.

## Genetics

Glutaric acidemia type 1 or glutaric aciduria type 1 occurs due to the deficiency of glutaryl-CoA dehydrogenase (GCDH) enzyme, a member of the acyl-CoA dehydrogenase family and a key enzyme in the catabolic pathways of the amino acids—tryptophan, lysine and hydroxylysine. Deficiency of GCDH causes increased urinary organic acid excretion of glutaric acid, 3-hydroxyglutaric acid, glutaconic acid and elevated glutaryl carnitine (C5) in plasma.

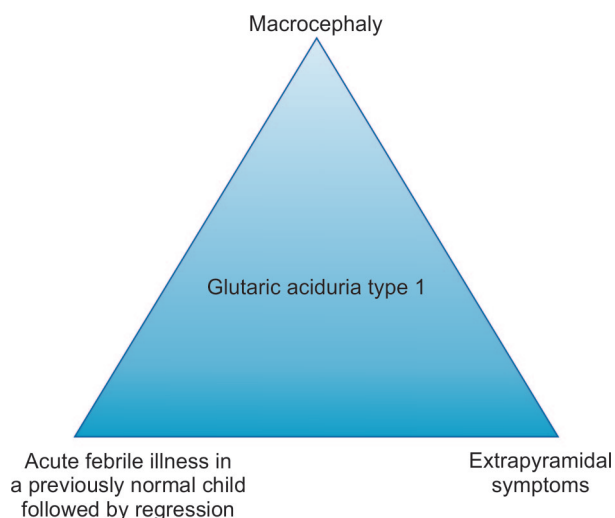
## Clinical Features

These children have a variable course of illness, majority of patients presenting with neuroregression precipitated by an acute febrile illness, macrocephaly and extrapyramidal symptoms (**Fig. 4**). About 90% of the affected children present classically between 2 months and 37 months of age with extrapyramidal symptoms, predominantly dystonia superimposed on axial hypotonia after an acute encephalopathic crisis precipitated by intercurrent febrile illness, infection, fasting or immunization. About 75% of the patients have macrocephaly with soft neurological signs, such as head lag, irritability and feeding difficulties. Extrapyramidal symptoms are due to bilateral striatal injury during the acute episode.

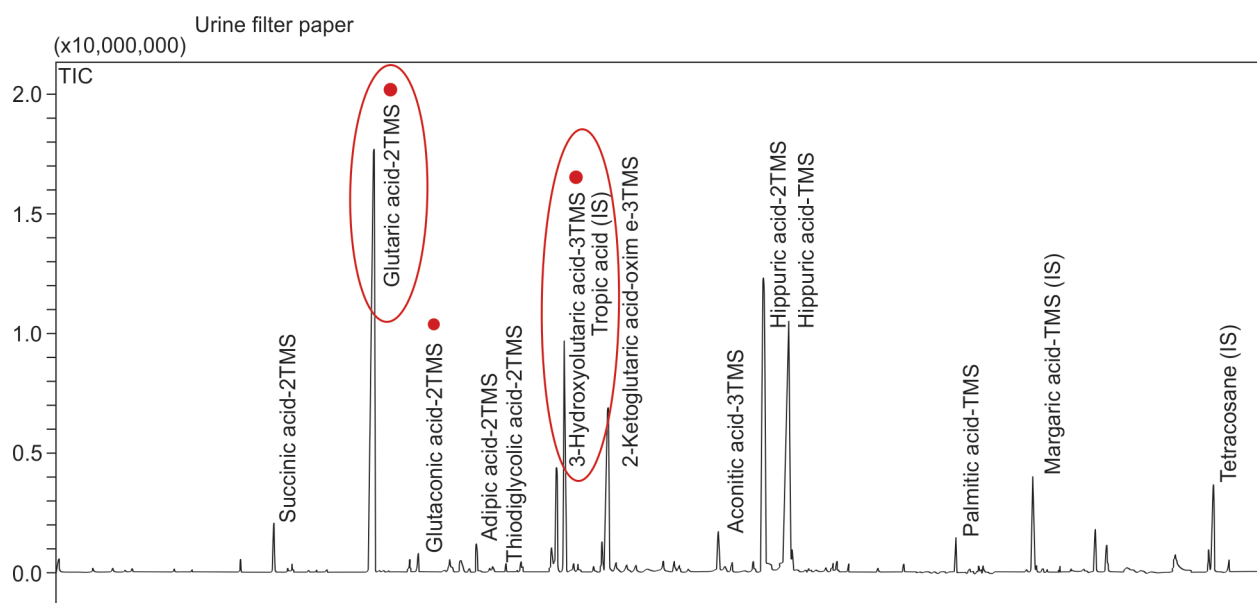
## Diagnosis

There may be fluctuating and inconsistent metabolic abnormalities. In acute episodes, there may be hypoglycemia, metabolic acidosis and hyperammonemia.

- TMS shows elevated glutaryl carnitine and/or low free carnitine levels.
- Urine organic acids show variable degree of elevation of glutaric acid and 3-hydroxyglutarate (**Fig. 5**).



**Figure 4** Three frequently observed features in patients with glutaric acidemia type 1



**Figure 5** Urinary organic acid profile in a patient with glutaric aciduria type 1

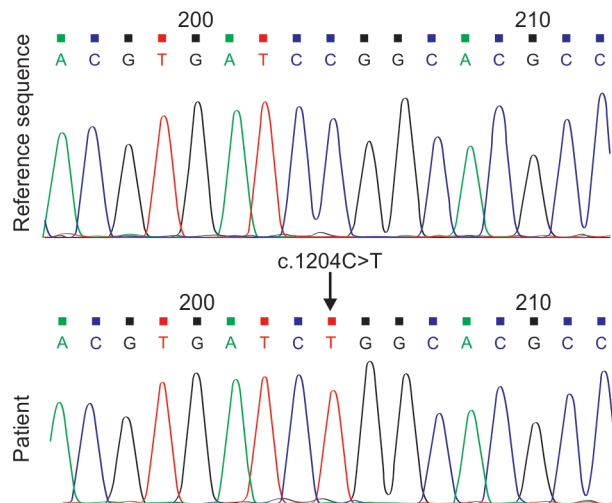
- Neuroimaging shows presence of both striatal (hyperintensities in basal ganglia) and extrastriatal (subdural hygroma, wide sylvian fissure, frontotemporal atrophy) abnormalities.
- Enzyme analysis or mutation analysis of GCDH gene provides a definitive diagnosis. **Figure 6** shows the presence of a common mutation c.1204C>T(p.Arg402Trp) in one of the patients.

### Management

Management of acute episodes for restoring the normal acid base and electrolyte balance is followed as per standard management.

**Long-term management** The aim of dietary treatment is to reduce the accumulation of the presumed toxic agent glutaric acid by reducing its rate of formation. Patients are kept on lysine and tryptophan restricted low protein diet along with riboflavin (100–300 mg/day). Baclofen is given for dystonia. Patients are also given carnitine supplementation (100 mg/kg/day) to avoid carnitine depletion secondary to the excretion of glutaryl carnitine.

As early diagnosis and prompt initiation of treatment can prevent the long-term complications and mortality, it is one of the potential disorders that can be included in newborn screening program.



**Figure 6** A homozygous mutation c.1204 C>T (p.Arg402Trp) in exon 11

### IN A NUTSHELL

1. Organic acidemias are a group of disorders characterized by increased urinary excretion of organic acids.
2. These usually present around 7–10 days after birth with sepsis like illness, metabolic acidosis and increased anion gap. Glutaric acidemia is an exception that usually presents during late infancy.
3. The basic metabolic screen includes measurement of blood glucose, electrolytes, acid-base status for metabolic acidosis, blood lactate levels, ammonia levels and urinary ketones.
4. Characterization of a particular organic acidemia needs measurement of urine organic acids and TMS. Definitive diagnosis is possible by specific enzyme estimation or DNA analysis for the defective genes.
5. Initial management of any child with acute presentation involves elimination of dietary protein, maintenance of hydration and correction of various metabolic and electrolyte imbalance. Patient should not be kept protein deprived for a long time after initial stabilization and is started on protein-restricted diet (excluding the offending amino acids) gradually.
6. Drugs such as sodium benzoate and/or carnitine may be given to reduce the formation or increase the excretion of toxic metabolites.
7. All organic acidemias are autosomal recessive in nature and hence carry a recurrence risk of one in four in future pregnancies.

### MORE ON THIS TOPIC

- Carrillo-Carrasco N, Chandler RJ, Venditti CP. Combined methylmalonic acidemia and homocystinuria, cblC type. I. Clinical presentations, diagnosis and management. *J Inherit Metab Dis.* 2012;35:91-102.
- Hoffmann GF, Köller S. Defects in amino acid catabolism and the urea cycle. *Handb Clin Neurol.* 2013;113:1755-73.
- Knerr I, Weinhold N, Vockley J, et al. Advances and challenges in the treatment of branched-chain amino/keto acid metabolic defects. *J Inherit Metab Dis.* 2012;35:29-40.
- Kölker S, Christensen E, Leonard JV, et al. Diagnosis and management of glutaric aciduria type I—revised recommendations. *J Inherit Metab Dis.* 2011;34:677-94.
- Schreiber J, Chapman KA, Summar ML, et al. Neurologic considerations in propionic acidemia. *Mol Genet Metab.* 2012;105:10-5.
- Vatanavicharn N, Champattanachai V, Liammongkolkul S, et al. Clinical and molecular findings in Thai patients with isolated methylmalonic acidemia. *Mol Genet Metab.* 2012;106:424-9.



## Chapter 3.5

# Fatty Acid Oxidation Defects

Manisha Goyal, Seema Kapoor

Fatty acids are largest source of energy in the body and play an essential role for exercising muscles and heart. It is clear from **Figure 1** that preferential utilization substrate for the brain is glucose followed by ketones. When glucose diminishes (during fasting) and the rehabilitative metabolic systems fail, ketones may not increase and the hypoglycemia is hypoketotic. In such an event, brain relies on the fatty acid oxidation (FAO) system for providing energy.

## LENGTH OF FATTY ACIDS AND THEIR NOMENCLATURE

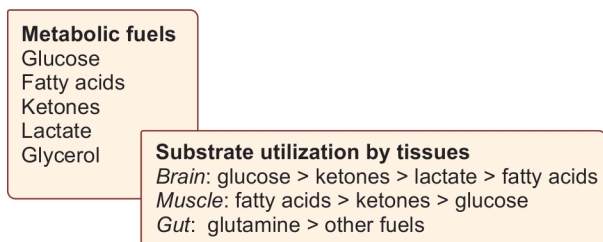
*Short-chain fatty acids* have carbon atoms which are less than 6 carbon atoms while *medium chain* varies from 6–12 carbon atoms, *long chain* between 14 and 21 carbon atoms and *very long chain* more than 21 fatty acids. The term saturated and unsaturated is the presence of double bonds between carbon atoms. Those unsaturated fatty acids with single double bond are monounsaturated and those with no double bonds are polyunsaturated fatty acids. Long-chain fatty acids (LCFAs) play a role in phospholipid synthesis, protein post-translational modifications, cell signaling, membrane permeability and transcription control. LCFA are also substrates in the situations of increased energy demands.

## FATTY ACID OXIDATION PATHWAY

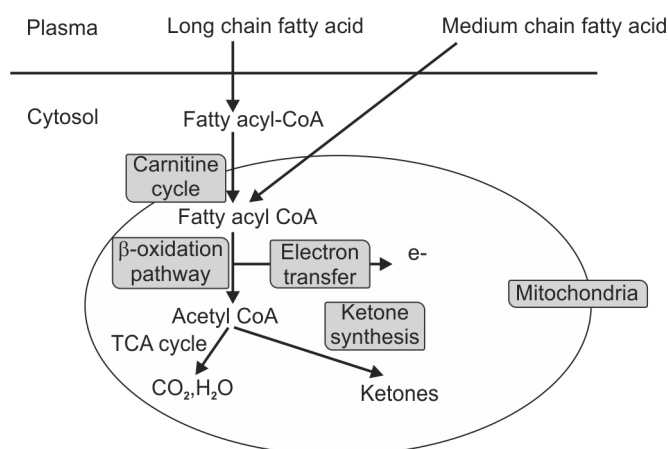
Fatty acid oxidation process takes place in the mitochondrion and plays an important role during periods of fasting and stress when glycogen stores of the tissue become depleted. FAO process becomes a major source of energy (nearly 80%) to organs like skeletal muscles, heart and liver especially during fasting. Fatty acids are completely utilized and converted to carbon dioxide and water in the skeletal muscles and heart. In the liver, ketone bodies (acetoacetate and  $\beta$ -hydroxybutyrate) are produced which are the substrate used by peripheral tissues and brain. Disorders of this pathway would result in fatty acid oxidation defects (FAOD) with symptoms including hepatic encephalopathy, myopathy, cardiomyopathy and peripheral neuropathy. Other conditions suggesting FAOD are sudden infant death syndrome (SIDS), Reye syndrome and maternal complications of pregnancy caused by fetal FAOD.

**Figure 2** represents a schematic diagrams of the mitochondrial FAO pathway from cellular uptake of fatty acids to generate acetyl-CoA in the  $\beta$ -oxidation spiral, its association with respiratory chain and ketogenesis. The short- and medium-chain fatty acids can diffuse directly across the plasma and mitochondrial membranes into the mitochondrial matrix. In contrast, LCFAs ( $C_{14}$ – $C_{21}$ ) and carnitine are transported by specific plasma membrane transporters. Fatty acids are converted to their respective acyl CoA esters by individual acyl CoA synthetases. Short-chain and medium-chain fatty acids are activated within the mitochondrial matrix, whereas LCFAs are esterified outside the mitochondria and then enter into the mitochondrial matrix.

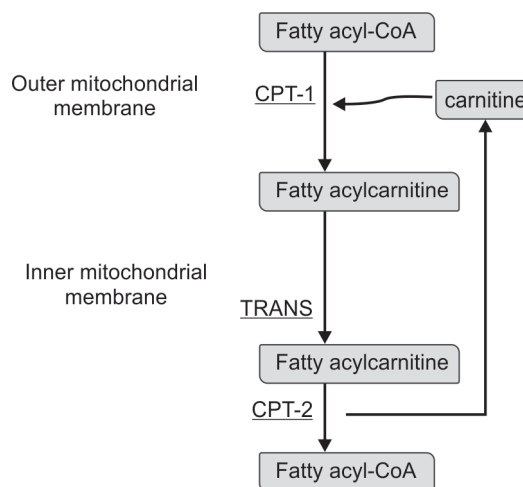
In the carnitine cycle (**Fig. 3**), LCFAs are transported across the mitochondrial membrane involving the enzymes carnitine-I, carnitine palmitoyltransferase-II and carnitine acylcarnitine translocase with carnitine as a cofactor. Within the mitochondria, the fatty acyl CoA esters undergo repeat cycles of reactions catalyzed



**Figure 1** Metabolic fuels and their priority of utilization



**Figure 2** Fatty acid oxidation pathway

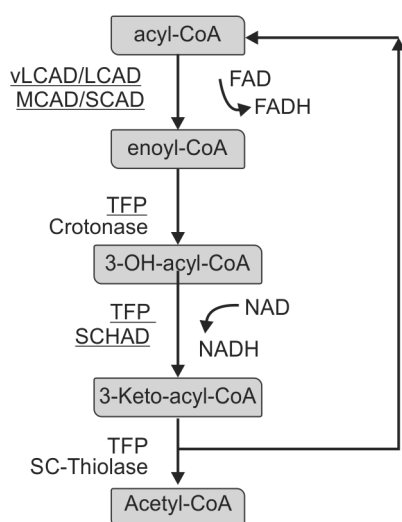


**Figure 3** Carnitine cycle

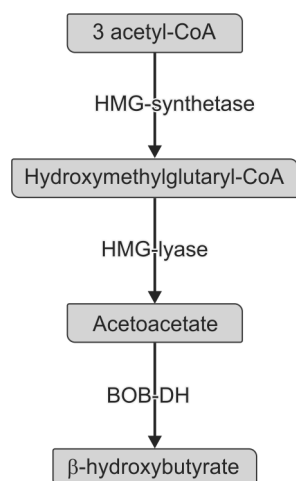
by enzymes and convert into acetyl CoA units through  $\beta$ -oxidation cycle (**Fig. 4**). The electrons generated in the  $\beta$ -oxidation step enter into the electron transfer pathway for ATP production and in the respiratory chain. Acetyl CoA generated in liver is transformed to ketone bodies ( $\beta$ -hydroxybutyrate and acetoacetate) through ketogenesis pathway (**Fig. 5**).

## FATTY ACID OXIDATION DEFECTS

Fatty acid oxidation defects are inherited as autosomal recessive disorders. Mutations have been identified for most of the disorders. Incidences of individual FAOD may vary from 1:8000 to 1:100,000. The clinical and biochemical features of major FAOD are



**Figure 4**  $\beta$ -Oxidation cycle



**Figure 5** Ketone synthesis

**Abbreviations:** CoA, coenzyme A; CPT, carnitine palmitoyltransferase; FAD, flavin adenine dinucleotide; FADH, reduced FAD; HMG-3, hydroxy-3-methylglutaryl; TCA, tricarboxylic acid; TFP, trifunctional protein; TRANS, carnitine/acylcarnitine translocase; NAD, nicotinamide adenine dinucleotide; NADH, reduced NAD; vLCAD, very long-chain acyl-CoA dehydrogenase; LCAD, long-chain acyl CoA dehydrogenase; MCAD, medium-chain acyl CoA dehydrogenase; SCAD, short-chain acyl CoA dehydrogenase; SCHAD, short-chain 3-hydroxyacyl-CoA dehydrogenase.

summarized in **Table 1**. FAODs become apparent during periods of increased energy demands, such as prolonged fasting, febrile illness or any other stressful situation during which the inability to use fatty acids causes metabolic decompensation. There are overlapping phenotypes between the various enzyme defects of FAO and the same defective enzyme may be associated with considerable clinical heterogeneity.

## CLINICAL PHENOTYPE

Affected patients may be asymptomatic or may show wide variety of symptoms, such as severe metabolic acidosis, hypoglycemia without ketosis, hyperammonemia, cardiomyopathy, liver failure, sudden death in the neonatal period, episodic myopathy, neuropathy or retinopathy in the later age. It can broadly be categorized into neonatal hypoketotic hypoglycemia, childhood hepatic form, adult onset myopathic form or the form with retinopathy. Clinical features become more apparent during periods of increased energy demands

such as prolonged fasting, febrile illness. This is an important clinical clue for ascertaining the diagnosis. The phenotype is severest with long-chain defects, milder with medium chain and none to minimal in short-chain defects.

## Association of Sudden and Unexpected Death with FAOD

Sudden death after a relatively short prodromal illness is the first manifestation of medium-chain acyl CoA dehydrogenase (MCAD) deficiency in 18% of patients and is also reported in adulthood. A protocol for postmortem investigation for FAOD is thus suggested for all cases of unexplained death to detect present and future siblings in the family of patients with SIDS.

## Association of Fetal FAOD with Severe Complications during Pregnancy

The association of severe complications such as preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes and low platelet counts), AFLP (acute fatty liver of pregnancy) with women carrying long-chain L3-hydroxyacyl CoA dehydrogenase (LCHAD) deficient fetus has been well documented. While the causes of maternal pregnancy complications with fetal FAOD are not clear, these cases suggest that derangement of mitochondrial fatty acid metabolism may play a role in the pathogenesis of maternal liver disease. Investigation for FAOD should be considered in all babies born of a pregnancy complicated by HELLP syndrome or AFLP.

## Association of Fatty Acid Oxidation Disorders with Endocrinopathy (Hormonal Imbalance)

Hypoparathyroidism has been detected in patients with LCHAD deficiency. One patient with hypopituitarism and the other with secondary hypothyroidism have been reported with short-chain acyl CoA dehydrogenase (SCAD) deficiency. Intermittent and unpredictable hyperinsulinism in an infant with short-chain L3-hydroxyacyl CoA dehydrogenase (SCHAD) deficiency has also been documented.

## DIAGNOSTIC TESTS

The biochemical manifestations of FAOD include accumulation of free fatty acids (FFAs) and toxic acyl CoA intermediates and deficient production of acetyl CoA and ketone bodies.

### Plasma Acylcarnitines

Fatty acid oxidation defects can be diagnosed by analyses of acylcarnitines on dried blood spot (DBS) on filter paper followed by confirmation on plasma. Most of the FAOD may be differentiated by levels of disease-associated acylcarnitine types. Some medications such as valproic acid, pivalic acid or propofol can produce increased concentrations of abnormal acylcarnitine.

### Plasma and Tissue Total Carnitine

Fatty acid oxidation defects are associated with either decreased or increased total carnitine in plasma and tissues. In carnitine transport defects, transport of carnitine across the plasma membrane is absent, leads to severe reduction of total carnitine (primary carnitine deficiency). Total carnitine levels are increased in carnitine palmitoyltransferase-I (CPT-I) deficiency. Total carnitine levels are reduced to 25–50% of normal in all other defects, except 3-hydroxy-3-methylglutaryl (HMG) CoA synthase deficiency known as secondary carnitine deficiency. It is recommended that samples should be taken in the well-fed state with normal carnitine intake because patients during prolonged fasting or illness may show abnormal increases in the plasma total carnitine with FAOD, thereby missing the diagnosis.

**Table 1** Fatty acid oxidation defects

Defects	Gene	Clinical features	Dried blood spot (carnitine and acylcarnitine)	Urine organic acid profile or acylglycine
<i>Plasma membrane cellular uptake and activation of long-chain fatty acids</i>				
Plasma membrane carnitine transporter (primary carnitine deficiency)	OCTN2	Liver disease, heart disease (cardiomyopathy, endocardial fibroelastosis), myopathy, sudden death	Total and free carnitine: ↓, acylcarnitines: N	N
Long-chain fatty acid transporter protein	FATP1–6	Rare, acute liver failure	Free carnitine: N/↑, acylcarnitine: N	N
<i>Defects in the carnitine cycle</i>				
Carnitine palmitoyltransferase-I (CPT-IA) deficiency	CPT-IA	Liver failure, tubulopathy of kidney, maternal preeclampsia or HELLP syndrome	Free carnitine: N/↑, acylcarnitine: N	N
Carnitine acylcarnitine translocase (CACT) deficiency	CACT	Hypertrophic cardiomyopathy, chronic progressive liver failure	Free carnitine: N/↓, acylcarnitine: abnormal	-/N
Carnitine palmitoyltransferase-II (CPT-II) deficiency	CPT-II	Liver disease, cardiomyopathy, skeletal myopathy, encephalopathy, renal cystic changes	Free carnitine: N/↓; acylcarnitine: ↑ C <sub>16</sub> , C <sub>16:1</sub> , C <sub>18</sub> , C <sub>18:1</sub>	-/N
<i>Defects in the β-oxidation cycle</i>				
Short-chain acyl CoA dehydrogenase (SCAD) deficiency	SCAD	Variable presentation, vary from normal to inconsistent sign and symptoms	Free carnitine: N/↓; acylcarnitine: abnormal C <sub>14:1</sub> , C <sub>14:0</sub>	Elevated urine ethylmalonic acid, butyryl acylglycines
Medium-chain acyl CoA dehydrogenase (MCAD) deficiency	MCAD	Sudden death, hypoglycemia, hepatic encephalopathy, maternal preeclampsia or HELLP syndrome	Free carnitine: N/↓, plasma acylglycine: ↑, plasma C <sub>6</sub> -C <sub>10</sub> Free fatty acids: ↑, C <sub>8</sub> -C <sub>10</sub> acylcarnitine: ↑	Elevated suberyl and phenylpropionyl acylglycines
Very long chain acyl CoA dehydrogenase (VLCAD) deficiency	VLCAD	Heart (dilated cardiomyopathy, arrhythmias), hypoglycemia, hepatic steatosis, episodic myopathy, rhabdomyolysis	Free carnitine: N/↓; C <sub>14:1</sub> , C <sub>14</sub> acylcarnitine: ↑; plasma C <sub>10</sub> -C <sub>16</sub> free fatty acids: ↑	+/-/N
Short-chain L-3-hydroxyacyl CoA dehydrogenase (SCHAD) deficiency	SCHAD	Hypoglycemia, cardiomyopathy, myopathy, hyperinsulinemia	Free carnitine: N/↓, free fatty acids: elevated, acylcarnitine: abnormal	Abnormal
Long-chain L-3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiency	LCHAD	Maternal complications: Pre-eclampsia, HELLP syndrome, AFLP	Free carnitine: N/↓, acyl to free carnitine ratio: ↑, free fatty acids: ↑, C <sub>16</sub> -OH and C <sub>18</sub> -OH carnitines: ↑	+/-/N
Mitochondrial trifunctional protein (TFP) deficiency	MTP	Deranged LFT, hypoglycemia, myopathy, retinopathy	Free carnitine: N/↓, acyl to free carnitine ratio: ↑, free fatty acids: ↑, C <sub>16</sub> -OH and C <sub>18</sub> -OH carnitines: ↑	+/-/N
<i>Defects in electron transfer pathway</i>				
Electron transfer flavoprotein dehydrogenase deficiency/Glutaric aciduria type II or multiple acyl CoA dehydrogenase deficiency (MADD)	ETF-DH	Liver disease, nonketotic fasting, hypoglycemia, congenital anomalies, myopathy (cardiac and skeletal)	Free carnitine: N/↓, acyl to free carnitine ratio: ↑, acylcarnitine: ↑	↑ acylglycines (isovaleryl and hexanoyl) Elevated ethylmalonic organic acid
Electron transfer flavoprotein-α and β	α/β-ETF	Liver disease, hypoglycemia, congenital anomalies, myopathy (cardiac and skeletal)	Free carnitine: N/↓, acyl to free carnitine ratio: ↑, acyl-carnitine: ↑	↑ acylglycines
Long-chain 3-ketoacyl-CoA thiolase deficiency	LKAT	Hypoglycemia, cardiomyopathy, neuropathy, acidosis, ↑ CPK, sudden death	Free carnitine: N/↓, acyl to free carnitine ratio: ↑, acylcarnitine: ↑, 2-trans, 4-cis-decadienoylcarnitine: ↑	+/-/N
2,4-dienoyl-CoA reductase deficiency	DECR1	Hypotonia, myopathy, respiratory failure	Free carnitine: N/↓, acyl to free carnitine ratio: ↑, acylcarnitine: ↑	↑ acylglycines

Contd...

Contd...

Defects	Gene	Clinical features	Dried blood spot (carnitine and acylcarnitine)	Urine organic acid profile or acylglycine
<i>Defects in the ketone synthesis pathway</i>				
3-hydroxy-3-methylglutaryl CoA (HMG CoA) synthetase deficiency	HMGCS2	Hypoglycemia, hypoketosis	Total free fatty acids: ↑	
3-hydroxy-3-methylglutaryl CoA (HMG CoA) lyase deficiency	HMGCL	Hypoglycemia, hypoketosis	Free carnitine: N, C <sub>5</sub> -OH and methylglutaryl-carnitine: ↑	↑ 3-hydroxy-3-methyl glutaric acid

Abbreviations: N, normal; CPK, creatine kinase; HELLP, hemolysis, elevated liver enzymes, low platelets; AFLP, acute fatty liver of pregnancy.

### Urinary Organic Acids

Compounds produced by urinary analyses of organic acids are indicator of FAOD which include the saturated and unsaturated dicarboxylic acids, hydroxydicarboxylic acids, acylglycines and acylcarnitines. All of the disorders are associated with an inappropriate dicarboxylic aciduria during fasting or illness without ketonuria. It is usually normal in patients with FAOD when they are well. Thus, in the intermittent phase, the urinary metabolomic profile would be completely normal and, therefore, misleading.

### Urinary Acylglycines

Quantitative analysis of urinary acylglycines is diagnostic in MCAD and the severe form of multiple acyl CoA dehydrogenase (MAD) deficiency.

### Plasma Fatty Acids

Analysis of plasma total fatty acid (TFA) and FFA profiles can detect MCAD deficiency. Increased levels of free 3-hydroxyl fatty acids are found in LCHAD, SCHAD and MTP (mitochondrial trifunctional protein) deficiencies. Deficiencies of SCAD, CPT-1A, CPT-II and CT may not be identified as these defects did not show any specific alteration of the FFA profiles.

### Enzyme Assays

Measuring enzyme activity is necessary for confirmation of the diagnosis. Enzyme assays defective in the FAO pathway may be performed in cultured skin fibroblasts, tissue biopsies or lymphocytes.

### Molecular Studies

Mutation analysis can be performed on peripheral blood leukocytes, or obviating the need for cell culture or biopsies. This study provides specific confirmation; establish genotype-phenotype relationships in some disorders which have implications for prognosis and options of treatment and essential for prenatal diagnosis.

## TREATMENT

### Reduce Production of Circulating Free Fatty Acids

The mainstay of treatment is to modify diet to prevent fasting state in which fatty acids are used to produce energy. For long-chain fat disorders, dietary modifications include maintaining a very low intake of natural fats with supplementary medium-chain triglycerides (MCTs), high carbohydrate and adequate essential fatty acids. It is recommended that feeding should be done at regular intervals during day and night and can be given in the continuous nasogastric mode overnight. In states of significant anorexia, a gastrostomy may need to be performed.

### Increase Residual Enzyme Activity

Riboflavin is known to improve enzyme activity in MAD deficiency. It has been used for mild variants of electron transfer flavoprotein/electron transfer flavoprotein dehydrogenase (ETF/ETF-DH) and SCAD deficiency. Dose is 100 mg/kg. Benzaifibrate (agonist to peroxisome proliferator-activated receptors) plays an important role by up-regulating gene expression in lipid metabolism and  $\beta$ -oxidation pathway. It is used for very long chain acyl CoA dehydrogenase (VLCAD) and CPT-II deficiency.

### Replace the Missing Product

Since ketone production is defective in FAOD, it would be helpful to supply the missing ketones. Sodium 3-hydroxybutyrate has been found to be effective in MAD deficiency.

### Carnitine Therapy

Treatment with carnitine has been reported to improve skeletal and heart muscle function to nearly normal in primary carnitine deficiency. It also corrects hepatic ketogenesis. Dose of carnitine is 100 mg/kg/day, should be started with low dose. Role of carnitine in secondary carnitine deficiency disorders remains controversial.

### Other Therapy

Dietary MCT is helpful in patients with LCHAD deficiency. Triheptanoin is suggested to be beneficial in VLCAD.

### Monitoring

Clinical assessment, measurement of acylcarnitines and FFA including essential fatty acids are useful indicators.

### Management of Acute Illness (Emergency Treatment)

When patients with FAOD become ill or with fever and irritability, they should be admitted in hospital. Treatment with IV fluids 10% dextrose in N/4 saline at infusion rates of 10 mg/kg/min should be given immediately to maintain high to normal levels of plasma glucose. Stop all natural protein intakes. Carnitine dose should be increased.

### Long-term Therapy (Maintenance Treatment)

Mainstay of therapy is to prevent period of fasting which would require fatty acids as a fuel. This can be done by educating the patients or parents to take adequate carbohydrate feeding specially at bedtime and do not fast more than 12 hours overnight. Riboflavin and carnitine should be given. Some studies recommend fat restriction, although this remains controversial.

## PROGNOSIS

Although acute illness is associated with high risk, many patients can be easily managed by avoidance of prolonged fasting. These patients have good prognosis. Patients with chronic disease have a more guarded prognosis.



### IN A NUTSHELL

1. Fatty acid oxidation defects in the neonate could present with SIDS, encephalopathy, hypoketotic hypoglycemia, cardiomyopathy, myopathy and rarely with certain dysmorphic features.
2. In infancy and childhood, other presentation could be as Reyes syndrome or with hepatic decompensation.
3. Severity of the defect also depends on its chain length, i.e., more with long-chain, less with medium-chain and least with short-chain defects.
4. Fasting, exercise, intercurrent illness and treatment with intuitive drugs can uncover an underlying defect.
5. Diagnosis can usually be established by acylcarnitine profile on tandem mass spectrometry and by dicarboxylic acids in urine or the glycine conjugates in urine. Mutation analysis is confirmatory and enzyme analysis using fibroblast cultures is important.

### MORE ON THIS TOPIC

- Bennett MJ. Pathophysiology of fatty acid oxidation disorders. *J Inherit Metab Dis.* 2010;33:533-7.
- Lang TF. Adult presentations of medium-chain acyl-CoA dehydrogenase deficiency (MCADD). *J Inherit Metab Dis.* 2009;32:675-83.
- Spiekerkoetter U, Bastin J, Gillingham M, et al. Current issues regarding treatment of mitochondrial fatty acid oxidation disorders. *J Inherit Metab Dis.* 2010;33:555-61.
- Tein I. Disorders of fatty acid oxidation. *Handb Clin Neurol.* 2013;113:1675-88.
- Wanders RJ, Ruiters JP, IJLst L, et al. The enzymology of mitochondrial fatty acid beta-oxidation and its application to follow-up analysis of positive neonatal screening results. *J Inherit Metab Dis.* 2010;33:479-94.

## Chapter 3.6

# Mitochondrial Disorders

Sheffali Gulati, Biswaroop Chakrabarty

Mitochondrial diseases are one of the most diverse, dynamic and evolving group of disorders in modern medicine. The presence of independent DNA in mitochondria was discovered in 1963, which is derived from the ovum and, hence, the inheritance of diseases with mitochondrial DNA defects is known as maternal or cytoplasmic. The differences in mitochondrial and nuclear DNA are enumerated in **Table 1**. Of the 37 genes present in mitochondrial genome, 13 encode for structural proteins in the respiratory chain and the remaining 24 (2 ribosomal and 22 transfer RNAs) are involved in protein synthesis.

There are 3 attributes of mitochondrial genome central to the manifestations of its dysfunction, namely *plasmidy*, *threshold effect* and *replicative segregation*. *Plasmidy* refers to the distribution of mutated and wild type genome (homoplasmy and heteroplasmy), *threshold effect* is the proportion of the mutated genome beyond which disease manifests (varies from disease to disease) and *replicative segregation* is the random redistribution of mitochondrial DNA during replication.

## GENETIC AND BIOCHEMICAL CLASSIFICATION OF MITOCHONDRIAL DISORDERS

Of the 80 proteins overall present in mitochondria, only 13 are encoded by mitochondrial DNA, rest all are nuclear DNA encoded proteins. Thus, genetically mitochondrial disorders are either of nuclear or mitochondrial origin. Biochemically, they manifest primarily as impaired protein synthesis or deficient respiratory chain complexes. The biochemical and genetic basis of common mitochondrial disorders are enumerated in **Table 2**.

## EPIDEMIOLOGY

Prevalence data for this rare group of disorders are lacking from across the world. This is because mitochondrial disorders represent a very heterogeneous group of diseases, both phenotypically as well as genotypically. Moreover, facilities for molecular studies of mitochondrial disorders are sparingly available across the world and, hence, it is an underdiagnosed entity. Because of high childhood mortality, incidence figures are more reliable than prevalence data. Keeping these issues under consideration and allowing for incomplete ascertainment, the lifetime risk of developing mitochondrial disease is to the tune of 1 in 5,000 livebirths. The most common pediatric mitochondrial disorder is Leigh's disease.

## ETIOPATHOGENESIS

The function of mitochondria is to convert the chemical energy of food to adenosine triphosphate (ATP), a process known as oxidative phosphorylation. This is mediated through the Krebs cycle and fatty acid  $\beta$ -oxidation pathways which generates nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH<sub>2</sub>), (both acting as potential electron donors) and the electrons from these reducing agents pass through the electron transport chain complex (comprising of five multiprotein complexes I-V) located in the inner mitochondrial membrane, creating a proton gradient, which mediates ATP synthesis.

Mitochondrial DNA is susceptible to oxidative damage because of the close vicinity to the place where reactive oxygen species are produced, lack of protective histone proteins and the limited availability of proofreading machinery. Certain nuclear DNA encoded factors are also required for mitochondrial biogenesis,

**Table 1** Differences between nuclear and mitochondrial DNA

Characteristics	Nuclear DNA	Mitochondrial DNA
Location	Nucleus	Mitochondria
Genomic constitution	$3 \times 10^9$ base pair/haploid genome	$1.6 \times 10^4$ base pair/genome
Introns	Present	Absent
Ploidy	Diploid in somatic cells	Polyploid
Chromosomal organization	23 linear chromosomes	One circular chromosome
Genes	23,000	37
Messenger RNAs	Encode all cellular functions	Only respiratory chain functions
Genetic code	Universal	Modified
Replication	Many symmetric replication origins	One asymmetric origin
Transcription	Monocistronic	Polycistronic

**Table 2** Biochemical and genetic basis of common mitochondrial disorders

Disorder	Biochemistry	Genetics
Kearns-Sayre syndrome	Impaired protein synthesis	Mitochondrial DNA
MELAS	Impaired protein synthesis	Mitochondrial DNA
MERRF	Impaired protein synthesis	Mitochondrial DNA
NARP/MILS	Impaired ATP synthesis	Mitochondrial DNA
LHON	Decreased complex I	Mitochondrial DNA
Leigh's syndrome	Decreased complex I/II/IV	Nuclear DNA
GRACILE	Decreased complex III	Nuclear DNA
Fatal infantile multisystemic disease	Decreased complex V	Nuclear DNA
MNGIE	Impaired protein synthesis	Nuclear DNA
PEO	Impaired protein synthesis	Nuclear DNA

**Abbreviations:** MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers, NARP, neuropathy, ataxia and retinitis pigmentosa; MILS, maternally inherited Leigh's syndrome; ATP, adenosine triphosphate; LHON, Leber's hereditary optic neuropathy; GRACILE, growth retardation, aminoaciduria, cholestasis, lactic acidosis, early death; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; PEO, progressive external ophthalmoplegia.

assembly, mitochondrial DNA replication, transcription and translation. Mitochondria also plays major role in apoptosis, autophagy and free-radical turnover in the body.

The mutation rates in mitochondrial DNA are 10–20 times higher than that in nuclear DNA. The defects in mitochondrial DNA secondary to impaired mitochondrial genome are of 2 types, namely, point mutation and depletion. The most common diseases are secondary to point mutations.

The common mitochondrial disorders, the genes involved and their inheritance are enumerated in **Table 3**. Some common acquired causes of mitochondrial dysfunction are Reye's syndrome, toxin (MPTP: mitochondrial permeability transition pore), drugs (zidovudine) and aging.

**Table 3** Common mitochondrial disorders, the genes involved and their pattern of inheritance

Disorders	Gene involved	Inheritance
<i>Primary defect in mitochondrial genome</i>		
MELAS	m.3243A > G mutation in tRNA <sup>leu(uur)</sup>	M
MERRF	m.8344A > G mutation the tRNA <sup>lys</sup>	M
LHON	m.11778G > A mutation in ND1	M
NARP/MILS	m.8993T > G mutation in ATP6	M
<i>Primary defect in nuclear gene</i>		
Alpers' syndrome	POLG	AR
MNGIE	TP	AR
Leigh's syndrome	SURF1	AR
PEO	POLG, TWINKLE	AR/AD

**Abbreviations:** MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers, NARP, neuropathy, ataxia and retinitis pigmentosa; MILS, maternally inherited Leigh's syndrome; ATP, adenosine triphosphate; LHON, Leber's hereditary optic neuropathy; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; PEO, progressive external ophthalmoplegia; M, mitochondrial; AR, autosomal recessive; AD, autosomal dominant.

## CLINICAL FEATURES

Defects in any of the 1,500 genes targeted towards mitochondria ultimately effect the organs with high energy demand, viz., muscle (skeletal, cardiac and smooth), nerve, brain, auditory and visual pathway, pituitary, pancreas, thyroid, kidney, liver and the immune system. The rule of thumb is that in involvement of three or more organ systems without any unifying disease, an underlying mitochondrial disorder should be considered. Red flag signs and symptoms that should raise the suspicion of mitochondrial disorder are listed in **Box 1**. Clinical features of some of the common mitochondrial disorders relevant to a pediatrician are being discussed here.

### BOX 1 Red flag clinical features for mitochondrial disorder

1. **Neurological:** Cognitive decline, recurrent episodic encephalopathy, movement disorder, epilepsy partialis continua, myoclonus, ataxia, sensorineural hearing loss.
2. **Cardiovascular:** Cardiomyopathy, arrhythmia.
3. **Ophthalmological:** Pigmentary retinopathy, optic atrophy, ptosis, ophthalmoparesis, impaired vision.
4. **Gastrointestinal:** Unexplained liver failure, pseudo-obstruction, dysmotility, cyclical vomiting.
5. **Endocrine:** Growth hormone deficiency, features of hypothyroidism and hypoparathyroidism.
6. **Renal:** Renal tubular acidosis, nephrotic syndrome.
7. **Constitutional:** Short stature, microcephaly, failure to thrive.

## Leigh's Syndrome

Most patients present with varying degrees of cortical, brain stem and basal ganglia dysfunction like encephalopathy, somnolence, ataxia, nystagmus, respiratory dysfunction, ataxia, dyskinesia and dystonia. Age at onset can vary from neonatal period to later in life. The neonatal onset is associated with facial dysmorphism and the later ones usually have episodic deterioration.

## MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like Episodes)

MELAS is the prototypical mitochondrial disease presenting with stroke in individuals younger than 45 years with predilection for involvement of parietal and occipital lobes. These lesions are

usually very epileptogenic and patients may present with epilepsy partialis continua (EPC). Other associated clinical features include migraine with aura, exercise intolerance, progressive external ophthalmoparesis and visual hallucinations.

## MERRF (Myoclonic Epilepsy with Ragged Red Fibers)

This disorder represents the prototype progressive myoclonic epilepsy phenotype amongst mitochondrial disorders. Clinically the salient features are progressive cerebellar symptoms, generalized seizures, myoclonus, cognitive decline, central hearing loss, optic atrophy and short stature.

## Alpers Syndrome

A triad of intractable seizures (usually EPC), psychomotor deterioration and liver failure (worsening with valproate) characterizes this disorder. Onset is usually at any time from 1 month of age to 25 years. Usually the onset is in early childhood with most patients dying by the age of 3 years. The late onset variant is also characterized by a peripheral sensory neuropathy.

## Kearns-Sayre Syndrome (KSS)

The criteria for labeling a patient with KSS include onset before the age of 20; progressive external ophthalmoparesis; and salt and pepper pigmentary retinopathy, plus any one of the following: complete heart block, cerebellar ataxia and cerebrospinal fluid more than 100 mg/dL. Other associated features include cognitive decline, sensorineural hearing loss, optic atrophy, multiple endocrine abnormalities, renal tubular acidosis and Lowe syndrome.

## LHON (Leber's Hereditary Optic Neuropathy)

This entity is characterized by sudden onset usually progressive unilateral or bilateral painless vision loss secondary to optic atrophy in adolescence or early adulthood. It affects males more than females.

## LABORATORY EVALUATION

There is no uniform standard set of guidelines for biochemical or metabolic studies in diagnosing mitochondrial disorders. Enzymatic assays are not standardized among diagnostic centers. Tissue diagnosis, although preferable, is limited by geographical constraints. Although molecular studies have better inter- and intralaboratory reproducibility, low levels of disease causing heteroplasmy may remain undetected in peripheral blood.

## Biochemical Investigations

Blood investigations include complete blood count, liver and kidney function tests, serum ammonia and electrolytes. Elevated fasting arterial and cerebrospinal fluid lactate (beyond 2.1 mmol/L) is a nonspecific marker of mitochondrial disease, at times only seen during an acute crisis. Certain disorders like LHON, KSS, mitochondrial DNA polymerase gamma (POLG1) associated diseases and Leigh's disease have normal lactate most of the time. Spurious elevations of lactate also happen if there is a lot of struggle in obtaining blood sample from a child or tourniquet is placed for a prolonged period while sampling. The ideal way to do it would be to collect the sample 30 minutes after placement of the intravenous catheter. It is more useful to estimate the lactate to pyruvate ratio. However, sample drawn for pyruvate has to be immediately (within 30 seconds) stored in 8% perchlorate ice and then analyzed. Lactate or pyruvate ratio of less than 25 in the setting of lactic acidemia points towards the diagnosis of pyruvate dehydrogenase deficiency or gluconeogenic defects, whereas a value of greater than 25 indicates respiratory chain defects or pyruvate carboxylase deficiency.



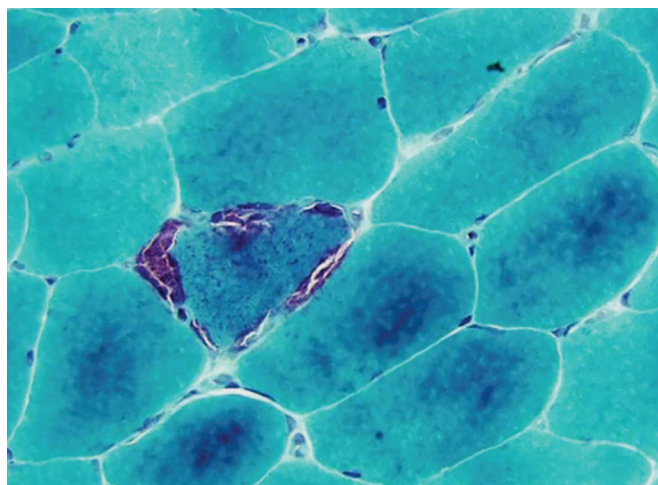
Although fasting serum amino acid estimation (tandem mass spectrometry, TMS), particularly alanine, is not a very sensitive tool to diagnose mitochondrial disorder, it can be useful in oxidative phosphorylation disorders as it is less prone to get changed by improper collection methods. Other amino acids which may be elevated are proline, glycine and sarcosine. TMS also yields acylcarnitine and carnitine values which may denote secondary carnitine deficiency and impaired fatty acid oxidation with underlying oxidative phosphorylation defects.

Urine gas chromatography and mass spectrophotometry may show tricarboxylic acid intermediates and dicarboxylic aciduria consequent to underlying secondary impaired fatty acid oxidation.

## Invasive Tissue Investigations

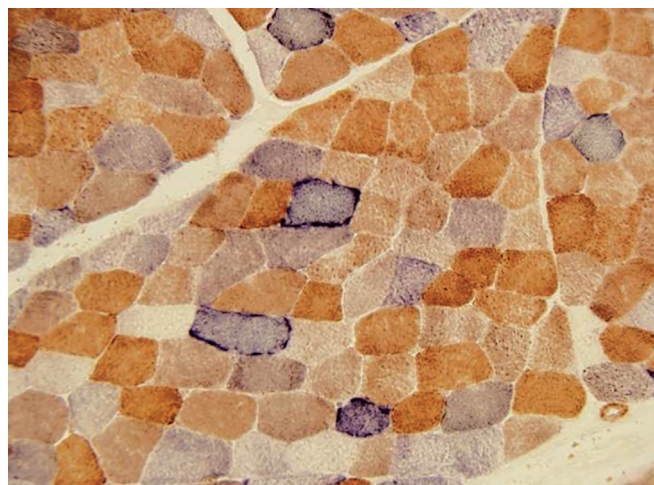
### Skeletal Muscle Analysis

Ragged red fibers (RRF) seen as subsarcolemmal red granular deposits against a background of atrophic muscle fibers on modified gomori trichrome staining indicate abnormal mitochondrial proliferation (**Fig. 1**). However, this is also seen at times in muscular dystrophies, metabolic, inflammatory and congenital myopathies. Other histochemical stains which increase the diagnostic yield are NADH dehydrogenase, cytochrome C oxidase [cytochrome C oxidase (COX), evaluates complex IV] and succinate dehydrogenase (SDH, evaluates complex II). RRF with low COX activity with strong SDH staining is



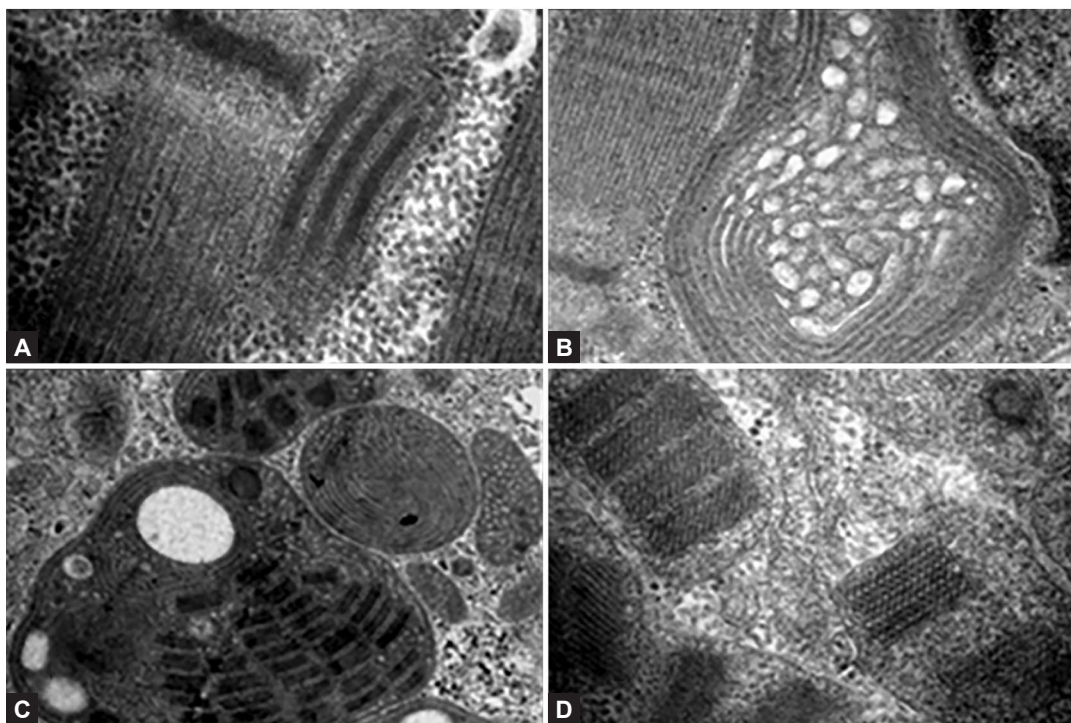
**Figure 1** Modified Gomori trichrome stain of muscle biopsy showing ragged red fiber (MGT x 400)

Source: Dr MC Sharma, Professor, Pathology, AIIMS, New Delhi



**Figure 2** COX with SDH stain of muscle biopsy demonstrating COX negative to be positive for SDH (x 200)

Source: Dr MC Sharma, Professor, Pathology, AIIMS, New Delhi



**Figures 3A to D** Electromicrophotographs of muscle biopsy showing (A) paracrystalline inclusion; (B) finger print like inclusions; (C) parking lot inclusions; and (D) zipper like inclusions in the mitochondria

Source: Dr MC Sharma, Professor, Pathology, AIIMS, New Delhi



seen in KSS, MERRF and progressive external ophthalmoplegia (PEO) (**Fig. 2**), whereas RRF with normal COX staining is seen in MELAS. Electron microscopy shows ultrastructural changes like increased mitochondrial number and size, distorted or decreased cristae, osmophilic, paracrystalline, fingerprint, parking lot and zipper like inclusions (**Figs 3A to D**). Skeletal muscle biopsy can also be used to estimate mitochondrial enzymes and coenzyme Q10 and extraction of DNA for molecular studies.

### Other Tissues

Liver and skin fibroblast can be used occasionally for enzyme analysis and DNA testing (POLG in liver biopsy).

### Neuroimaging

A wide spectrum of neuroimaging changes are seen in mitochondrial disorders. Diffuse cerebral (complex V defect) and cerebellar atrophy (Alpers syndrome) can be seen. Bilateral basal ganglia, brainstem including periaqueductal gray matter and substantia nigra, diencephalon and cerebellar lesions are seen in Leigh's syndrome (**Fig. 4**). MELAS usually shows multifocal gray matter involvement predominantly in the parieto-occipital region without conforming to any vascular territory. Leukodystrophy like picture is seen in electron transport chain defects and mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). Patients with mitochondrial disorder may have cerebral lactic acidosis

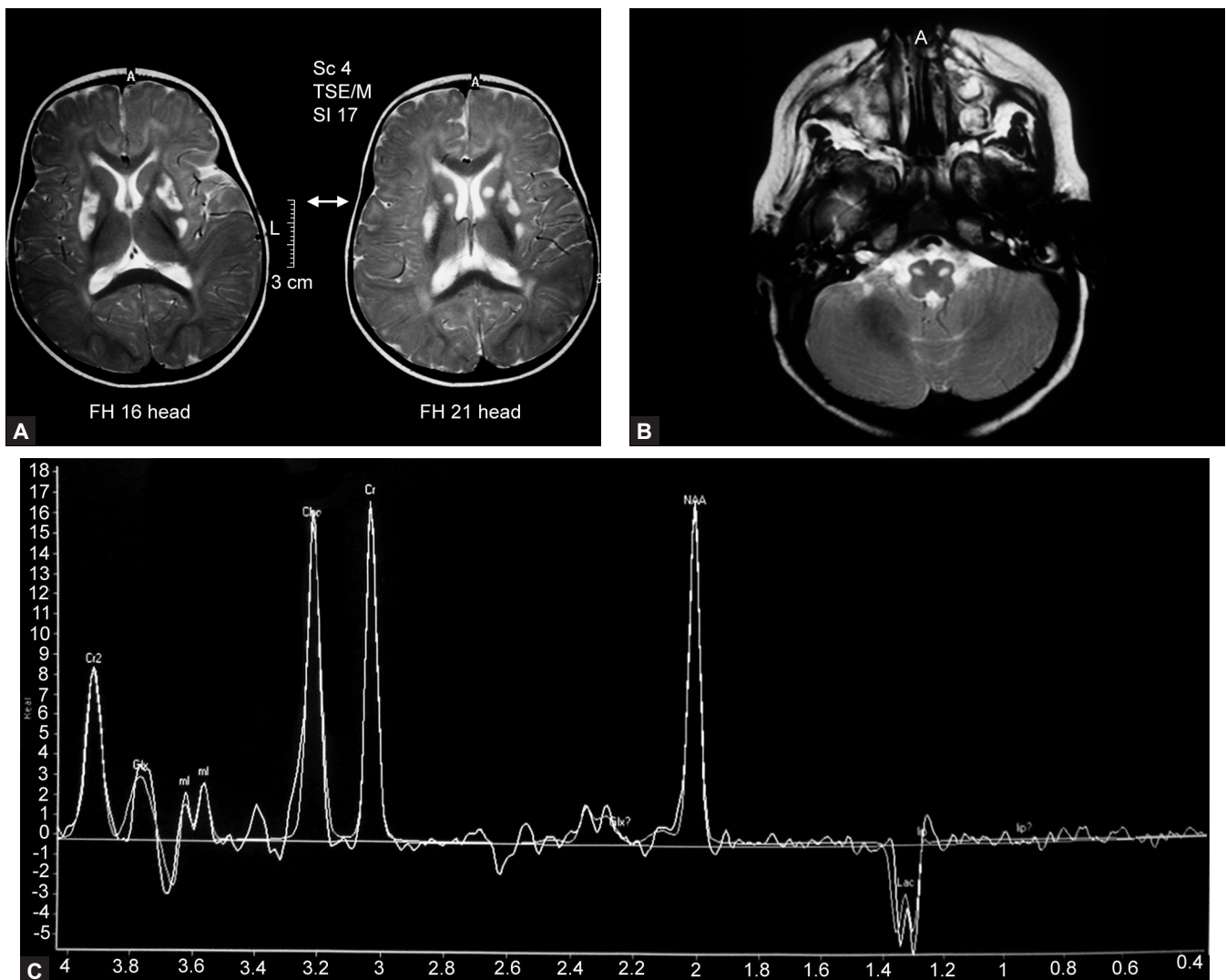
without any peripheral blood lactic acidemia. Magnetic resonance spectroscopy of the brain with appropriate voxel placement offers a suitable alternative to cerebrospinal fluid lactate estimation as it produces a negative lactate peak (1.33 ppm) in mitochondrial cytopathies with cerebral lactic acidosis (**Fig. 4C**).

### Molecular Testing

For the recurrent common mitochondrial point mutations, the methodology usually employed is either polymerase chain reaction (PCR) or restriction fragment length polymorphism, PCR or allele-specific oligonucleotide dot-blot analysis, allele refractory mutation system or direct sequencing. As 75–90% of the mitochondrial disorders are mediated through nuclear genes, sequence analysis of a group of candidate genes is also helpful. Even with all these advance techniques, only around 10% of the candidate genes for mitochondrial disorders are currently identifiable. So, the current ongoing research effort for increasing the diagnostic yield is development of a high throughput sequencing technology which can identify and quantify majority of nuclear and mitochondrial genomic mutations.

### Ancillary Diagnostic Modalities

Echocardiography, electrocardiogram, detailed ophthalmological and audiological investigation should be tailored for each patient on an individual basis.



**Figures 4A to C** MRI brain (T2 weighted images) of a Leigh's disease patient showing (A) bilateral basal ganglia; (B) brain stem hyperintensities with; (C) MR spectroscopy from the basal ganglia lesion showing characteristic inverted lactate peak

## TREATMENT

Apart from symptomatic treatment of various organ system effects, there is no established, standard of care treatment protocol for mitochondrial disorders. Extensive research is underway both at the level of animal as well as human models. These novel therapeutic strategies are being developed targeting the following pathways:

- **Preventing transmission of defective mitochondrial DNA** This approach, also known as germline therapy, is aimed at preventing maternal transmission of disease mitochondrial DNA to the child.
- **Modifying heteroplasmy levels** The pathological threshold levels of mutated mitochondrial DNA can be reduced by degrading selectively the mutated DNA or enrichment of the wild type DNA.
- **Replacement of defective mitochondrial DNA, tRNA and proteins** This utilizes the technique of protein transduction, which is a novel strategy to transport target mitochondrial sequence across the membranes and localize within the mitochondria.
- **Utilization of vitamins and cofactors** Various agents like dichloroacetate (in conditions with lactic acidosis like MELAS), coenzyme Q and its congeners mitoQ and idebenone (for electron transport chain defects), L-arginine (MELAS), folinic acid (KSS), carnitine, creatine, thiamine, riboflavin, vitamins C and E, dihydrolipoate and glutathione have been tried as free radical scavengers or remover of toxic metabolites or electron acceptors or as vitamins and cofactors with encouraging reports; however, a recent Cochrane review has emphasized the need for further well designed, adequately numbered studies for definite conclusive role.
- **Optimizing ATP synthesis** The fact that mitochondrial disorders retain some residual minimal oxidative phosphorylation activity has been utilized by either modulation of mitochondrial calcium levels, increasing mitochondrial biogenesis or by allosteric activation of protein kinase A.
- **Bypassing oxidative phosphorylation defects** Animal models have explored alternate pathways for bypassing oxidative phosphorylation.

The summary of therapeutic approaches in mitochondrial disorders is enumerated in **Table 4**.

### IN A NUTSHELL

1. The lifetime risk of developing mitochondrial disease is around 1 in 5,000 livebirths.
2. Primary mutations in mitochondrial DNA are either due to point mutations or deletions, whereas in nuclear DNA mediated cases, it is secondary to multiple deletions or depletions.
3. The most common pediatric mitochondrial disorder is Leigh's disease. Other common mitochondrial disorders are MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes), MERRF (myoclonic epilepsy with ragged red fibers), Alpers' syndrome, Kearns-Sayre syndrome, and Leber's hereditary optic neuropathy.
4. Red flag clinical features for mitochondrial disorders exist, whenever 3 or more organ systems are involved without any unifying pathology, mitochondrial disorder should be suspected.
5. Currently noninvasive and invasive baseline biochemical investigations and neuroimaging can direct to appropriate molecular testing, which can diagnose up to 10% of cases.
6. Apart from symptomatic treatment, as of now, there is no standard of care treatment protocol for mitochondrial disorders.

**Table 4** Summary of therapeutic approaches in mitochondrial disorders

Therapeutic strategy	Components
Preventing transmission of defective mitochondrial DNA	Cytoplasmic transfer Pronuclear transfer
Modifying heteroplasmy	Selective degradation of mitochondrial DNA (restriction endonucleases, zinc finger nucleases) Enrichment of wild type DNA (ketogenic diet, resistant exercise)
Replacement of defective mitochondrial DNA, tRNA and proteins	Protofection Recombinant virus-mediated gene transfer Targeted tRNA import Allotropic expression
Vitamins and cofactors	Dichloroacetate (in conditions with lactic acidosis like MELAS), coenzyme Q and its congeners mitoQ and idebenone (for electron transport chain defects), L arginine (MELAS), folinic acid (KSS), carnitine, creatine, thiamine, riboflavin, vitamins C and E, dihydrolipoate and glutathione
Optimizing ATP synthesis	Modulation of mitochondrial calcium levels Mitochondrial biogenesis Allosteric activation
Bypassing oxidative phosphorylation defects	Rotenone insensitive NADH dehydrogenase Cyanide insensitive alternative oxidase

**Abbreviations:** MELAS, mitochondrial encephalomyopathy; NADH, nicotinamide-adenine dinucleotide; KSS, Kearns-Sayre Syndrome.

### MORE ON THIS TOPIC

- De Vivo DC, Di Mauro S. Mitochondrial diseases. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF. *Pediatric Neurology Principles and Practice*. 5<sup>th</sup> ed. Philadelphia: Mosby; 2012. pp. 452-67.
- Friedman SD, Shaw DW, Ishak G, et al. The use of neuroimaging in the diagnosis of mitochondrial disease. *Dev Disabil Res Rev*. 2010;16(2):129-35.
- Haas RH, Parikh S, Falk MJ, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics*. 2007;120:1326-34.
- Mitochondrial Medicine Society's Committee on Diagnosis, Haas RH, Parikh S, et al. The in-depth evaluation of suspected mitochondrial disease. *Mol Genet Metab*. 2008;94(1):16-37.
- Pfeffer G, Majamaa K, Turnbull DM, et al. Treatment for mitochondrial disorders. *Cochrane Database Syst Rev*. 2012;4:CD004426.
- Tein I. Metabolic myopathies. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors. *Pediatric Neurology Principles and Practice*. 5<sup>th</sup> ed. Philadelphia: Mosby; 2012. pp. 1613-57.
- Wenz T, Williams SL, Bacman SR, et al. Emerging therapeutic approaches to mitochondrial diseases. *Dev Disabil Res Rev*. 2010;16:219-29.
- Wong LC. Molecular genetics of mitochondrial disorders. *Dev Disabil Res Rev*. 2010;16:154-62.

## Chapter 3.7

# Peroxisomal Disorders

Madhulika Kabra, Neerja Gupta

Peroxisomal disorders, more appropriately addressed as peroxisomal biogenesis disorders (PBD) are a group of disorders with highly heterogeneous phenotype. Majority of the disorders are autosomal recessive except adrenoleukodystrophy (ALD) which is X-linked recessive. In peroxisomal disorders, the assembly of peroxisomes is impaired which results in complex enzyme abnormalities causing diverse phenotypes. Three broad phenotypic groups and many atypical phenotypes have been described.

Common disorders amongst these include X-linked ALD, Zellweger syndrome (ZS), neonatal ALD, infantile Refsum disease, and rhizomelic chondrodysplasia punctata (RCDP). Diagnosis is complicated and is based on biochemical studies and molecular tests. ALD is the most common of the peroxisomal disorders, affecting about one in 20,000 males. ZS is rare affecting one in 50,000–100,000 livebirths.

## PATHOPHYSIOLOGY

Peroxisomes are single membrane-bound organelles which are small and spherical or oval in shape. These are present in large numbers in each cell. A peroxisome must contain catalase enzyme which breaks down hydrogen peroxide. The pathophysiology is complex and involves many pathways. This is evident by the fact that as many as 50 different biochemical reactions take place in a peroxisome. These include both anabolic and catabolic reactions. During  $\beta$ -oxidation in the peroxisomes, very long-chain fatty acids (VLCFA) are utilized ( $> C22$ ) but the reaction is not completed and ends in shorter fatty acids that are then transported to mitochondria for complete oxidation.

There are 16 *PEX* genes involved in this complex system. Mutations in 14 of these genes cause various PBD. All *PEX* genes except *PEX 7* cause Zellweger spectrum disorder (ZSD). The protein product is peroxin and usually the severity of the disorder correlates well with the type and consequence of mutations, residual enzyme function and number of peroxisomes.

## CLASSIFICATION

These disorders can be broadly classified in two groups, namely assembly or biogenesis deficiencies and single enzyme deficiency. In assembly deficiency, there is loss of multiple enzyme activities leading to abnormal morphology of organelle. In most of these disorders, there is defect in importing the protein in the peroxisomes. In the single enzyme defect, only one enzyme is involved and the structure of the peroxisome is not disrupted. Classification of these disorders is listed in **Box 1**.

### BOX 1 Classification of peroxisomal disorders

1. Assembly deficiencies
  - Zellweger syndrome
  - Infantile Refsum disease
  - Hyperpipecolic acidemia
  - Rhizomelic chondrodysplasia punctata (classical type)
  - Neonatal adrenoleukodystrophy
  - Pseudo-infantile Refsum disease
  - Zellweger-like syndrome
2. Single enzyme deficiency
  - Single peroxisomal enzyme deficiency involving oxidation pathway
    - X-linked adrenoleukodystrophy (ALD protein)
    - Pseudoneonatal adrenoleukodystrophy (Acyl-CoA oxidase)
    - Pseudo-Zellweger (Thiolase)
    - Bifunctional enzyme deficiency (bifunctional protein)
  - Single peroxisomal enzyme deficiency without involving oxidation pathway
    - Refsum disease (phytanic acid oxidase)
    - Pseudo-rhizomelic chondrodysplasia (plasmalogen synthesis)
    - Di-(tri)-hydrocholestanic acidemia (bile acid synthesis)
    - Mevalonic aciduria (cholesterol synthesis)

Laboratory diagnosis is usually based on studying function of the peroxisome and molecular studies. **Table 1** summarizes the diagnostic strategy for PBD. Common disorders are discussed below. ALD is detailed in Section 42, chapter 42.26 on Neurodegenerative diseases.

## ZELLWEGER SYNDROME

This syndrome has a characteristic phenotype when presenting as a classical form. It is also called cerebrohepatorenal syndrome. The inheritance is autosomal recessive.

**Table 1** Laboratory work-up for peroxisomal disorders

Test	Metabolite/gene	Disorder	Comments
Plasma VLCFA	Increased C26:0, C26:1 and C24/C22, C26/C22 ratio	ZS, NALD, IRD	May be false positives in patients on ketogenic diet, and in hemolyzed samples; normal in RCDP1
Plasma phytanic and pristanic acid	Increased	ZS, NALD, IRD, RCDP1 (phytanic only)	Normal in neonatal period as accumulates after dietary intake
RBC plasmalogens	Decreased	ZS, NALD, IRD, RCDP1	Most significant reduction in RCDP1
Plasma pipecolic acid	Increased	ZS, NALD, IRD	Adjunct to other metabolites
Cultured fibroblasts	Enzyme assay, abnormal metabolites	ZS, NALD, IRD, RCDP1	Though confirmatory but not easily available
Molecular genetic testing	<i>PEX1</i> , 2, 3, 5, 6, 10, 11b, 12, 13, 14, 16, 19, 26	ZS, NALD, IRD	80% of cases with ZSD are due to defects in <i>PEX1</i> , 2, 6, 10, 12, 26
	<i>PEX 7</i>	RCDP1	Four common <i>PEX7</i> alleles in exons 7 and 9 account for 70% of cases of RCDP1

**Abbreviations:** VLCFA, very long-chain fatty acids; ZS, Zellweger syndrome; NALD, neonatal adrenoleukodystrophy; IRD, infantile Refsum disease; RCDP1, rhizomelic chondrodysplasia punctate; ZSD, Zellweger spectrum disorder.

**Source:** Adapted from Braverman, et al. Dev Disabilities Res Rev. 2013.



## Clinical Features

The usual presentation is in the neonatal period with a recognizable clinical phenotype of high forehead with widely open anterior fontanel, flat facial profile with hypertelorism and epicanthic folds (at times confused with Down's syndrome), small chin and high arched palate. Severe hypotonia is an important clinical sign. These babies often have seizures. Other manifestations include direct hyperbilirubinemia, liver dysfunction and hepatomegaly, cataract, glaucoma, pigmentary retinopathy, hearing loss, renal stones and poor weight gain. **Figure 1** shows typical phenotype of a baby with ZS. All patients with classical ZS die in the first few months of life.

## Investigations

Magnetic resonance imaging of brain may show neuronal migration defects like polymicrogyria (typically lateral), pachygyria (medial) and heterotopias. X-rays may show chondrodysplasia punctata. The diagnosis is confirmed by analysis of plasma VLCFA and plasmalogens in red blood cells. Plasma VLCFA shows increased C26:0, C26:1 and C24/C22, C26/C22 ratio, increased phytanic acid and pipelicolic acid, and reduced RBC plasmalogens. Increased urine and plasma bile acid intermediates are also reported. Cultured fibroblasts may be used for enzyme assays. Molecular genetic studies involve mutation analysis of *PEX1*, 2, 3, 5, 6, 10, 11b, 12, 13, 14, 16, 19, 26 as mutations have been reported in all these genes. However, defects in *PEX1*, 2, 6, 10, 12, 26 account for approximately 80% of cases with ZS.

## Treatment

Management is symptomatic and multidisciplinary. No curative therapy is available. Dietary interventions by restriction of accumulated metabolites and supplementation of deficient ones has been tried but with no conclusive results. Oral bile acid therapy has been reported to improve hepatobiliary function. Restriction of phytanic acid has also been tried.

Prenatal diagnosis is opted by most families in view of the nature of disease and high recurrence risk of 25%. Prenatal testing can be offered by analysis of amniotic fluid or chorionic villus sampling (CVS) using cultured cells for biochemical markers or by mutation testing of the fetal DNA sample.



**Figure 1** A neonate with Zellweger syndrome. Note flat facial profile, hypertelorism with epicanthic folds and high forehead

## RHIZOMELIC CHONDRODYSPLASIA PUNCTATA

### Clinical Features

This is another severe and easily recognizable disorder. The disorder presents in early life with shortening of the proximal part of the long bones affecting femur more than the humerus and typical facial features. These include frontal bossing, midface hypoplasia and small nose with depressed nasal bridge. Cataracts are either noticed at birth or develop early. Failure to thrive, seizures and developmental delay are also seen. **Figure 2A** shows clinical features of RCDP. Occasional patients are reported to have cleft palate, renal malformations and congenital heart defects. Some children die in the first year of life but individuals with milder forms may survive.

Three types of RCDP are described with similar phenotype but different pathogenesis. RCDP1 being caused by mutations in *PEX 7* genes while RCDP2 and RCDP3 are due to defects in peroxisomal enzymes.

### Investigations

Skeletal survey shows generalized calcific epiphyseal stippling referred to as chondrodysplasia punctata (**Fig. 2B**). This may disappear with time. MRI brain does not show characteristic abnormalities as reported in ZS but nonspecific changes may be seen including cerebellar degeneration. Confirmation of diagnosis is by biochemical analysis of plasma as in ZS. RBC plasmalogen levels are very significantly reduced particularly in RCDP1, plasma VLCFA is not increased and phytanic acid is reduced (**Box 1**). Mutations in *PEX7* gene commonly in exons 7 and 9 account for approximately 70% of cases of RCDP1.

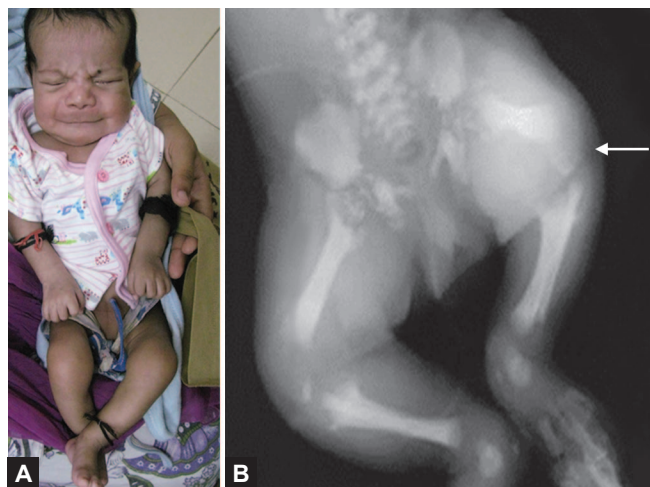
Treatment is supportive and symptomatic. Prenatal diagnosis is possible by biochemical analysis of amniotic fluid or molecular testing.

## NEONATAL ADRENOLEUKODYSTROPHY

Neonatal ALD is a peroxisomal disorder with intermediate severity and is autosomal recessive in inheritance.

### Clinical Features

These patients present with hypotonia, seizures, encephalopathy, visual and hearing abnormalities with onset at birth or early infancy but may not be diagnosed due to nonspecific phenotype. Leukodystrophy may develop around 3–5 years and may



**Figures 2A and B** (A) Baby with characteristic features (flat facies, smooth long philtrum, thin upper lip, joint contractures at elbow and knee) rhizomelic chondrodysplasia punctata; (B) Arrow shows the epiphyseal stippling at knee



manifest as neuroregression. Other features include peripheral neuropathy, poor growth, developmental delay and facial dysmorphism which may be subtle with mid-face flattening and hypertelorism. Eye findings include cataract, optic nerve dysplasia and chorioretinopathy. Some patients may have hepatic dysfunction and even coagulopathy.

### Investigations

Magnetic resonance imaging scan may show leukodystrophy, neuronal migration defects or other malformations. Active demyelination is seen in the cerebrum, midbrain and cerebellum. Definitive diagnosis requires biochemical studies or molecular testing. Plasma VLCFA are elevated particularly C26:0 and C26:1 and elevated ratios of C24/C22 and C26/C22. RBC plasmalogens are reduced. Plasma pipecolic acid levels and bile acid intermediates are elevated. Sequence analysis of the 13 *PEX* genes can give confirmatory diagnosis.

### Management

Prenatal diagnosis can be offered by culturing the amniocytes and CVS for VLCFA and plasmalogen synthesis. If causative mutations are identified, prenatal diagnosis can be offered using molecular tests.

There is no cure and treatment is symptomatic. Hepatic coagulopathy can be treated with vitamin K supplementation and liver function may improve with primary bile acid therapy. Foods rich in phytanic acid may be restricted. Standard epileptic drugs are used for seizures.

Prognosis is poor with most patients dying in infancy and early childhood. Some have lived until their teenage years.

### REFSUM DISEASE

This disease has a variable onset of symptoms usually in late childhood or adolescence, but may present even in later life. Acute and subacute progression has been reported in few cases but it usually follows a chronic progressive course.

### Clinical Features

Important clinical features include a demyelinating neuropathy which may be associated with hypertrophy of nerves. Other manifestations include pes cavus, cerebellar ataxia, sensorineural deafness, anosmia and cranial nerve involvement. Visual problems in the form of night blindness are present due to retinitis pigmentosa. Cataracts and photophobia are also reported. Other manifestations like miosis may be due to generalized dysautonomia. Cardiac conduction abnormalities have also been reported which may be life-threatening. Skin may show rough, thick scaly lesions. Epiphyseal dysplasia may present as characteristic shortening of the fourth toe, which may be an important diagnostic clue.

Differential diagnosis includes Friedreich ataxia, mitochondrial cytopathies, other hereditary motor and sensory neuropathies, and vitamin E deficiency.

### Investigations

Nerve conduction studies demonstrate slowing of conduction velocities. Cerebrospinal fluid protein levels may be high. Due to retinal pigmentary changes, electroretinogram may be abnormal. Nerve biopsies, though usually not resorted to, may show *onion bulb* appearance and other inclusions. Confirmation of diagnosis is by measuring plasma levels of phytanic acid using gas chromatography-mass spectroscopy, which are significantly elevated as compared to other ZSD. Pristanic acid is low/normal in Refsum disease due to lack of production from phytanate (Table 1). Mutations in the *PEX* genes have been reported to cause RCDP.

### Treatment

Refsum disease is amenable to dietary therapy and may show partial improvement if started early. Restriction of phytanic acid has been reported to be useful. It is easily possible as phytanic acid is almost exclusively of exogenous origin. Important sources include fish, beef, lamb, dairy products and vegetables. The average daily intake of phytanic acid is about 50–100 mg/day, and the recommendation is to reduce it to 10–20 mg/day. This may affect palatability and, hence, compliance. The neurological, cardiac and dermatological sequelae can be reversed by reduction of phytanic acid levels, but the visual and hearing impairments are less responsive to treatment. In acutely presenting cases, plasma phytanic acid level may be reduced by plasma exchange with a significant clinical improvement. Dietary treatment has to be continued lifelong.

### ATYPICAL PHENOTYPES

Atypical presentations of ZSD are now being reported and patients may have preserved intellect. These include the following:

- Cerebellar ataxia, with or without peripheral neuropathy, and relative preservation of intellect. MRI brain may show cerebellar atrophy.
- Another group including patients have no cognitive defects but present with progressive spastic paraparesis and ataxia in early childhood. MRI shows cerebellar trophy and cerebral leukodystrophy. These patients may develop peripheral neuropathy later.
- A lethal phenotype with microcephaly, optic atrophy and lactic acidemia has also been reported. MRI brain showed dysmyelination and abnormal gyration.

### IN A NUTSHELL

1. In peroxisomal disorders, the assembly of peroxisomes is impaired which results in complex enzyme abnormalities causing diverse phenotypes.
2. Common disorders among these include X-linked ALD, ZS, neonatal ALD, infantile Refsum disease and RCDP.
3. Zellweger syndrome can be clinically confused with Down's syndrome.
4. Diagnosis can be made by plasma biochemical studies and DNA-based tests.
5. Most disorders are untreatable except Refsum disease and very early stages of ALD.

### MORE ON THIS TOPIC

- Aubourg P, Wanders R. Peroxisomal disorders. *Handb Clin Neurol*. 2013;113:1593-609.
- Barry DS, O'Keefe GW. Peroxisomes: the neuropathological consequences of peroxisomal dysfunction in the developing brain. *Int J Biochem Cell Biol*. 2013;45:2012-5.
- Braverman NE, D'Agostino MD, Maclean GE. Peroxisome biogenesis disorders: biological, clinical and pathophysiological perspectives. *Dev Disabil Res Rev*. 2013;17:187-96.
- Farrell DF. Neonatal adrenoleukodystrophy: a clinical, pathologic and biochemical study. *Pediatr Neurol*. 2012;47:330-6.
- Lee PR, Raymond GV. Child neurology: Zellweger syndrome. *Neurology*. 2013;80:e207-10.
- Vamecq J, Cherkaoui-Malki M, Andreoletti P, Latruffe N. The human peroxisome in health and disease: the story of an oddity becoming a vital organelle. *Biochimie*. 2014;98:4-15.
- Wanders RJ, Ferdinandusse S. Peroxisomes, peroxisomal diseases and the hepatotoxicity induced by peroxisomal metabolites. *Curr Drug Metab*. 2012;13:1401-11.

## Chapter 3.8

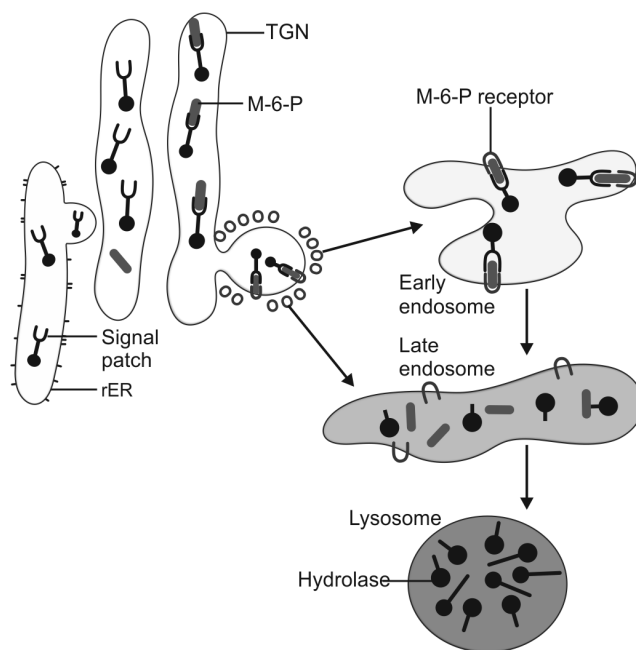
# Lysosomal Storage Disorders

IC Verma

Lysosomes, initially discovered by Christian de Duve in 1955, are organelles in the cytosolic compartment of the cell. They contain acid hydrolytic enzymes, which are synthesized in the rough endoplasmic reticulum (rER), fold in a specific way so that an N-terminal signal patch is formed, which allows for further modification by the addition of mannose-6-phosphate (M-6-P). The enzymes then move across the ER membrane to the lumen of the ER. From here, they proceed to the trans-Golgi network (TGN) where the lysosomal enzymes are sorted and packaged into vesicles, later transported to the early or late endosomes. Here dissociation occurs; the hydrolases translocate into the lysosome and the receptor is recycled either to the Golgi apparatus or to the plasma membrane. **Figure 1** illustrates the synthesis and cycling of lysosomes.

The lysosomal enzymes are involved in the breakdown and recycling of macromolecules, such as glycos-aminoglycans, glycoproteins, oligosaccharides and lipids. The micromolecules formed after breakdown are either reused by the cell or are eventually eliminated from the body. The lysosomes are thus the catabolic centers of the cell.

For degradation of cellular material, lysosomes use four distinct pathways: (A) Macroautophagy starts with the formation of isolation membranes that sequester regions of the cytosol containing denatured proteins, lipids, carbohydrates and old or damaged organelles into encapsulated vesicles known as autophagosomes. These are then cleared by the lysosomes; (B) The endosomes engulf the waste material, and fuse with lysosomes for final disposition; (C) Microautophagy involves the pinocytosis of cytosolic regions surrounding lysosomes that contain micromolecules; (D) Chaperone-mediated autophagy

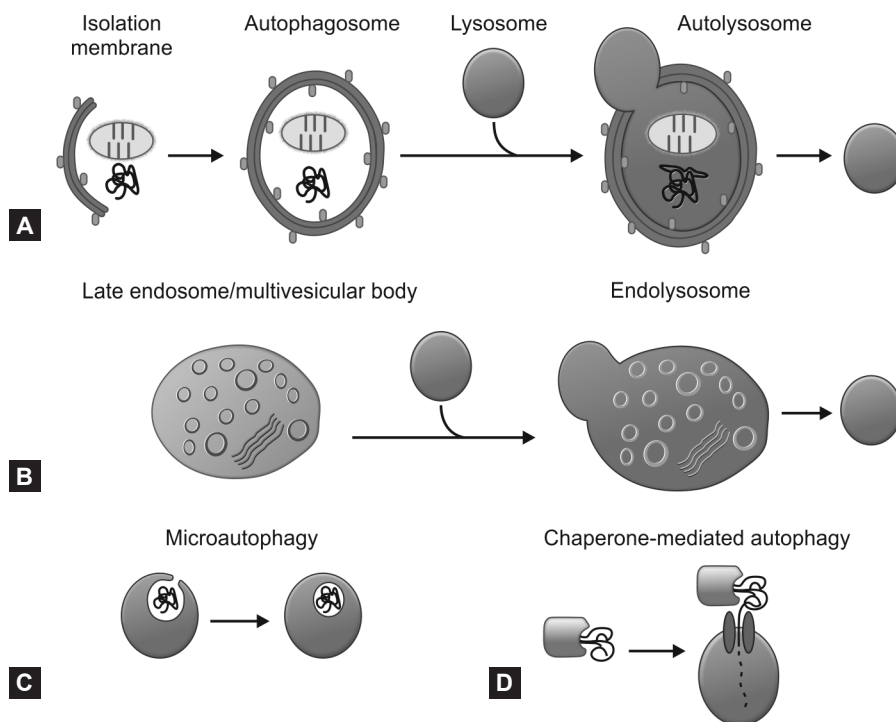


**Figure 1** Synthesis and movement of lysosomal enzymes  
Adapted from Ross, Michael H. *Histology: A Text and Atlas with Correlated Cell and Molecular Biology*, 5<sup>th</sup> ed. Lippincott Williams & Wilkins, 2005.

(CMA) selectively targets proteins with a KFERQ motif for delivery to lysosomes using Hsc-70 as its chaperone and LAMP-2A as its receptor. These pathways of degradation are depicted in **Figure 2**.

## EPIDEMIOLOGY

The lysosomal storage disorders (LSDs) are categorized according to the type of substrate that accumulates [e.g., mucopolysaccharidoses (MPSs), oligosaccharidoses, sphingolipidoses, gangliosidoses, etc.], or the type of enzyme defect. Over 70 lysosomal disorders



**Figure 2** Lysosomes as catalytic centers of the cell  
Adapted from Platt et al. *J Cell Biol.* 2012.

have been recognized. Individually, they are rare but collectively they have a prevalence of 1 in 5,000 population worldwide. The true figure is likely to be greater when undiagnosed or misdiagnosed cases are included. In India, the incidence is expected to be higher due to consanguinity and endogamous marriages in large sections of the population. This frequency makes LSD a disease category that a pediatrician is likely to come across in medical practice.

Two disorders of ganglioside biosynthesis have been genetically proven in the human population within the past decade—GM2-synthase deficiency which results in spastic paraplegia (progressive lower limb weakness and spasticity), and GM3-synthase deficiency, which was discovered in the Old Order Amish community in Ohio, and presents as a severe epilepsy syndrome.

All the LSDs are inherited in an autosomal recessive fashion, except four—Fabry, Hunter (MPS type II) and Danon disease, and a variant type of adult NCL (Kuf disease), which are X-linked. Some disorders are more prevalent among particular population groups (e.g., Gaucher and Tay-Sachs disease are more common in Ashkenazi Jews, due to ancestral founder mutations). For many diseases, such as Fabry, most families have private mutations. Founder mutations in some lysosomal disorders have been identified among Indian populations (e.g., Hexosamine A mutations in Gujarat), although more studies are required.

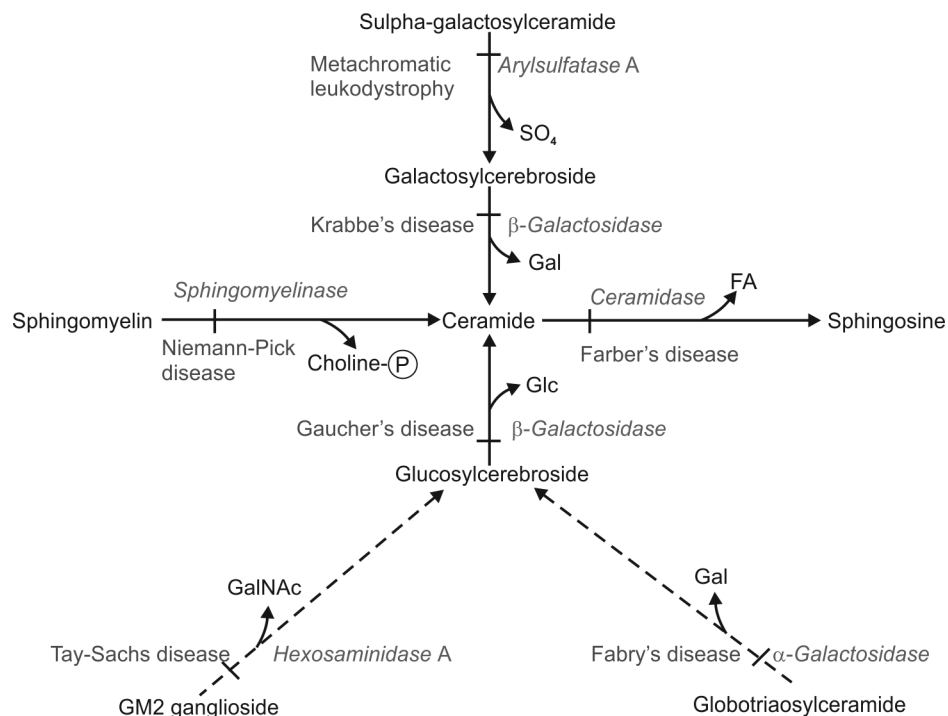
## ETIOPATHOGENESIS

Classical LSDs result from abnormalities in the gene coding for the specific acidic hydrolase enzyme, or its receptor, which leads to a deficient activity of the enzyme. As a result, the relevant substrate accumulates in a progressive manner within the lysosome. The physical enlargement of the lysosome, when it reaches a critical level, leads to dysfunction of multiple organelles in the cell, and eventually results in the enlargement of specific organ involved, leading to symptomatic disease. The dysfunction is due to the initiation of a complex downstream pathogenic cascade, the steps of which are only partially determined. Several studies in mouse models of LSDs involving ganglioside storage (for example,

Sandhoff disease and GM1 gangliosidosis) have provided evidence for a form of programmed cell death called caspase-dependent apoptosis. Other studies have uncovered an unusual cell-death mechanism in two sphingolipid storage diseases, type 2 Gaucher disease and Krabbe disease—necroptosis. This pathway is dependent on the kinases RIPK1 and RIPK3, and these mediate caspase-independent cell death.

Most LSDs result from deficiency of acidic hydrolase enzymes as mentioned above. However, some disorders result from defects in lysosomal membrane proteins (such as defective GM3-synthase in GM3-gangliosidosis), or by trafficking defects (Niemann-Pick disease, type C), or due to faulty lysosome-associated membrane protein 1 (LAMP-1), or LAMP-2, as in Danon disease and action myoclonus-renal failure syndrome, respectively. Under this categorization, neuronal ceroid-lipofuscinosis (NCLs) can also be included in the LSD spectrum.

The pathways in sphingolipidosis and the resultant disorders are depicted in **Figure 3**. In the glycol-sphingolipids, the central piece is the ceramide backbone (2-N-acylsphingosine), which is modified by the addition of a carbohydrate head group. The various sphingolipids are derived by substitution of hexoses, phosphorylcholine, or one or more sialic acid residues on the terminal hydroxyl group of the ceramide molecule. The simplest GSLs have a single monohexoside (glucose or galactose) moiety linked to ceramide. Over evolutionary time, the carbohydrate head group has increased in complexity—more than 300 structures have been described, with those derived from the core structure glucosylceramide (GlcCer) being the most common. Galactosylceramide (GalCer) and its sulfated derivative have a much more restricted distribution and are generally confined to myelin and the kidney. When the oligosaccharide head group of GlcCer-derived GSLs contains a sialic acid, the GSL is charged, and these GSLs are termed gangliosides and are the major glycoconjugates found in the nervous system. The complexity of sphingolipids is not just the result of the glycan head group, but also the ceramide chain-length heterogeneity that arises owing to the differential chain-length specificity of ceramide synthases.



**Figure 3** Sphingolipids showing ceramide and its derivatives and the enzymes involved

Progressive lysosomal accumulation of glycosphingolipids in the central nervous system (CNS) leads to neurodegeneration, whereas storage in visceral cells results in organomegaly, skeletal abnormalities, pulmonary infiltration, and other manifestations. Although the enzymes are expressed in many parts of the body, however, the accumulation occurs only in cells where the substrate is available. Therefore, only some organs are affected in certain types of LSDs. Liver, spleen and bone marrow are commonly involved organs, e.g., in Gaucher disease. The neurologic system is the most involved in diseases like Gm2 gangliosidosis or Krabbe disease.

## CLASSIFICATION

Lysosomal storage disorders can be grouped according to various classifications. In the past, they were classified on the basis of the

nature of the accumulated substrate(s), more recently they have tended to be classified by the molecular defect (**Table 1**).

## Clinical Phenotypes

The age of clinical onset and spectrum of symptoms exhibited by different LSDs vary, depending on the degree of cellular function affected by specific mutations, the biochemistry of the stored material, and the cell types where storage occurs. Apart from lysosomal diseases involving substrate storage in bone and cartilage (e.g., the MPSs), most babies born with these conditions appear normal at birth. LSDs present either with organomegaly or as a neurodegenerative disease of infancy/childhood, but adult-onset variants also occur.

The different types of substrate stored, the different cell types affected by storage, as well as the resultant differences in organ

**Table 1** Lysosomal storage disorders

Disease	Defective protein	Main storage materials	Gene involved
<i>Mucopolysaccharidoses (MPSs)</i>			
MPS I (Hurler, Scheie, Hurler/Schie)	$\alpha$ -Iduronidase	Dermatan sulfate, heparan sulfate	IDUA
MPS II (Hunter)	Iduronate sulfatase	Dermatan sulfate, heparan sulfate	IDS
MPS III A (Sanfilippo A)	Heparan sulfamidase	Heparan sulfate	SGSH
MPS III B (Sanfilippo B)	Acetyl $\alpha$ -glucosaminidase	Heparan sulfate	NAGLU
MPS III C (Sanfilippo C)	Acetyl CoA: $\alpha$ -glucosaminide N-acetyltransferase	Heparan sulfate	HGSNAT
MPS III D (Sanfilippo D)	N-acetyl glucosamine-6-sulfatase	Heparan sulfate	GNS
MPS IV A (Morquio A)	Acetyl galactosamine-6-sulfatase	Keratan sulfate, chondroitin 6-sulfate	GALNS
MPS IV B (Morquio B)	$\beta$ -Galactosidase	Keratan sulfate	GLB1
MPS VI (Maroteaux—Lamy)	Acetyl galactosamine 4-sulfatase (arylsulfatase B)	Dermatan sulfate	ARSB
MPS VII (Sly)	$\beta$ -Glucuronidase	Dermatan sulfate, heparan sulfate, chondroitin 6-sulfate	GUSB
MPS IX (Natowicz)	Hyaluronidase	Hyaluronan	HYAL1
<i>Sphingolipidoses</i>			
Fabry	$\alpha$ -Galactosidase A	Globotriasylceramide	GLA
Farber	Acid ceramidase	Ceramide	ASAH1
Gangliosidosis GM1 (Types I, II, III)	GM1- $\beta$ -galactosidase	GM1 ganglioside, Keratan sulfate, oligos, glycolipids	GLB1
Gangliosidosis GM2, Tay-Sachs	$\beta$ -Hexosaminidase A	GM2 ganglioside, Oligos, Glycolipids	HEXA
Gangliosidosis GM2, Sandhoff	$\beta$ -Hexosaminidase A + B	GM2 ganglioside, Oligos,	HEXAB
Gaucher (Types I, II, III)	Glucosylceramidase	Glucosylceramide	GBA
Krabbe	$\beta$ -Galactosylceramidase	Galactosylceramide	GALC
Metachromatic leucodystrophy	Arylsulfatase A	Sulfatides	ARSA
Niemann-Pick (Types A, B)	Sphingomyelinase	Sphingomyelin	SMPDI
<i>Oligosaccharidoses (glycoproteinoses)</i>			
Aspartylglucosaminuria	Glycosylasparaginase	Aspartylglucosamine	AGA
Fucosidosis	$\alpha$ -Fucosidase	Glycoproteins, glycolipids, Fucose-rich oligos	FUCA1
$\alpha$ -Mannosidosis	$\alpha$ -Mannosidase	Mannose-rich oligos	MAN2B1
$\beta$ -Mannosidosis	$\beta$ -Mannosidase	Man (b $\rightarrow$ 4) G1nNAc	MANBA
Schindler	N-acetylgalactosaminidase	Sialylated/asialoglycopeptides, glycolipids	NAGA
Sialidosis	Neuraminidase	Oligos, glycopeptides	NEUI

Contd...



Contd...

<i>Disease</i>	<i>Defective protein</i>	<i>Main storage materials</i>	<i>Gene involved</i>
<i>Glycogenoses</i>			
Glycogenosis II/Pompe	$\alpha$ 1, 4-glucosidase (acid maltase)	Glycogen	GAA
<i>Lipidoses</i>			
Wolman/CESD	Acid lipase	Cholesterol esters	LIPA
<i>Non-enzymatic lysosomal protein defect</i>			
Gangliosidosis GM2, activator defect	GM2 activator protein	GM2 ganglioside, oligos	GM2A
Metachromatic leucodystrophy	Saposin B	Sulfatides	PSAP
Krabbe	Saposin A	Galactosylceramide	PSAP
Gaucher	Saposin C	Glucosylceramide	PSAP
<i>Transmembrane protein defect</i>			
<i>Transporters</i>			
Sialic acid storage disease; infantile form (ISSD) and adult form (Salla)	Sialin	Sialic acid	SLC17A5
Cystinosis	Cystinosin	Cystine	CTNS
Niemann-Pick Type C1	Niemann-Pick type 1 (NPC1)	Cholesterol and sphingolipids	NPC1
Niemann-Pick, Type C2	Niemann-Pick type 2 (NPC2)	Cholesterol and sphingolipids	NPC2
<i>Structural Proteins</i>			
Danon	Lysosome-associated membrane protein 2	Cytoplasmatic debris and glycogen	LAMP2
Mucopolidosis IV	Mucolipin	Lipids	MCOLN1
<i>Lysosomal enzyme protection defect</i>			
Galactosialidosis	Protective protein cathepsin A (PPCA)	Sialyloligosaccharides	CTSA
<i>Post-translational processing defect</i>			
Multiple sulfatase deficiency	Multiple sulfatase	Sulfatides, glycolipids, GAGs	SUMF1
<i>Trafficking defect in lysosomal enzymes</i>			
Mucopolidosis IIa/b, III a/b	GlcNAc-1-P transferase	Oligos, GAGs, lipids	GNPTAB
Mucopolidosis IIIg	GlcNAc-1-P transferase	Oligos, GAGs, lipids	GNPTG
<i>Polypeptide degradation defect</i>			
Pycnodysostosis	Cathepsin K	Bone proteins	CTSK
<i>Neuronal ceroidlipofuscinoses (NCLs)</i>			
NCL 1	Palmitoyl protein thioesterase (PPT1)	Saposins A and D	PPT1
NCL 2	Tripeptidyl peptidase 1 (TPP1)	Subunit c of ATP synthase	TPP1
NCL 3	CLN3, lysosomal transmembrane protein	Subunit c of ATP synthase	CLN3
NCL 5	CLN5, soluble lysosomal protein	Subunit c of ATP synthase	CLN5
NCL 6	CLN6, transmembrane protein of ER	Subunit c of ATP synthase	CLN6
NCL 7	CLC7, lysosomal chloride channel	Subunit c of ATP synthase	MFSD8
NCL 8	CLN8, transmembrane protein of endoplasmic reticulum	Subunit c of ATP synthase	CLN8
NCL 10	Cathepsin D	Saposins A and D	CTSD

Modified from Filocamo and Marrone Human Genomics, 2011.

involvement lead to tremendous clinical variability, even within a single disease. The disease tends to be progressive, as more waste substrate accumulates over time and more secondary pathology evolves. Early recognition of presenting symptoms and timely diagnosis are essential and require good cooperation between medical specialists. If diagnosed late and/or left untreated, patients are at risk of developing significant, irreversible damage and loss of body functions, and life-threatening complications.

The CNS seems to be particularly vulnerable to LSDs: most of these disorders manifest with neurological signs, and in some LSDs, the brain and/or peripheral nervous system is the sole affected organ, such as in Tay-Sachs disease or metachromatic leukodystrophy, respectively. A single clinically defined disorder may be caused by more than one enzymatic defect, such as Sanfilippo disease (MPS III), which can be caused by a deficiency in any one of four hydrolases. Conversely, a disorder caused by a single enzyme deficiency usually gives rise to a spectrum of manifestations depending on the amount of residual enzyme activity and currently unknown modifiers.

Specific mutations can be associated with certain outcomes, such as in Gaucher or Pompe disease patients. In other disorders there is no clear-cut genotype-phenotype correlation. Patients with the same mutation may present in childhood or be asymptomatic throughout adult life. For women with X-linked LSDs, such as Fabry disease, the severity and extent of disease manifestations may be determined primarily by the degree of X-chromosomal inactivation, although evidence of random inactivation has been shown.

Our understanding of pathogenesis has progressed greatly due to the availability of a large number of animal models for these disorders. These mutants arise either spontaneously (as, for example, in domestic cats, dogs, sheep, cattle), or are engineered. These animal models have played an important role in the development of therapies for specific conditions.

## CLINICAL FEATURES

The signs and symptoms of LSDs vary depending on disease type and other factors such as age at onset. Some LSDs are evident at birth, such as  $\beta$ -glucuronidase deficiency, or are diagnosed at 2–6 months of age, such as in infantile GM1-gangliosidosis, Krabbe disease or Tay-Sachs disease. Other LSDs, such as metachromatic leukodystrophy (MLD), become symptomatic in late infancy or childhood, as with some of the MPSs. Although many LSDs present in childhood, some manifest during the second decade or adulthood, as exemplified by adult GM2-gangliosidosis.

Symptoms of LSDs include failure to reach developmental milestones, visual disturbances, organomegaly (most notable in Gaucher and Niemann-Pick disease), hypersplenism and anemia, dysmorphic features and bony disease (which typify MPSs), seizures and neuromotor regression. Some of the late-onset (adult) forms have psychiatric manifestations of depression or psychosis in addition to neurological deficits, as seen in adult forms of MLD and adult GM2-gangliosidosis. The neurological and other complications that ensue over time in LSDs cause substantial morbidity and diminished quality of life for patients and their families, with death occurring in early life in most cases.

## DIAGNOSIS

Although the first clinical descriptions of patients with LSDs were reported at the end of the 19th century by Warren Tay (1881) and Bernard Sachs (1887)—Tay-Sachs disease, and by Philippe Gaucher in 1882 (Gaucher disease), the biochemical nature of the accumulated products was only elucidated some 50 years later (1934). Considerably more time was then required for the

demonstration by Hers (1963) that there was a link between an enzyme deficiency and a storage disorder (Pompe disease). In the following years, the elucidation of several enzyme defects led to the initial classification of the various types of LSDs according to their clinical pictures, pathological manifestations and the biochemical nature of the undegraded substrates.

**Flow chart 1** presents an algorithm for diagnosis of LSDs with dysmorphic facies, organomegaly, or multiplex dysostosis. A thorough physical examination is essential. Presence of organomegaly or coarse facial features or corneal clouding should be carefully looked for, as they provide important clues for establishing the diagnosis. Fundus examination is very useful because the presence of retinal changes or cherry red spot narrows down the possibilities. A careful neurologic examination is indispensable. In the presence of neurologic abnormalities, obtaining an MRI study with MRS is quite helpful. The relevant changes are discussed in the appropriate sections.

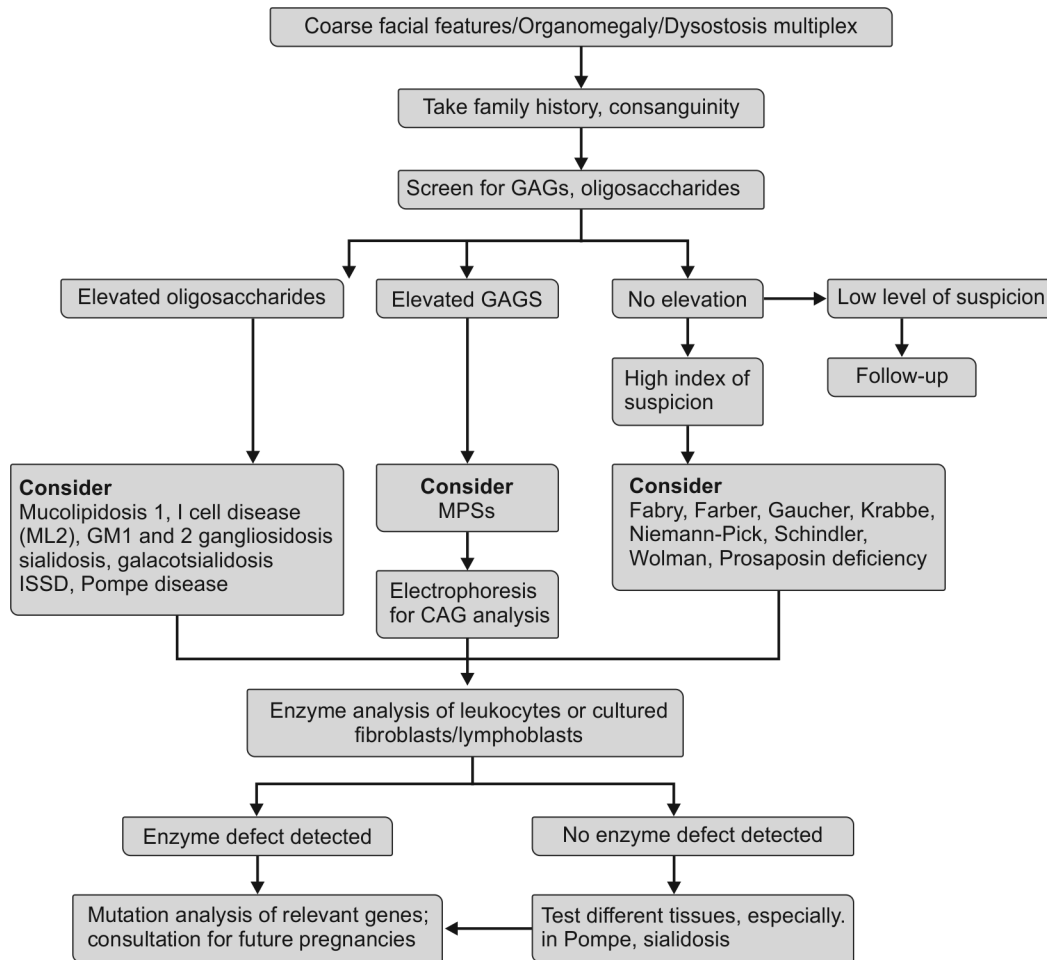
Neuronal ceroid lipofuscinosis (NCL) disorders have recently been added to group of LSDs. Most childhood subtypes of NCL are characterized by a combination of cognitive and motor decline, loss of vision, seizures and early death. In general, the NCLs are pathologically characterized by storage of autofluorescent material (including protein subunit C of mitochondrial ATP synthase or saposins) within neuronal lysosomes. The various NCLs are characterized by electron-dense ultrastructural features that are unique to each disorder, and the aberrant storage is accompanied by neuronal death and cerebral and/or cerebellar cortical atrophy.

## Laboratory Diagnosis

Once suspected from clinical features, it is useful to carry out some screening tests:

- i. Urine:
  - a. Toluidine blue spot test and excretion of glycosaminoglycans in urine (mg/creatinine) for MPS disorders.
  - b. Urine oligosaccharide excretion patterns for diagnosis of oligosaccharidoses.
  - c. Assessment of urinary sulfatide storage, increased in MLD (due to arylsulfatase A enzyme deficiency or saposin B activator defect);
  - d. Urinary excretion of free sialic acid is increased in sialic acid storage disorders [the severe infantile form (ISSD) or the slowly progressive adult form (Salla)].
- ii. Serum levels of metabolites/proteins:
  - a. Serum creatine kinase (CK) concentrations, elevated in Pompe disease;
  - b. Chitotriosidase is raised in Gaucher disease and, to a lesser extent, in other lipidoses.

These preliminary tests may be false positive or negative, and, therefore, specific enzymatic assay or molecular analyses should be performed if there is strong clinical suspicion.
- iii. Many LSDs are due to a *deficiency in lysosomal hydrolase activity*; therefore, the specific enzyme assay should be performed for reliable diagnosis. The enzyme can be measured in leukocytes, serum and fibroblasts. Measurement in the fibroblasts is the gold standard, although most often measuring in leukocytes suffices. Recently measuring the enzyme in blood collected on filter paper (DBS, dried blood spot), has gained importance, as the enzyme stays stable and the sample is easy to collect and transport.
- iv. In affected subjects, the enzyme activity is less than 5% of mean normal, while in Gaucher disease the cut off is often taken as 10%. In all cases if doubt molecular studies are carried out.
- v. Tandem mass spectrometry is increasingly being applied for the diagnosis of LSDs. The equipment is costly, but a single

**Flow chart 1** Algorithm for diagnosis of lysosomal storage disorders

Modified from Staretz-Chacham, et al. *Pediatrics*. 2009

blood spot can be used to diagnose many LSDs. It is indeed a useful technique, and is also being applied for diagnosis of LSDs in the newborn.

- vi. Molecular analysis and demonstration of the mutation in the specific gene is the definitive test. It also provides genotype-phenotype information, and is useful for genetic counseling, carrier screening and prenatal diagnosis.
- vii. Some individuals show greatly reduced enzyme activity but remain clinically healthy. This condition is called enzymatic *pseudodeficiency* (PD). It has been identified in at least nine lysosomal enzymes, including: arylsulphatase A (ARSA gene),  $\beta$ -hexosaminidase (HEXA gene),  $\alpha$ -iduronidase (IDUA gene),  $\alpha$ -glucosidase (GAA gene),  $\alpha$ -galactosidase (GLA gene),  $\beta$ -galactosidase (GLB1 gene),  $\alpha$ -fucosidase (FUCA1 gene) and  $\beta$ -glucuronidase (GUSB gene). The most common among these is the arylsulphatase A (ASA) pseudodeficiency which has a frequency of 7.3–15 %. Subjects with neurological symptoms and homozygous for arylsulphatase A Pd are likely to be misdiagnosed as MLD. It is, therefore, necessary to perform a combination of enzymatic and molecular analyses to determine the actual genetic make-up of MLD patients and their family members, in order to distinguish individuals carrying Pd alleles from those carrying MLD alleles.

#### Activator Proteins

Another complication that can potentially lead to missed diagnoses is represented by defects of cofactors required for the function

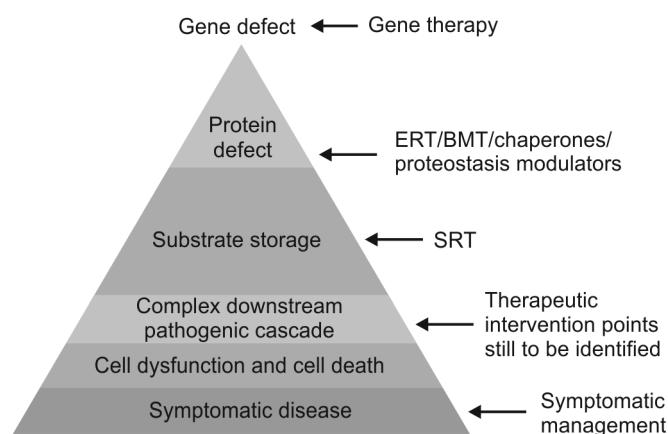
of certain lysosomal enzymes involved in glycosphingolipid breakdown. Variant forms of GM2 gangliosidosis, Krabbe disease, MLD and Gaucher disease can result not only from a deficiency of an enzymatic activity, but also from defects of sphingolipid activator proteins or saposins. In these cases, conclusive diagnosis requires a comprehensive evaluation based on neuroradiological, neurophysiological, biochemical/enzymatic and molecular tests. Conversely, if affected subjects with a clinical/paraclinical picture resembling some glycosphingolipidoses show normal activity of the relevant lysosomal enzyme, they should be evaluated for a defect of an activator protein.

#### TREATMENT

Lysosomal storage disorders require a multidisciplinary, team approach to treatment. Comprehensive management generally combines disease-specific therapy with symptom-specific measures. Apart from enzyme replacement therapy taking care of nutrition, and administering iron and vitamin D, and correcting other deficiencies improves the outlook. Orthopedic and neurologic advice should be available. There have been significant advances in therapy for LSDs in the past two decades. These are depicted in **Figure 4**. Details are provided in the section on respective disorders.

#### Enzyme Replacement Therapy (ERT)

This is the single most significant therapeutic advance. The critical element for success of ERT was the recognition that the



**Figure 4** The pyramid of therapy for LSDs  
Adapted from Platt, *Nature* 2014.

enzymes use a mannose-6-phosphate receptor to enter into the macrophages. ERT was first developed for type 1 Gaucher disease. Initially, the therapeutic enzyme was derived from placental tissue, but subsequently it has been manufactured by recombinant DNA technology. Later on, ERT was developed for Fabry disease, Pompe disease, MPS 1, MPS 2, and for MPS VI. Clinical trials are ongoing for enzyme therapies for  $\alpha$ -mannosidosis, Wolman cholesteryl storage disease, Morquio syndrome (MPS IV A) and Niemann-Pick disease B. ERT is usually given to the patients by intravenous route every week or every 2 weeks. ERT has changed the life of many individuals with LSDs, especially where there is no neurologic involvement.

Important challenges to ERT remain: (i) Production of antibodies to the administered enzyme. Many patients do not produce native enzyme (CRIM negative and cross-reacting immunologic material negative); or make native enzyme that differs significantly from administered enzyme, and consequently make antibodies to the exogenous enzyme, which may reduce efficacy and often causes adverse infusion reactions; (ii) ERT has to be given lifelong, and the cost is prohibitive. Thus, only a few patients have access to ERT. In most countries, the Government or the insurance companies cover the cost, but this is a great limitation for use of ERT in developing countries; (iii) The lysosomal enzymes do not cross the blood-brain barrier, so these cannot be used in the presence of significant brain disease.

### Bone Marrow Stem Cell Transplantation

Bone marrow transplantation (BMT) from healthy HLA-matched donors has been used for therapy in Gaucher disease, and other LSDs in the presence of neurologic involvement. In the latter instance, to be effective, it has to be carried out in early stage of the disease before severe neurologic disease has set it in. After BMT, some donor-derived monocytes enter the CNS and serve as local sites of normal enzyme production, which can be taken up by nearby host cells. BMT has been successful in cases of MPS1, provided it is performed before 2 years of age.

### Substrate Reduction Therapy

Substrate reduction therapy (SRT) with oral small molecule miglustat (imino sugar drug) has been used for treating LSDs. Miglustat inhibits the Golgi enzyme, glucosylceramide, and it reduces the synthesis of glycosphingolipids, thereby reducing

substrate requiring lysosomal catabolism and reducing storage. This drug is approved for type 1 Gaucher disease. Miglustat also crosses the blood-brain barrier, hence, it proved useful in treating Niemann-Pick type C disease. Its primary side effect is the development of gastrointestinal symptoms, due to the inhibition of disaccharidases. The more recent molecule to be approved in this category, eliglustat tartrate, has shown good effect in the treatment of type 1 Gaucher disease as an oral substrate reduction therapy. It has also proved beneficial in bone disease in Gaucher disease. However, it does not cross blood brain barrier. Preliminary studies have shown this to be as effective as ERT, and the future therapy with this drug will be watched with great interest. However, for SRT to reduce lysosomal storage, there must be residual enzyme activity, which is always the case in GD but not in other disorders.

### Gene Therapy

The only cure for any single gene disorder is gene therapy. LSDs are attractive candidates for gene therapy because lysosomal enzymes are secreted and recaptured by neighboring cells so that not every cell needs transducing. However, so far, this form of therapy has not yet reached routine clinical practice. Proof-of-concept studies have shown efficacy in animal disease models. Gene therapy would have to be given early before irreversible CNS pathology has occurred. It would have to be given intravenously to correct both peripheral tissues and the CNS, and the body organs. However, many hurdles must be overcome before gene therapy can be applied to the LSDs including delivery to the correct cells, random integration, sustained expression and immune reactions.

### Chaperon Therapy

Oral small molecule chaperones are compounds that improve the folding and trafficking of lysosomal proteins with specific missense mutations. Folding allows to bypass the endoplasmic reticulum (ER) quality-control system, and enhances their trafficking to Golgi and lysosomes, which ultimately raises residual enzyme activity. Clinical trials for Fabry disease are underway. Ataluren causes the ribosome to read through nonsense codons and yet allows the ribosome to end translation normally at the correct stop codon. This drug currently is being tested in other disorders and could be useful for some patients with LSDs caused by nonsense mutations.

## PREVENTION

### Genetic Counseling and Prenatal Diagnosis

In developing countries, counseling regarding mode of inheritance and risk of recurrence is important, so that the parents can opt for prenatal diagnosis in future pregnancies in order to avoid having another affected child, so as to reduce the burden of the disease.

### Newborn Screening

This is being done in LSDs as, for therapy to be effective, it has to be given early before irreversible changes have occurred. This is especially important for classical Pompe disease that manifests with cardiomegaly in infancy. Many patients with LSD remain undiagnosed till a later age, so that a second affected child is often born before the first is diagnosed. Newborn screening also provides information regarding the incidence of the disorder in the population, which is so critical for public health approach to the problem of LSDs.



### IN A NUTSHELL

1. Storage disorders are complex groups of disorders with heterogeneous clinical and biochemical features.
2. Most present chronically with multisystem involvement and pediatricians are likely to come across these cases in clinical practice.
3. In most disorders, diagnosis is made by enzyme assays but it is preferable to confirm the diagnosis by mutation testing.
4. Most are inherited in autosomal recessive manner and prenatal diagnosis is possible.
5. Promising and proven therapies are already in clinical use for some LSDs and more are likely to be available in the near future.

### MORE ON THIS TOPIC

- Boustany RMN. Lysosomal storage diseases—the horizon expands. *Nat Rev Neurol*. 2013;9:583-98.
- Filocamo M, Morrone A. Lysosomal storage disorders: Molecular basis and laboratory testing. *Human Genomics*. 2011;5:156-69.
- Maxfield FR. Role of endosomes and lysosomes in human disease. *Cold Spring Harb Perspect Biol*. 2014;6:a016931.
- Sheth J, Mistri M, Sheth F, et al. Burden of lysosomal storage disorders in India: experience of 387 affected children from a single diagnostic facility. *JIMD Rep*. 2014;12:51-63.
- Mehta A, Beck M, Linhart A, et al. History of lysosomal storage diseases: an overview. In: Mehta A, Beck M, Sunder-Plassmann G. *Fabry Disease: Perspectives from 5 Years of FOS*. Oxford: Oxford PharmaGenesis; 2006.
- Platt FM, Boland B, van der Spoel AC. Lysosomal storage disorders: The cellular impact of lysosomal dysfunction. *J Cell Biol*. 1999;5:723-34.
- Platt FM. Sphingolipid lysosomal storage disorders. *Nature*. 2014;510:68-75.
- Staretz-Chacham O, Lang TC, LaMarca ME, et al. Lysosomal storage disorders in the newborn. *Pediatrics*. 2009;123:1191-207.
- Wang RY, Bodamer OA, Watson MS, Wilcox WR, on behalf of the ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases: Diagnostic confirmation and management of presymptomatic individuals. *Gen in Med*. 2011;13:457-84.
- Weinreb NJ. Oral small molecule therapy for lysosomal storage diseases. *Pediatr Endocrinol Rev*. 2013;11Suppl 1:77-90.
- Yew NS, Cheng SH. Gene therapy for lysosomal storage disorders. *Pediatr Endocrinol Rev*. 2013;11Suppl 1:99-109.

## Chapter 3.9

# GM1 and GM2 Gangliosidosis

Parag M Tamhankar

Gangliosidosis are a group of autosomal recessive genetic disorders caused by accumulation of substances known as ganglioside. These include Tay-Sachs disease, Sandhoff disease, GM2 activator deficiency and GM1 gangliosidosis caused by mutations in *HEXA*, *HEXB*, *GM2A* and *GLB1* genes, respectively. The first three genes are necessary for normal catabolism of GM2 ganglioside and the *GLB1* is important for catabolism of GM1 ganglioside. These disorders are characterized by progressive neurological deterioration with early childhood forms proving fatal. These diseases have been naturally found in animals.

## EPIDEMIOLOGY

Gangliosidoses are panethnic diseases. However, incidence varies in different population groups. Tay-Sachs disease is the most frequent disorder in this group with founder mutations accounting for high incidence in communities or geographic regions with high inbreeding. Before community-based screening programs, 1 per 2,500–3,500 newborns in the Ashkenazi Jews was affected. In the general population, the carrier rate is estimated to be 1/258. The incidence of Sandhoff disease is approximately 1 per 3,10,000 non-Jewish newborns and 1 per 1 million Jewish newborns. The incidence of GM1 gangliosidosis is estimated to be 1:100,000–1:200,000 livebirths. High prevalence has been found in Malta and Brazil, and in the Cypriot and Roma populations.

## ETIOPATHOGENESIS

A ganglioside is a molecule composed of glycosphingolipid (ceramide and oligosaccharide) with one or more sialic acids (e.g., N-acetyl neuraminic acid) linked on the sugar chain. They are predominantly found in the nervous system where they constitute 6% of the phospholipids. They are present on cell surface, with the oligosaccharide groups projecting into extracellular space. They are thought to be involved in neuritogenesis, synaptogenesis, neuronal differentiation and regeneration, cell-to-cell interactions and to act as receptors for certain hormones and bacterial toxins. The gangliosides are stepwise degraded in the lysosomes from GM1 to GM3 into ceramides by sequential removal of sugar units in the oligosaccharide group. Glycohydrolases such as  $\beta$ -galactosidase (GM1-GM2 breakdown) and hexosaminidase (Hex) A (GM2-GM3 breakdown) are needed. Deficiency of  $\beta$ -galactosidase which removes the terminal galactose leads to GM1 gangliosidosis. The hydrolysis of GM2-ganglioside requires three gene products. Whereas two of these are the  $\alpha$ -(*HEXA*) gene and  $\beta$ -(*HEXB*) subunits of  $\beta$ -hexosaminidase A, the third is a small glycolipid transport protein, the GM2 activator protein (GM2A), which acts as a substrate-specific cofactor for the enzyme. A deficiency of any one of these proteins leads to one of the three forms of GM2-gangliosidosis, Tay-Sachs disease, Sandhoff disease or the AB-variant form.

Neuropathological features observed include widespread neuronal degeneration characterized by varying degrees of swelling, cytoplasmic vacuolation, loss of Nissl bodies and margination of nuclei. The accumulated ganglioside stains Periodic acid-Schiff positive. The exact mechanisms that translate the accumulation of gangliosides in neuronal cells to cell death are yet to be determined. One hypothesis links the activation of inflammatory pathway by the accumulating lipids leading to microglial and astrocyte activation, neuronal cell death and reactive gliosis.

## CLINICAL FEATURES

Gangliosidoses can be clinically classified as per age of onset of symptoms; type I: classical acute forms (infantile), type II: subacute (late infantile and juvenile forms) and type III: chronic forms (adult onset).

Children with *acute form* are usually normal until 3–6 months of age, at which time motor weakness, hypotonia, poor head control and decreasing attentiveness begin to cause parental concern. One of the earliest universal signs noticed by parents in infantile Tay-Sachs disease includes an exaggerated startle reaction to sharp (not necessarily loud) sounds, characterized by blinking of eyes, sudden extension of head, with or without extension of arms and legs. This sign is less frequent in other gangliosidoses. *Cherry red spot* sign is seen on ophthalmoscopy usually by 6 months of age. The sign is produced due to macular pallor due to deposition of gangliosides in the ganglion cell layer, while the normal foveal pit which lacks ganglion cells, continues to retain its reddish appearance. By the end of first year, motor skills previously developed are completely lost. By 18 months, signs of lower and upper motor neuron involvement are evident. Progressive enlargement of head is a result of reactive gliosis. Seizures become more frequent. In the second year, further deterioration affects the swallowing and gag reflexes, necessitating tube feeding. Frequent bronchopneumonia may result and is usually antecedent to death.

Infantile GM1 gangliosidoses and Sandhoff disease may have hepatosplenomegaly, skeletal involvement in form of dysostosis multiplex and extensive and unusually persistent skin Mongolian spots as differentiating features from Tay-Sachs disease. GM1 gangliosidoses cases also have coarse facies, gum hypertrophy and corneal clouding. Angiokeratomas and cardiomyopathy (dilated or hypertrophic) can also occur in infantile GM1 gangliosidoses. **Figures 1A to G** show a 9-month-old child with GM1 gangliosidosis.

Subacute forms present around 2–6 years of age with motor ataxia. Neuroregression may lead to death at around 10–15 years of age. Adult forms can present from 3 years to 30 years of age with abnormalities of gait and posture. Symptoms of spinocerebellar ataxia and lower motor neuron dysfunction, such as weakness, wasting, cramps and fasciculations predominate. Movement disorders, such as dystonia and dyskinesia occur in 50% of all patients. Ocular findings include saccade abnormalities and gaze palsy. Schizophrenic symptoms with slow personality disintegration and episodic depression are present in one-third of patients. Patients usually survive into their third to fourth decade of life. As compared to the acute forms, cherry red spots are infrequent in juvenile forms and rare in adult forms of the disease. Clinical variability even within the same family is significant. They may be misdiagnosed as spinal muscular atrophy, or atypical Friedreich ataxia.

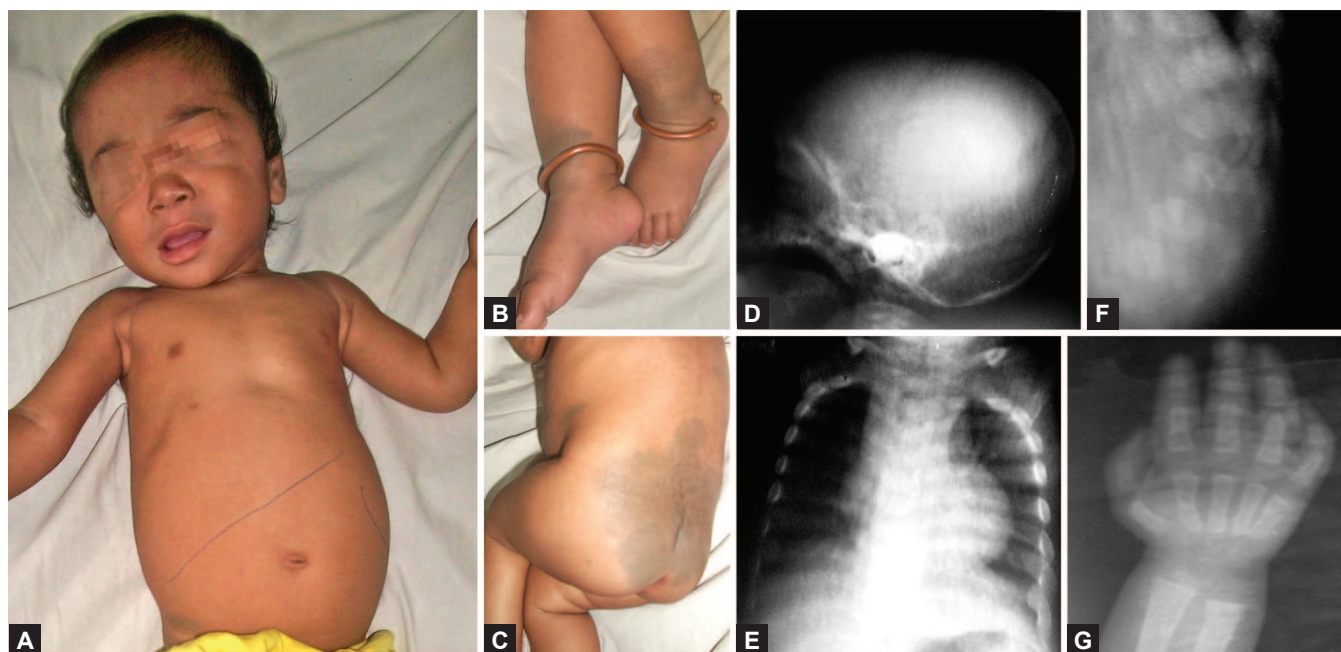
## Differential Diagnoses

Cherry red spots can occur in Niemann-Pick disease types A, B and C, sialidosis type I and II, mannosidosis, Farber lipogranulomatosis, central retinal artery occlusion and retinal edema secondary to trauma.

## INVESTIGATIONS

### Neuroimaging

Findings in gangliosidoses include thalamic lesions that are bilateral, diffuse hypointense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI images and hyperintense on T1-weighted images. Magnetic resonance spectroscopy may reveal decreased N-acetyl aspartate peak through deep gray matter structures suggestive of neuronal loss or dysfunction. White matter changes may occur late in disease as a result of secondary



**Figures 1A to G** (A) A 9-month-old child with GM1 gangliosidosis with mild coarsening of facial features, abdominal distension due to liver, spleen enlargement; (B and C) Extensive Mongolian spots; (D) Dysostosis multiplex including enlarged sella turcica; (E) Oar-shaped ribs; (F) Ovoid vertebral bodies; (G) Broad, proximally pointed bones of the hand. This child had absent  $\beta$ -galactosidase enzyme activity in leukocytes

demyelination following cortical neuronal death and axonal deterioration. They are demonstrated as homogenous or patchy T2 hyperintensity within frontal, temporal, occipital regions and periventricular white matter. Proton magnetic resonance spectroscopy may reveal progressive elevation in myoinositol : creatine ratios within white matter, gray matter and the thalamus. This signifies increased glial cell proliferation.

### Biochemical Diagnosis

This is based upon result of lysosomal enzyme assays, such as beta galactosidase assay for GM1 gangliosidosis and Hex assays for GM2 gangliosidoses. These assays are based on the hydrolysis of synthetic substrates releasing 4-methylumbelliferone producing fluorescence that can be measured. These assays can be performed on leukocytes, serum, plasma, cultured fibroblasts, amniocytes or chorion villus samples.

GM2 gangliosidoses are diagnosed using Hex assays. There are two major Hex isozymes in normal human tissue. Hex A is a heterodimer, alpha-beta, whereas Hex B is a homodimer, beta-beta. Tay-Sachs disease patients have decreased Hex A activity and normal or elevated Hex B activity. Sandhoff patients have decrease in both Hex A and Hex B activities, whereas GM2 activator deficiency patients will have normal Hex A and Hex B activities. Activities found for acute, subacute and chronic patients were  $\leq 0.1\%$ ,  $0.5\text{--}1\%$ , and  $1\text{--}4\%$  of normal controls, respectively.

Although reasonably accurate, the biochemical assays have limitations. As many as 10% of samples can lie in an indeterminate zone range in which carriers and noncarriers overlap. The calculated percentage of hex A is falsely reduced leading to being labeled as a carrier. This can be avoided using leukocyte (which does not contain HEX P) hex assay instead of serum/plasma. In about one-third of non-Jewish population, the enzyme levels may be falsely deficient in normal individuals. Pseudodeficiency is a phenomenon in which normal individuals may be detected as having enzyme deficiency due to failure to lyse artificial substrate but normal in vivo hex activity.

### DNA-based Tests

These can confirm the clinical and biochemical diagnosis. *GLB1* gene (3p22.3), *HEXA* gene (15q24.1), *HEXB* gene (5q13.3) and *GM2A* (5q33.1) are the only genes associated with GM1 gangliosidosis, Tay-Sachs disease, Sandhoff disease and GM2 activator deficiency, respectively. Polymerase chain reaction based techniques such as amplification refractory mutation screen, dot-blot hybridization, etc. for common mutations and Sanger sequencing covering all exons and exon-intron boundaries for identifying uncommon or novel mutations are employed. Southern blot or multiplex ligation-dependent probe amplification techniques are used to identify unknown large deletions or duplications that cannot be identified by Sanger sequencing. The frequency of mutations varies according to populations. In India, a founder mutation E462V was identified in infantile Tay-Sachs disease patients from Gujarat. Most SD mutant alleles are nonrecurrent. Exceptions include R284X, a panethnic mutation hotspot in *HEXB* gene and *c.445+1G>A*, a founder mutation in SD patients from Cordoba, Argentina.

### MANAGEMENT

At present, only symptomatic treatments are available for GM1 and GM2 gangliosidosis. Bone marrow replacement has been used in animal models and individual patients but has achieved mixed results. Enzyme replacement therapies are not applicable to gangliosidoses because of inability to penetrate the blood-brain barrier. Miglustat is a reversible inhibitor of glucosylceramide synthase, the enzyme that catalyzes the first committed step in the synthesis of lacto- and globo-series glycolipids. Miglustat [N-butyldeoxynojirimycin (NB-DNJ)] is licensed for the treatment of adult patients with mild-to-moderate type 1 Gaucher disease for whom enzyme replacement therapy is unsuitable or not a therapeutic option. It has specific physicochemical properties that facilitate wide tissue distribution, including the brain. In vivo studies have demonstrated the ability of miglustat to prevent storage of GM2 ganglioside in the peripheral tissues and central

nervous system of mouse models of TSD and Sandhoff disease. Miglustat has also been used for chronic GM2 gangliosidosis type Sandhoff.

A growing body of evidence suggests that misfolding of a mutant protein followed by its aggregation or premature degradation in the endoplasmic reticulum is one of the main mechanisms that underlie inherited neurodegenerative diseases, including lysosomal storage diseases. Chemical or pharmacological chaperones are substrate analog competitive inhibitors bind to and paradoxically stabilize mutant lysosomal enzyme proteins in the endoplasmic reticulum, enter the lysosome and restore catalytic activity of mutant enzyme after spontaneous dissociation under acidic conditions. A number of chaperone compounds for lysosomal hydrolases have been identified in the last decade. They have gained attention because they can be orally administered, and also because they can penetrate the blood-brain barrier. Several chemical chaperones investigated in vitro include galactose, fluorouracil, iminoalcohols and valienamine derivatives, N-octyl-4-epi- $\beta$ -valienamine and N-octyl- $\beta$ -valienamine in GM1 gangliosidosis, pyrimethamine in Sandhoff disease.

## PROGNOSIS

The infantile and juvenile cases are relentlessly progressive, leading to early death. Chronic or adult cases also have reduced life expectancy but may have improved survival with good supportive care.

## PREVENTION

Gangliosidoses are autosomal recessively inherited genetic disease. The recurrence risk in progeny of carrier couples is 25%. Prenatal diagnosis is possible by performing enzyme assays or DNA tests on fetus but prerequisites include biochemical and/or molecular confirmation in the carrier couple. Carrier diagnosis can be performed using leukocyte enzyme assays (70% sensitive) and molecular assays (99%). Primary prevention of Tay-Sachs disease has been demonstrated by community screening in high-risk populations.

## IN A NUTSHELL

1. Gangliosidoses are characterized by cherry red spot, progressive neurological regression, liver/spleen enlargement (GM1 and storage diseases), and skeletal dysostoses (GM1).
2. Lysosomal enzyme assays employing artificial substrates [4-methylumbelliferyl N-acetylglucosamine (MUG, MUGS)] can diagnose these disorders with more than 90% sensitivity. Sulfated substrate (MUGS) is needed to diagnose B1 variant.
3. Advantage of molecular tests over biochemical is the ability to diagnose pseudodeficiency and AB variant (GM1 activator deficiency).
4. Treatment is still in drug designing or preclinical stage.
5. Preventive strategies to reduce incidence are possible by carrier detection and prenatal diagnosis, which remains the focus of management.

## MORE ON THIS TOPIC

- Caciotti A, Garman SC, Rivera-Colón Y, et al. GM1 gangliosidosis and Morquio B disease: an update on genetic alterations and clinical findings. *Biochim Biophys Acta*. 2011;1812:782-90.
- Mistri M, Tamhankar PM, Sheth F, et al. Identification of novel mutations in HEXA gene in children affected with Tay-Sachs disease from India. *PLoS One*. 2012;7:e39122.
- Ohno K, Saito S, Sugawara K, Sakuraba H. Structural consequences of amino acid substitutions causing Tay-Sachs disease. *Mol Genet Metab*. 2008;94:462-8.
- Sandhoff K, Harzer K. Gangliosides and gangliosidoses: principles of molecular and metabolic pathogenesis. *J Neurosci*. 2013;33:10195-208.
- Shapiro BE, Pastores GM, Gianutsos J, et al. Miglustat in late-onset Tay-Sachs disease: a 12-month, randomized, controlled clinical study with 24 months of extended treatment. *Genet Med*. 2009;11:425-33.
- Sheth J, Mistri M, Sheth F, et al. Burden of lysosomal storage disorders in India: experience of 387 affected children from a single diagnostic facility. *JIMD Rep*. 2014;12:51-63.
- Stenson PD, Ball EV, Howells K, et al. The Human Gene Mutation Database: providing a comprehensive central mutation database for molecular diagnostics and personalized genomics. *Hum Genomics*. 2009;4:69-72.
- Verma PK, Ranganath P, Dalal AB, Phadke SR. Spectrum of lysosomal storage disorders at a medical genetics center in northern India. *Indian Pediatr*. 2012;49:799-804.



## Chapter 3.10

# Gaucher Disease

Mamta Muranjan

Gaucher disease is the most common and one of the most extensively studied lysosomal storage disorder. It is a lifelong multisystemic disease demonstrating marked clinical heterogeneity. It is an autosomal recessive condition that results from mutations of the glucosidase, beta, acid (*GBA1*) gene located on chromosome 1q21. More than 400 mutations of the *GBA1* gene (MIM no. 606463) have been identified to date. The gene codes for the lysosomal membrane-bound protein, the enzyme acid  $\beta$ -glucocerebrosidase (EC 3.2.1.45). Sources of glucocerebroside differ among tissues. In the visceral organs, it is derived from cell membranes of senescent red and white blood cells and platelets that contain glycosphingolipids, whereas the source in the central nervous system (CNS) is gangliosides. Those with non-neuronopathic Gaucher disease have sufficient residual enzyme activity to degrade ganglioside-derived glucosylceramide and, hence, lack substrate accumulation in the brain.

### EPIDEMIOLOGY

Gaucher disease is panethnic with a global prevalence of 1 in 40,000 to 1 in 60,000. The highest frequency of Gaucher disease is amongst Ashkenazi Jews with an incidence of 1 in 855 and a carrier frequency of 1 in 18. In India, Gaucher disease is frequent among the tribal population of Mappila Muslims of Kerala.

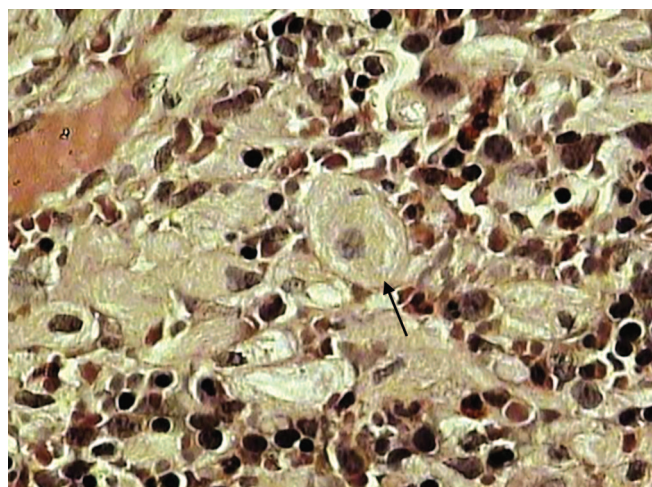
The N370S allele accounts for almost 70% of disease alleles in Ashkenazi Jews. This along with four other alleles (L444P, 84insG and IVS2+1G>A and R463C) account for 90% of the mutations. The L444P allele is the most common worldwide. From the limited published data on genotype of Indian patients with Gaucher disease, the L444P mutation is the single most common mutation in 63% while the N370S mutation is rare. Molecular analysis of 58 patients with Gaucher disease, from three centers in India (Center for Human Genetics, Bangalore; KEM Hospital, Mumbai and Amrita Institute of Medical Sciences and Research, Kochi) revealed homozygous L444P genotype in 58%. In Japanese and East Asian patients, the frequency of L444P mutation is 50%, indicating higher proportion of neuronopathic disease.

Geographic and probably ethnic differences in manifestations are also observed. Jewish and European populations have onset of symptoms of type 1 disease in late childhood or adult life. The predominant symptoms are visceral, hematological and skeletal. In contrast, Asian, Chinese and Indian patients have early onset of severe visceral, hematological and neurological symptoms.

### PATHOPHYSIOLOGY

The pathophysiology of Gaucher disease is a complex interplay of several mechanisms which includes infiltration of viscera by storage cells, macrophage activation by glucosylceramide storage, production of deleterious complex glycolipids like glucosyl-sphingosine, perturbed microenvironment, focally compromised microvasculature, dysregulation of calcium homeostasis and misfolding and impaired intracellular trafficking of the mutant protein giving rise to the unfolded protein response which leads to activation of inflammation/apoptosis.

Glucosylceramide accumulates within the macrophages and transforms them into the pathognomonic storage cells—the Gaucher cell (**Fig. 1**). This is a large uninucleate or multinucleate cell measuring 20–100  $\mu$ m in diameter. The nucleus is small, round



**Figure 1** Gaucher cells (arrow) in the bone marrow

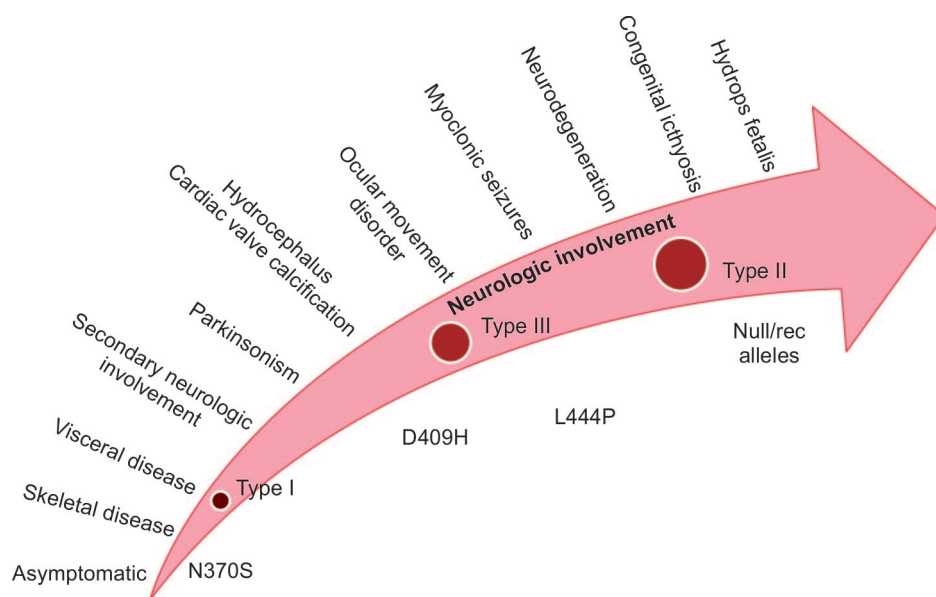
or oval and eccentric and the cytoplasm is abundant, staining pale pink with hematoxylin and eosin with delicate striations producing *crumpled silk* or *wrinkled tissue paper* appearance. The storage material stains positive with periodic acid-Schiff. The Gaucher cells infiltrate the bone marrow medullary cavity, liver, spleen, lungs, lymph nodes and rarely the kidney. In contrast, the pathology in the CNS is neuronal death.

### CLINICAL MANIFESTATIONS

Traditionally, the clinical phenotypes of Gaucher disease were classified into three major groups based on the presence and severity of neurological symptoms. Absence of neurological involvement was characteristic of type 1 disease. Type 2 disease (formerly acute neuronopathic variant) has an onset of severe neurological symptoms in early infancy and death by 2 years of age, whereas type 3 disease (formerly chronic neuronopathic variant also known as the Norrbottnian type after the description in the Norrbotten region in North Sweden) had a variable age of onset of neurological symptoms, rate of progression and life span. The incidence, distinguishing clinical features and life span of the three major phenotypes are presented in **Table 1**.

Recent insights have expanded the knowledge of clinical variants of Gaucher disease, which is now considered to have an overlapping clinical spectrum (**Fig. 2**) ranging from asymptomatic individuals or delayed onset of symptoms in the eighth or ninth decades of life to severe perinatal/lethal variant of type 2 disease with in utero manifestations. Presymptomatic children may be diagnosed through newborn screening or because of an affected sibling with Gaucher disease. Research has also revealed an increased frequency of late onset parkinsonism in homozygous individuals with type 1 Gaucher disease and in heterozygous carriers. Brain pathology has shown astrogliosis, abnormalities in the hippocampal regions and  $\alpha$ -synuclein reactive Lewy bodies in the brain of individuals with Gaucher disease and parkinsonism.

Study of mutations in Gaucher disease has revealed a phenotype-genotype correlation. The N370S mutation in homozygous or heterozygous state confers protection from neurological disease, whereas the L444P mutation predicts neurological disease. In type 2 disease, the L444P mutation occurs in heterozygous state with null or recombinant complex mutations, whereas L444P mutation in the homozygous state predicts type 3 disease. Those homozygous for the N370S mutation have significant skeletal disease while typical symptoms like splenomegaly, hepatomegaly, anemia and thrombocytopenia are mild. The compound



**Figure 2** Spectrum of Gaucher disease: clinical continuum

Source: Adapted from figure available at [http://www.physio-pedia.com/index.php?title=Gaucher\\_Disease&oldid=35158](http://www.physio-pedia.com/index.php?title=Gaucher_Disease&oldid=35158).

**Table 1** Distinguishing features of the three phenotypic variants of Gaucher disease

Phenotypic variant	Type 1	Type 2	Type 3
<i>Prevalence</i>			
Worldwide	1 in 50,000 to 1 in 100,000	1 in 500,000	<1 in 50,000 to <1 in 100,000
Ashkenazi Jews	1 in 850		
Frequency (%)*	94	1	5
Age at onset of symptoms	Any age	<2 years of age	<2 years of age
Life span	6 to >80 years	2–4 years of age	3rd–4th decade
Hepatosplenomegaly	Mild to severe	Moderate	Mild to severe
Hematologic abnormalities	Mild to severe	Severe	Mild to severe
Bone disease	Mild to severe	Very rare	Absent to severe
Neurological symptoms	Absent (exception: parkinsonism and secondary neurologic involvement)	Severe (bulbar and pyramidal signs, cognitive impairment)	Mild to severe (seizures, myoclonic epilepsy, oculomotor apraxia)

\*Data from the International Collaborative Gaucher Group

heterozygous genotype of N370S/L444P results in severe type 1 disease. A cardiac variant of type 3 Gaucher disease is associated with homozygous D409H mutation.

### NON-NEURONOPATHIC (TYPE 1) GAUCHER DISEASE

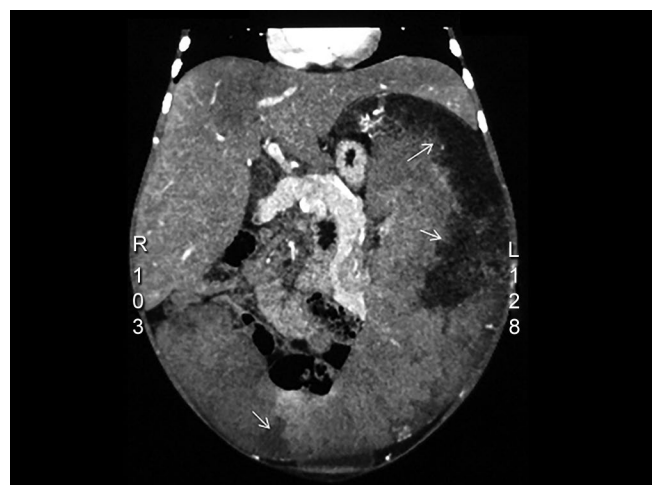
Type 1, formerly classified as adult-onset Gaucher disease, accounts for 94% of all individuals with Gaucher disease. However, 55–60% of these individuals are detected before 20 years of age and 30% before 10 years of age. The younger the age at presentation, the

more rapid the disease progression and greater is the severity in terms of hematological and visceral symptoms and bone disease.

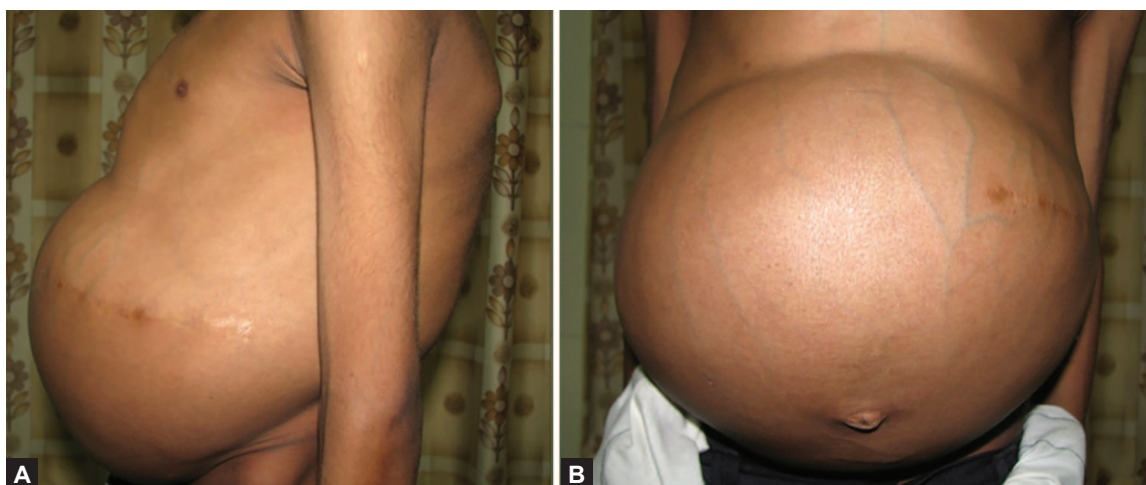
### Visceral Involvement: Splenomegaly and Hepatomegaly

More than 80% of children have enlarged liver and spleen at the time of diagnosis. Moderate to severe splenomegaly is noted in 95% and 87% have moderate to severe hepatomegaly. Splenomegaly is an almost consistent feature. Absence of splenomegaly, though unusual, does not exclude the diagnosis of Gaucher disease. It can be seen in older adults with N370S/N370S genotype.

Symptoms of splenic enlargement are abdominal distension, early satiety and dragging pain in the left hypochondrium. The spleen can enlarge more than five times the normal and median spleen volumes exceeding 20 times the normal have been observed (**Fig. 3**). The resultant hypersplenism causes pancytopenia and



**Figure 3** Abdominal CT scan of a 39-month-old showing massive splenomegaly reaching up to the pelvis with heterogenous appearance suggestive of infiltration due to Gaucher disease. There are subcapsular hypodense areas (arrows) representing multiple infarcts. The liver also shows diffuse infiltration



**Figures 4A and B** Hepatopulmonary syndrome in a 10-year-old boy with type 1 Gaucher disease, who had undergone splenectomy at 3 years of age followed by bone crisis. (A) Massive abdominal distension with a horizontal surgical scar below the left costal margin; (B) Dilated and tortuous veins over the anterior abdomen wall indicating presence of portal hypertension. He died at 10 years of age following an acute intracranial hemorrhage

aggravates anemia and thrombocytopenia. Focal defects in the spleen are known to occur in 20% of cases and are attributed to focal infiltration by Gaucher cells or infarcts. Infarcts manifest with acute abdominal pain. Rupture of the spleen is rare.

Earlier, splenectomy was performed for massive symptomatic splenomegaly (**Fig. 4A**) but is now obsolete with availability of enzyme replacement therapy. Gaucher disease is sometimes first diagnosed by finding Gaucher cells on histopathological examination of the surgically removed spleens. Splenectomy invariably leads to severe accelerated disease in the liver, lungs and skeleton.

The magnitude of liver enlargement is less as compared to the spleen. Median liver size of more than 2 times the normal have been observed. Hepatic fibrosis, cirrhosis, portal hypertension (**Fig. 4B**) with ascites and esophageal varices and hepatic failure are rare. Manifestations of dyspnea, cyanosis and clubbing would suggest development of hepatopulmonary syndrome.

### Hematological Involvement

Anemia and thrombocytopenia are the hallmarks of Gaucher disease affecting 40% and 50% of children, respectively. Anemia presents with pallor, fatigue and congestive heart failure. Periodic blood transfusions are required, especially when hypersplenism coexists. Iron and vitamin B<sub>12</sub> deficiency are common in India and may contribute to the anemia. Thrombocytopenia would be symptomatic with petechiae, epistaxis, gum bleeds, bruising and bleeding associated with trauma, surgery or menorrhagia. Abnormal platelet aggregation and low-grade disseminated intravascular coagulopathy contribute to bleeding manifestations in Gaucher disease. Other hematological abnormalities include leukopenia and defective neutrophil function. A variety of acquired coagulation factor deficiencies have been described, namely fibrinogen, II, VII, VIII, X and XII.

### Skeletal Involvement

Recognition of bone involvement in Gaucher disease is suboptimal even though it is the most debilitating and disabling manifestation impairing quality of life. Radiologic bone disease is present in 81% of children with Gaucher disease, 27% had bone pain and bone crisis was observed in 9%. Significant bone disease can be asymptomatic

and does not correlate with severity of manifestations in other organs. Complex multifactorial mechanisms initiated by bone marrow infiltration, mediated by cytokines and perpetuated by interactions between osteoblasts/osteoclasts and immunological cells are implicated in the pathogenesis of bone disease. The various skeletal manifestations of Gaucher disease are described in **Table 2**.

Involvement of the skeleton by Gaucher disease is focal, local or generalized. Focal, irreversible pathology includes lytic or sclerotic bone lesions (**Fig. 5A**). Local, reversible disease includes lesions, such as cortical bone thinning, endosteal scalloping (**Fig. 5B**) and defective bone remodeling. Generalized bone involvement is in the form of osteopenia and osteoporosis (**Fig. 5B**). Plain radiographs may show osteopenia, cortical thinning and Erlenmeyer flask deformity of the distal femoral metaphysis in type 1 disease (**Fig. 6**). A manifestation of Gaucher disease unique in children is the impact on growth with suboptimal growth noted in 75% of children with 34–42% falling below the 5th percentile for height (**Fig. 7**). Pubertal delay has been observed in 60%.

Several unusual or atypical manifestations of Gaucher disease are being increasingly reported, contributing to the expanding spectrum. These are enumerated in **Table 3**.



**Figures 5A and B** Plain radiographs of the femur. (A) Osteopenia in the femur; (B) Osteopenia, cortical thinning and periosteal elevation (arrows) due to bone crisis



**Table 2** Skeletal abnormalities in Gaucher disease

<i>Nature of bone involvement</i>	<i>Description</i>	<i>Imaging modality of choice</i>
<i>Asymptomatic</i>		
Bone marrow infiltration	Begins in the lumbar spine, followed by metaphysis and diaphysis of the femur and humerus, epiphyses involved late	MRI
Osteopenia/reduction in BMD	Progressive, occurs at any age and in both genders, seen adjacent to areas of bone marrow infiltration but can be diffuse, contributes to risk of fractures and joint collapse	DEXA
Erlenmeyer flask deformity (Fig. 6)	Defect of remodeling, occurs in 59% of cases, distal femur and proximal tibia commonly affected, diaphyseal narrowing with widening of the metaphyseal end of long bones	Plain radiographs
<i>Symptomatic</i>		
Bone pain	Chronic, dull-aching nature	
Bone crisis/bone infarcts	Acute, prolonged episodes, initially dull aching and then excruciating; involved region is warm, swollen and tender, systemic signs of fever, leukocytosis and elevated erythrocyte sedimentation rate, sterile blood culture, often followed by osteonecrosis or fractures	MRI, plain radiographs may show periosteal elevation (Fig. 5B)
Osteomyelitis	Prone to osteomyelitis due to altered neutrophil chemotaxis or monocyte dysfunction, anaerobic organisms, often precipitated by surgical procedure	Bone scan
Osteonecrosis/avascular necrosis	Splenectomy and male gender are risk factors, medullary or subchondral (head of femur or humerus, proximal tibia and vertebral bodies are common sites, progresses to fracture and/or joint collapse, requires joint replacement surgery)	MRI Plain radiographs show increased bone density with medullary osteonecrosis
Pathologic fractures	Related to osteopenia, bone, infarcts, osteonecrosis and bone crisis	Plain radiographs

Abbreviations: MRI, magnetic resonance imaging; DEXA, dual-energy X-ray absorptiometry; BMD, bone mineral density.



**Figure 6** Plain radiographs showing osteopenia, cortical thinning and Erlenmeyer flask deformity of the distal femoral metaphysis and avascular necrosis of the right upper tibial epiphysis in a 10-year-old with type 1 Gaucher disease

## NEURONOPATHIC (TYPE 2) GAUCHER DISEASE

Typical type 2 disease manifests with hepatosplenomegaly, anemia, thrombocytopenia, oculomotor apraxia, seizures, bulbar signs (strabismus, stridor and dysphagia), and pyramidal signs (trismus, opisthotonus, neck retroflexion and spasticity);

(Figs 8A and B). The perinatal/lethal variant is rare. However, recognition and correct diagnosis are crucial for genetic counseling and prenatal diagnosis in subsequent pregnancies. The spectrum of manifestations includes nonimmune hydrops fetalis, lamellar ichthyosis, collodion membrane at birth, acute neonatal hepatic failure with hyperferritinemia, pulmonary hypoplasia, apnea, respiratory distress, hepatosplenomegaly, pancytopenia, arthrogryposis, facial dysmorphisms (low set ears, flat nasal bridge, anteverted nares and proptosis), microcephaly, poor sucking, stridor and opisthotonus. Death occurs in the first few weeks of life.

## TYPE 3 DISEASE

Type 3 disease progresses slowly. The clinical manifestations are hepatosplenomegaly, anemia, thrombocytopenia, bone and lung disease and variable severity of neurological symptoms. The mildest presentation is with failure of horizontal saccade initiation. Other characteristic neurological symptoms are vertical gaze palsy, slow tracking of objects and convergent squint. It is further classified into three subtypes: Type IIIa (mild visceral involvement but onset of neurodegeneration and severe myoclonic seizures in childhood); type IIIb (mild neurological involvement, horizontal gaze palsy and significant visceral and skeletal symptoms—chest deformity, kyphoscoliosis); (Figs 9A and B) and IIIc (cardiac variant), a distinct phenotype with ophthalmoplegia, calcification of the aortic valve and ascending aorta leading to congestive heart failure and arrhythmias, corneal opacities and hydrocephalus. The Norbottnian variant has mild cognitive impairment, oculomotor defects and progressive gibbus.



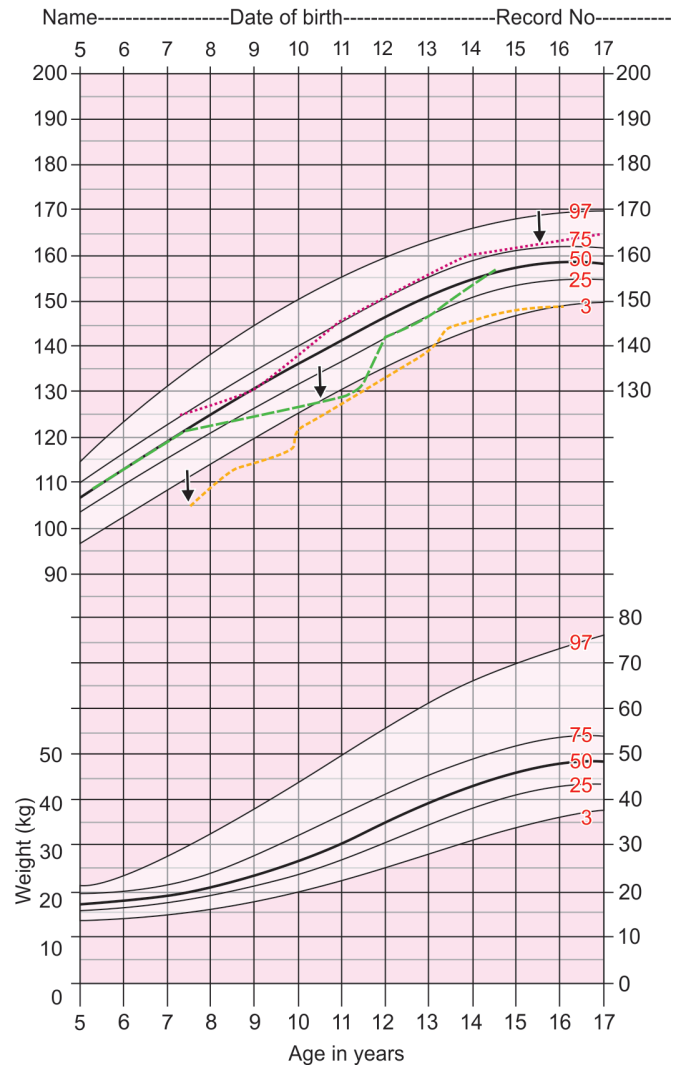
**Table 3** Atypical features of Gaucher disease

Pulmonary involvement	Interstitial lung disease, alveolar or lobar consolidation, pulmonary fibrosis, pulmonary hypertension
Kidney involvement	Infiltration of the interstitium and glomeruli, proteinuria, glomerulosclerosis, progressive renal insufficiency
Primary neurologic disease in Gaucher disease type 1	23-fold increased risk of Parkinson disease, positive family history for parkinsonism, typical and atypical parkinsonism, younger age at onset, respond inadequately to L-3,4-dihydroxyphenylalanine (L-DOPA)
Secondary neurologic disease in Gaucher disease type 1	Spinal cord or nerve root compression resulting from vertebral compression due to severe osteopenia, emboli following long bone fracture, or hematomyelia resulting from coagulopathy Peripheral neuropathy
Severe lymphadenopathy	Infiltration of lymph nodes by Gaucher cells mesenteric, retroperitoneal, inguinal and paraesophageal lymph nodes, trapping of intra-abdominal vasculature Persistently high chitotriosidase despite enzyme replacement therapy
Gaucheromas	Mass-like infiltration of Gaucher cells developing in the spleen, liver and bones
Protein-losing enteropathy	Diffuse leakage from intra-abdominal lymphatics due to obstruction
Cholelithiasis	Cholesterol gallstones
Immunologic abnormalities	Gammopathy (monoclonal or polyclonal) Monoclonal gammopathy of undetermined significance (MGUS) Decreased production of NK cells Reduction in number of normal dendritic cells Suboptimum T-cell function or proliferation Compromised IgM secretion
Malignancy	Multiple myeloma Hepatocellular carcinoma Non-Hodgkin's lymphoma Malignant melanoma Pancreatic cancer
Metabolic derangements	High resting energy expenditure Low circulating adiponectin and insulin
Heart	Thickening of aortic and mitral valve due to calcification Intramyocardial infiltration by Gaucher cells causing interstitial infiltrative fibrosis, dilated cardiomyopathy and low ejection fraction Recurrent pericarditis causing constriction Pericardial calcification
Amyloidosis	
Eye	Opacities over optic nerve head and retinal vessels, retinal thinning, macular atrophy, keratoconus

## DIFFERENTIAL DIAGNOSIS

Several diseases including other lysosomal storage disorders and hematological disorders have symptoms overlapping with Gaucher disease. The common differential diagnoses are tabulated in **Table 4**.

**Growth chart for Indian children**  
Weight-for-age and Height-for-age percentiles  
**Girls (5–17 years)**



**Figure 7** Growth trends in three girls with type 1 Gaucher disease before and after initiation of enzyme replacement therapy. Age at initiation of enzyme replacement therapy is marked by arrows. After initiation of enzyme replacement therapy, growth velocity has accelerated  
Source: Author's records.



**Figures 8A and B** Type 2 Gaucher disease. (A) Abdominal distension and umbilical hernia. Note the retroflexed posture of the neck; (B) Convergent squint and cachexia

**Table 4** Differential diagnosis of Gaucher disease

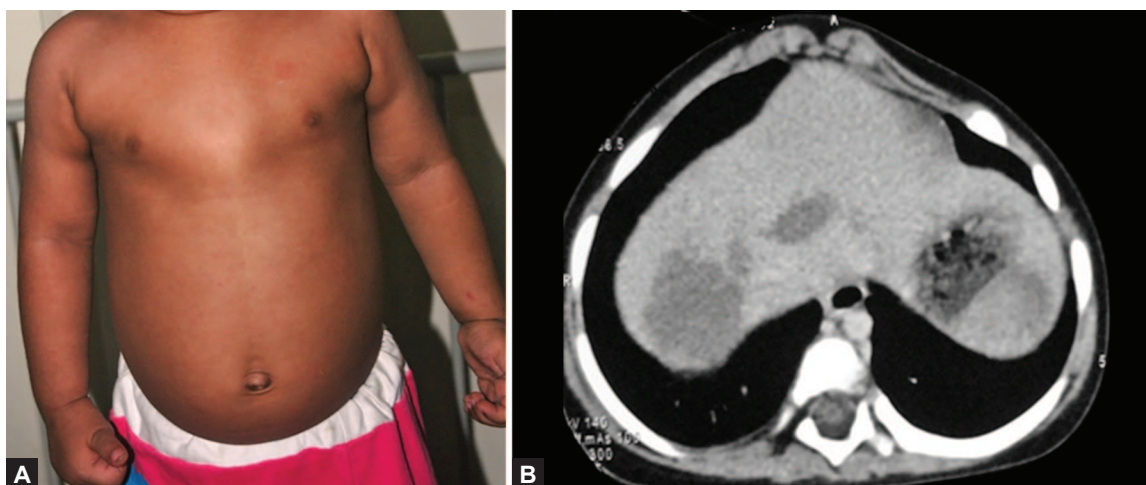
<i>Symptom complex mimicking Gaucher disease</i>	<i>Differential diagnosis</i>	<i>Distinguishing features in Gaucher disease</i>
Anemia Hepatosplenomegaly Horizontal gaze palsy Seizures including myoclonic seizures Pyramidal and cerebellar signs Gaucher cells in the bone marrow	Saposin C or prosaposin deficiency	Deficient $\beta$ -glucocerebrosidase activity ( $\beta$ -glucocerebrosidase activity is normal in Saposin C/prosaposin deficiency) Presence of pathogenic mutations in <i>GBA1</i> gene
Severe anemia Recurrent blood transfusions Hepatosplenomegaly Cells resembling Gaucher cells—pseudo-Gaucher cells in the bone marrow	Hemoglobinopathies	Disproportionately enlarged spleen in comparison to the liver, jaundice is uncommon Absence of characteristic red cell morphology on peripheral smear Manifestations of other organ involvement
Anemia Splenomegaly Hepatomegaly Abdominal pain Hypersplenism	Tropical splenomegaly	Presence of affected siblings Consanguinity Progressive splenomegaly not responding to antimalarial therapy Manifestations of other organ involvement Growth retardation Abdominal CT or MRI showing infiltration of the spleen and liver with or without infarcts or focal lesions
Severe anemia Thrombocytopenia Pancytopenia Bleeding manifestations Recurrent blood transfusions Hepatosplenomegaly Bone pains Cells resembling Gaucher cells—pseudo-Gaucher cells in bone marrow	Hematological malignancies <ul style="list-style-type: none"> <li>• Leukemia</li> <li>• Lymphoma</li> <li>• Myelodysplasia</li> </ul>	Leukopenia rather than very high white cell count Absence of blasts on peripheral smear Detection of characteristic Gaucher cell and absence of blast cells on bone marrow examination
Hepatosplenomegaly Psychomotor retardation Neurodegeneration Seizures Elevated chitotriosidase Chronic liver disease	Niemann-Pick disease type A/B GM1 gangliosidosis	Disproportionately enlarged spleen in comparison to the liver, absence of macular cherry red spot Detection of characteristic Gaucher cell and absence of histiocytes with foamy cells on bone marrow
Neonatal cholestasis Hepatosplenomegaly Psychomotor retardation Neurodegeneration Seizures Supranuclear ophthalmoplegia Mildly deficient $\beta$ -glucocerebrosidase activity Elevated chitotriosidase	Niemann-Pick disease type C	Disproportionately enlarged spleen in comparison to the liver, detection of characteristic Gaucher cell and absence of histiocytes with foamy cells on bone marrow
Hydrops fetalis	Several other lysosomal storage disorders like mucopolysaccharidosis, mucopolipidosis, sialidosis, GM1 gangliosidosis, Niemann-Pick disease type C, galactosialidosis, Farber disease and Wolman disease	Hepatosplenomegaly Absence of coarse facial features and dysostosis multiplex on radiographs Absence of vacuolated lymphocytes on peripheral blood smear Detection of characteristic Gaucher cell and absence of histiocytes with foamy cells on bone marrow
Osteonecrosis	Legg-Calve-Perthes disease	Multisystem involvement with hepatosplenomegaly and anemia, thrombocytopenia

## DIAGNOSTIC EVALUATION

Diagnosis is based on history to elicit typical symptoms. Family history for consanguinity and affected siblings should be obtained. Assessment on physical examination should include growth; skin for pallor, bruises and petechiae; abdomen for liver and spleen size; presence of clubbing and lymphadenopathy; heart, lungs, bones and neurological assessment. Undiagnosed splenomegaly and severe premature osteoporosis should be investigated for Gaucher disease.

## Bone Marrow Examination

This is not routinely required for diagnosis as reliable alternatives are available (enzyme activity and molecular diagnosis). Additionally, false-negative result is possible with bone marrow aspirate and false-positive result is obtained in the presence of pseudo-Gaucher cells. The latter can be found in a variety of disorders, such as multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma, myelodysplasia, sickle cell anemia, thalassemia, chronic myeloid leukemia and tuberculosis and other mycobacterial diseases. However, an indication for examining the bone marrow is for the



**Figures 9A and B** (A) Type 3 Gaucher disease with significant pectus carinatum; (B) CT scan of the chest showing pectus carinatum

diagnosis of hematological malignancies associated with Gaucher disease.

### Definitive Diagnosis

This is based on demonstration of deficiency of  $\beta$ -glucocerebrosidase activity or by detection of pathogenic mutations in the *GBA1* gene. A fluorimetric assay estimates  $\beta$ -glucocerebrosidase activity in peripheral white blood cells, skin fibroblasts, chorionic villus and cultured amniotic fluid cells using the artificial substrate 4-methylumbelliferyl- $\beta$ -D-glucopyranoside. Recently, tandem mass spectrometry based assay for  $\beta$ -glucocerebrosidase activity is available from dried blood spot specimens collected on a filter paper. Those with Gaucher disease have  $\beta$ -glucocerebrosidase activity 0–30% of normal. Borderline low enzyme activity in peripheral blood leukocytes needs confirmation by estimation of enzyme activity in skin fibroblasts. There is no correlation between degree of enzyme deficiency and disease severity or phenotype.  $\beta$ -glucocerebrosidase activity estimation is not accurate for identification of carriers. Carrier detection requires molecular analysis.

Identification of the genotype by molecular analysis is recommended in every individual with Gaucher disease. One approach is to perform targeted mutation analysis for the four common mutations (N370S, L444P, 84insG and IVS2+1G>A) followed by sequence analysis of the coding region of the *GBA* gene if no mutation or a single common mutation is identified. This will identify 99% of disease causing alleles.

Molecular analysis aids in discriminating neuronopathic from non-neuronopathic disease. This is particularly useful to discriminate between type 1 and type 3 disease in early childhood as the signs in childhood are identical in both and the characteristic eye signs of type 3 disease may develop in later childhood. Genotype can guide the decision to initiate therapy and individualize the dose of enzyme replacement therapy if it predicts a severe phenotype. Molecular analysis is also useful for carrier detection, particularly for siblings or extended family members of the affected person and for prenatal diagnosis.

### Supportive Evidence of Gaucher Disease

Elevated biomarkers (chitotriosidase and PARC/CCL 18), hyperferritinemia, hyperimmunoglobulinemia and low total and high-density lipoprotein cholesterol. Chitotriosidase levels are 100–5,000 times the normal value.

### Baseline Assessments

After establishing diagnosis of Gaucher disease, assessments are performed to establish overall and organ-specific disease burden. These assessments also serve to monitor disease progression and response to therapy. The assessment protocol and modalities are enumerated in **Table 5**. Detailed description of the protocol for assessment is available in a review by Kaplan et al. Objective scores have been developed by Kallish and Kaplan to grade severity of the disease in children.

### TREATMENT

The various therapeutic modalities and supportive management for Gaucher disease are summarized in **Tables 6 and 7**. Enzyme replacement therapy is the current standard of care for Gaucher disease.

### Enzyme Replacement Therapy

Alglucerase [Ceredase®; Genzyme Corporation, Cambridge, MA, USA] was the first therapeutic product approved for use by the Food and Drug Administration (FDA) in 1991. It was derived from the human placenta. The naturally occurring enzyme was modified by removal of the sialic acid residues from terminal N-linked oligosaccharides to expose mannose residues. This step is critical for uptake of the enzyme into the lysosomes expressing the mannose-6-phosphate receptor. This ensured high rate of uptake of the exogenously administered enzyme by target cells. Subsequently, a human recombinant product, Imiglucerase [Cerezyme®; Genzyme Corporation, Cambridge, MA, USA] was approved by FDA in 1994. Imiglucerase is derived from expression of the human *GBA* gene in Chinese hamster ovary cells. Imiglucerase differs from the natural enzyme by a R495H amino acid substitution. It is modified to expose mannose residues to enhance uptake of the therapeutic molecule by macrophages. Two other products are now available: Velaglucerase [VPRIV®, Shire Plc], a recombinant product expressed in human fibroblast cell line, was approved in 2010 and Taliglucerase [Elelyso™, Pfizer/Protalix BioTherapeutics, Inc], a recombinant product expressed in carrot cell culture, was approved in 2012. Enzyme replacement therapy modifies the natural history of Gaucher disease by reversing the signs of the disease or preventing manifestation in the various organs. Therapy is indicated in all symptomatic individuals with type 1 and type 3 diseases (**Box 1**). It is not



**Table 5** Baseline evaluations after diagnosis of Gaucher disease is confirmed

S. No.	Assessment	Parameter
1.	Anthropometry	Height and weight
2.	Hematological	Hemoglobin concentration Platelet count White cell count Coagulation status (symptoms of bleeding, before surgical or dental procedures) Serum iron, ferritin, transferrin saturation Vitamin B <sub>12</sub> Immunoglobulin profile and immunoelectrophoresis
3.	Other blood tests	25-hydroxyvitamin D concentration Serum calcium/phosphorus/alkaline phosphatase Aspartate aminotransferase, alanine aminotransferase Serum total protein/albumin Serology: Hepatitis B and C, HIV Plasma chitotriosidase/PARC/CCL18/ACE/TRAP
4.	Spleen and liver volumes	Ultrasonography Abdominal MRI
5.	Cardiac	ECG, echocardiography with Doppler
6.	Skeletal	Plain radiographs of the femur (AP view) Thoracodorsal spine (lateral view) MRI of the entire femur and spine (sagittal scans) DEXA (lumbar spine and femoral neck)

**Abbreviations:** DEXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; AP, anteroposterior; PARC, pulmonary and activation-regulating chemokine; TRAP, tartrate-resistant acid phosphatase; ACE, angiotensin-converting enzyme; CCL18, chemokine (C-C motif) ligand 18; HIV, human immunodeficiency virus.

indicated for type 2 disease. The recommended dose is 60 units/kg body weight administered as an infusion every 2 weeks. Response is dose-dependent. Doses should be individualized; lower doses of 30 units/kg have been used in children when the manifestations are not severe and titrated by the clinical response. In those having severe disease with hepatopulmonary syndrome or cirrhosis, the dose is increased to 120 units/kg body weight every 2 weeks.

**BOX 1** Indications for enzyme replacement therapy in symptomatic children with Gaucher disease

Any one or more of the following symptoms:

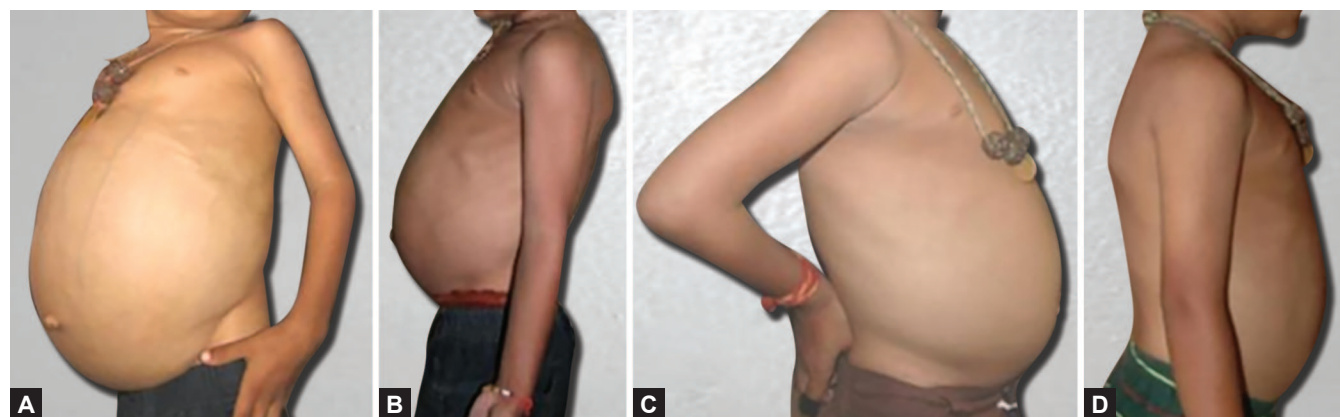
1. Symptomatic disease in the first two decades of life
2. Severe anemia; hemoglobin <8 mg/dL
3. Severe thrombocytopenia <60,000/mm<sup>3</sup>
4. Leukopenia, white cell count <3,000/mm<sup>3</sup>
5. Bone crisis and osteonecrosis in the past
6. Active bone disease, even if asymptomatic
7. Decreased growth velocity and/or growth retardation
8. Height <5th percentile or significantly decreased growth velocity
9. Delayed onset of puberty
10. Sibling with severe disease requiring enzyme replacement therapy
11. Genotype (L444P or D409H) associated with severe disease
12. A bone marrow density (BMD) Z score of – 2.0
13. Spleen and liver volumes >2.0 multiples of normal.

**Table 6** Therapeutic strategies and available modalities

S. No.	Strategy	Modality
1.	Enzyme enhancement therapy: Modification of mutated enzyme	Chaperones
2.	Supplement deficient enzyme • Direct	Enzyme replacement therapy Bone marrow transplant/ hematopoietic stem cell transplant
	• Indirect	Gene therapy
3.	Target substrate accumulation	Substrate reduction therapy

There is a variation in response of the various organs to enzyme replacement therapy. Anemia, thrombocytopenia and reduction of storage in the liver and spleen respond most dramatically (**Figs 10A to D**) whereas the response of the skeleton is slower. Organs such as lungs and lymph nodes are resistant to the effects of enzyme replacement therapy. The therapeutic enzyme does not cross the blood-brain barrier and, therefore, does not prevent or reverse neurological manifestations.

Therapeutic goals have been defined for monitoring response to enzyme replacement therapy to assess hematopoietic reconstitution, reduction in liver and spleen volumes and stabilization and improvement of bone disease. The goals are defined for each manifestation/organ system involved by the disease. A time frame to achieve each goal has also been defined (**Table 8**). After



**Figures 10A to D** Response to enzyme replacement therapy in type 3 Gaucher disease homozygous for L444P mutation. (A) Massive abdominal distension at initiation of enzyme replacement at 32 months of age; (B) Same child showing significant reduction in abdominal distension after 7 months of therapy; (C) After 1 year of therapy; (D) After 2 years of therapy



**Table 7** Supportive therapy of Gaucher disease

Blood transfusion
Splenectomy (total or partial; surgical or thromboembolism)
Treatment of bone crisis: <ul style="list-style-type: none"> <li>• Nonspecific pain: Nonsteroidal anti-inflammatory drugs</li> <li>• Excruciating pain: Prednisone 1 g/m<sup>2</sup> for 2 days, followed by lower doses</li> </ul>
Joint replacement surgery
Nutritional: <ul style="list-style-type: none"> <li>• Oral calcium and vitamin D supplements</li> <li>• Oral iron and/or vitamin B<sub>12</sub> supplements</li> </ul>
Bisphosphonates
Prevention of bleeding especially during surgical/dental procedures <ul style="list-style-type: none"> <li>• Desmopressin acetate (DDAVP)</li> <li>• Coagulation factor</li> <li>• Plasma transfusion</li> <li>• Platelet transfusion</li> </ul>

achieving therapeutic goals, the dose of enzyme replacement therapy may be reduced to maintain the goals.

## Alternative Modes of Treatment

### Substrate Reduction Therapy

N-butyldeoxynojirimycin available as Miglustat [Zavesca®; Actelion Pharmaceuticals, Allschwil, Switzerland] is an orally administered drug that inhibits production of the substrate glucosylceramide. It has been approved for use in adults with Gaucher disease in whom enzyme replacement therapy is not acceptable. It has not

been approved for treatment of children with Gaucher disease. A promising alternative oral substrate reduction drug is eliglustat tartrate, which is currently undergoing clinical trial in adults with type I disease.

### Enzyme Enhancement Therapy

Some mutations causing Gaucher disease like the N370S allele result in altered configuration of the protein. This misfolded protein may get destroyed before it reaches the lysosome or it can trigger a toxic cascade leading to cell apoptosis. Chaperones are small molecules that bind to misfolded proteins and result in correct refolding and/or maturation. Molecules such as iminosugars like isofagomine and the chemical chaperone N-nonyl-deoxynojirimycin have been shown to increase activity of mutant  $\beta$ -glucocerebrosidase. Ambroxol is being studied for its role as enzyme enhancement therapy in Gaucher disease, particularly in the neuronopathic type 3 variant.

### Bone Marrow and Hematopoietic Stem Cell Transplant

This therapy was previously advocated for Gaucher disease before the availability of enzyme replacement therapy. An advantage over enzyme replacement therapy is the effect on the CNS. Availability of a donor, need for immunosuppression and significant morbidity and mortality limit their use and enzyme replacement therapy currently continues to be the treatment of choice. Limited data indicate some benefit of hematopoietic stem cell transplant in type 3 disease.

## PREVENTION

As Gaucher disease is autosomal recessive, carrier parents have a 1 in 4 chance of having an affected offspring. The family should be

**Table 8** Therapeutic goals in children

Parameter	Goal	Time frame to achieve goal
Anemia	<ul style="list-style-type: none"> <li>• Increase hemoglobin levels to &gt;11 g/dL</li> <li>• Eliminate need for blood transfusions</li> <li>• Reduce fatigue and dyspnea</li> <li>• Maintain hemoglobin values achieved after the first 12–24 months</li> </ul>	1–2 years
Thrombocytopenia	<ul style="list-style-type: none"> <li>• Increase platelet count sufficient to prevent spontaneous and surgical bleeding</li> <li>• Avoid splenectomy</li> <li>• Moderate baseline thrombocytopenia <ul style="list-style-type: none"> <li>– Increase in platelet count by 1.5–2.0 fold</li> <li>– Approach low normal</li> </ul> </li> <li>• Severe baseline thrombocytopenia <ul style="list-style-type: none"> <li>– Increase in platelet count by 1.5 fold</li> <li>– Continue to increase</li> <li>– Normalization not expected</li> </ul> </li> <li>• Maintain stable platelet counts to eliminate risks of bleeding after a maximal response has been achieved</li> </ul>	First year  1 year 2 years  1 year 2nd to 5th year, doubling by second year
Hepatomegaly	<ul style="list-style-type: none"> <li>• Reduce and maintain liver volume to 1.0–1.5 times normal</li> <li>• Reduce liver volume by 20–30%</li> <li>• Reduce liver volume by 30–40%</li> </ul>	1–2 years 3rd to 5th year
Splenomegaly	<ul style="list-style-type: none"> <li>• Reduce and maintain spleen volume to 2–8 fold normal</li> <li>• Reduce spleen volume by 30–50%</li> <li>• Reduce spleen volume by 50–60%</li> <li>• Alleviate symptoms due to splenomegaly</li> <li>• Eliminate hypersplenism</li> </ul>	Within 1 year 2nd to 5th year
Bones	<ul style="list-style-type: none"> <li>• Lessen or eliminate bone pains</li> <li>• Prevent bone crisis</li> <li>• Prevent osteonecrosis and subchondral joint collapse</li> <li>• Improve bone mineral density (BMD); increase cortical and trabecular BMD</li> </ul>	1–2 years  2 years
Growth	<ul style="list-style-type: none"> <li>• Attain ideal or peak skeletal mass</li> <li>• Achieve normal height according to population standards</li> <li>• Achieve normal onset of puberty</li> </ul>	3 years

offered genetic counseling including information about the risk of recurrence. Prenatal diagnosis is possible in at-risk families by estimation of enzyme activity or genotyping in chorionic villi or cultured amniocytes.

### IN A NUTSHELL

1. Gaucher disease is an autosomal recessive single gene disorder caused by mutations of the *GBA1* gene leading to functional deficiency of the lysosomal enzyme  $\beta$ -glucocerebrosidase.
2. Spectrum of clinical manifestations is a continuum ranging from asymptomatic individuals to severe fetal manifestations. The major phenotypes, neuronopathic and non-neuronopathic disease are distinguished by the presence of primary neurological involvement.
3. Massive splenomegaly and hepatomegaly are the most consistent manifestations, often accompanied by anemia and thrombocytopenia.
4. Skeletal involvement is the most debilitating manifestation that is present in more than 80% of cases and may be suboptimally recognized.
5. Diagnosis requires demonstration of deficient  $\beta$ -glucocerebrosidase activity and/or molecular analysis to detect pathogenic mutations in the *GBA 1* gene. Bone marrow examination is not routinely recommended for diagnosis.
6. Carrier detection requires molecular analysis. Carrier couples must be offered genetic counseling and prenatal diagnosis.
7. The current standard of therapy is enzyme replacement therapy with macrophage targeted recombinant human glucocerebrosidase infusions administered intravenously. Enzyme replacement therapy reverses most manifestations of Gaucher disease but has no effect on CNS manifestations.

### MORE ON THIS TOPIC

- Beutler E, Grabowski GA. Gaucher disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D. The metabolic and molecular bases of inherited disease. 8<sup>th</sup> ed. New York, McGraw Hill; 2001. pp. 3635-68.
- Elstein D, Zimram A. Gaucher disease. In: Mehta A, Winchester B. Lysosomal storage disorders—a practical guide. Sussex: Wiley Blackwell; 2012. pp. 49-57.
- Feroze M, Arvindan KP, Jose L. Gaucher's disease among Mappila Muslims of Malabar. Indian J Pathol Microbiol. 1994;37:307-11.
- Futerman AH, Zimran A. Gaucher Disease. Boca Raton: Taylor and Francis; 2007.
- Kallish S, Kaplan P. A disease severity scoring system for children with type 1 Gaucher disease. Eur J Pediatr. 2013;172:39-43.
- Kaplan P, Andersson HC, Kacena KA, Yee JD. The clinical and demographic characteristics of non-neuropathic Gaucher disease in 887 children at diagnosis. Arch Pediatr Adolesc Med. 2006;160:603-8.
- Kaplan P, Baris H, De Meirleir L, et al. Revised recommendations for the management of Gaucher disease in children. Eur J Pediatr. 2013;172: 447-58.
- Mikosch P. Miscellaneous non-inflammatory musculoskeletal conditions. Gaucher disease and bone. Best Prac Res Clin Rheumatol. 2011;25:665-81.
- Mistry P, Cappellini D, Lukina E, et al. A reappraisal of Gaucher disease—diagnosis and disease management algorithms. Am J Hematol. 2011;86:110-5.
- Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol. 2004;41:4-14.
- Weinreb NJ, Aggio MC, Andersson H, et al. Gaucher disease type 1: Revised recommendations on evaluation and monitoring for adult patients. Semin Hematol. 2004;41:15-22.

## Chapter 3.11

# Niemann-Pick Disease

Ashwin Dalal

Niemann-Pick disease (NPD) is a subgroup of lysosomal storage disorders characterized by accumulation of lipids in various organs of the body. Traditionally, NPD has been classified into four groups based on biochemical and clinical criteria, i.e., group A (NP-A) with classic patients having neurodegenerative disease leading to death in infancy; group B (NP-B) patients having organomegaly without nervous system involvement; group C (NP-C) patients with slowly progressive neurologic illness; and group D (NP-D) patients who closely resembled group C, but were limited to Nova Scotia region of Canada. Genetic studies have revealed that NPD type A/B (NP-A/B) are sphingolipidosis disorders caused due to deficiency of acid sphingomyelinase (ASM) enzyme resulting from mutations in *SMPD1* gene, whereas NPD type C/D (NP-C/D) are cholesterol trafficking defects resulting from mutations in *NPC1* and *NPC2* genes. Although the etiopathology of both disorders is completely different, the two diseases are discussed together for historical reasons.

## EPIDEMIOLOGY

The prevalence among Ashkenazi Jews is estimated to be approximately 1 in 40,000 for NP-A/B whereas overall prevalence

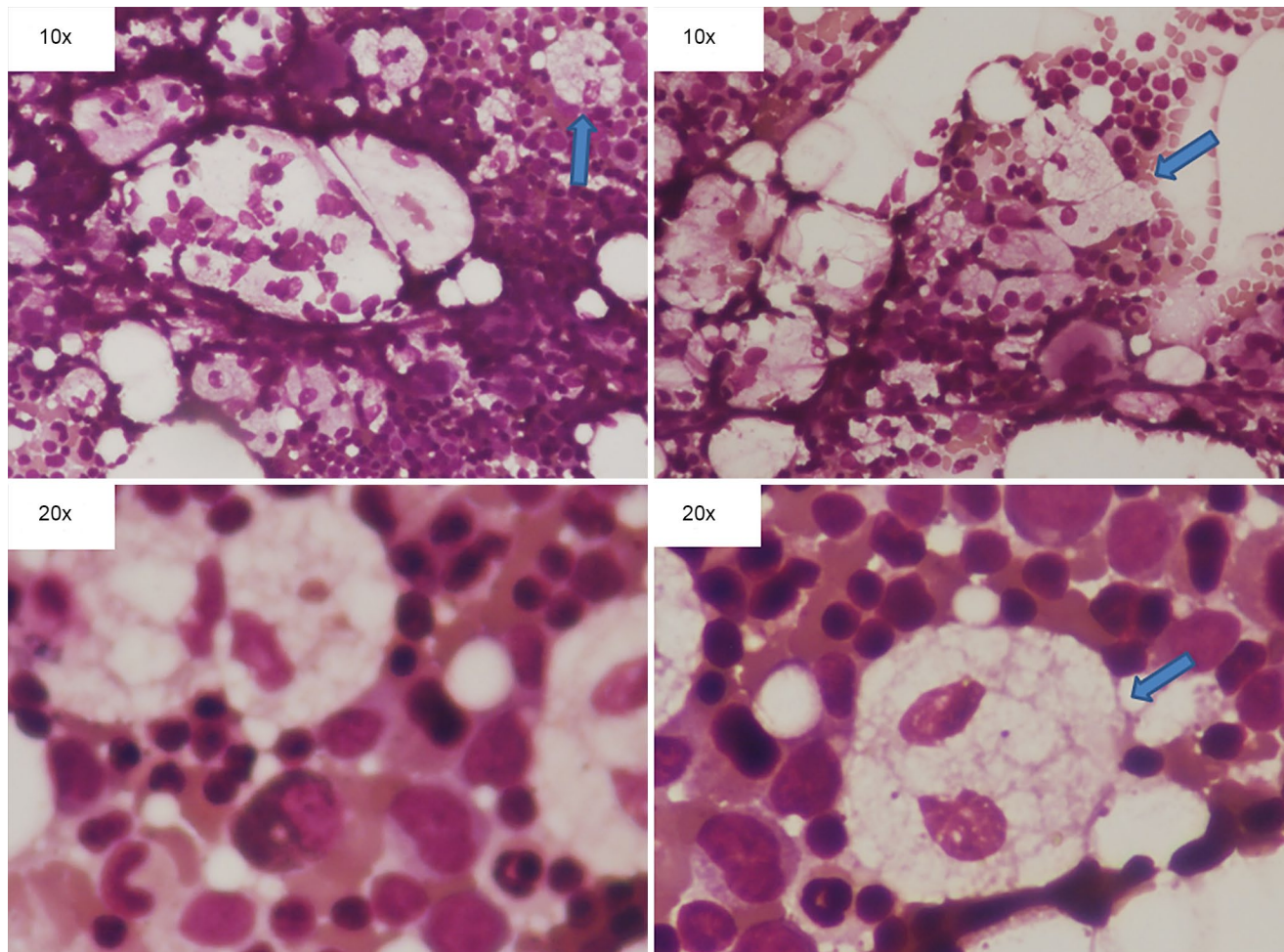
among other populations is estimated to be 1 in 250,000. The incidence of NPD type C is estimated to be 1 in 150,000. There are very few studies available from India and the exact prevalence is not known.

## PATHOLOGY

The histochemical hallmark of NPD is the foam cell, which is, in fact, lipid-laden macrophage. They are also called NPD cells and appear as sea blue histiocytes on bone marrow examination (**Fig. 1**). In NP-A, the brain is shrunken with reduced weight of cerebrum and cerebellum. Neurons are swollen and myelin is decreased. Similar changes are seen in spinal cord and peripheral nerves. Visceral involvement is seen as massively enlarged spleen along with involvement of lymph nodes, liver and kidneys. Lung involvement is more prominent in NP-B cases. The central defect in NP-C is defective intracellular trafficking of lipids which results in accumulation of cholesterol in the lysosomes and may lead to a deficiency in membrane cholesterol. Glycosphingolipid accumulation is seen as sea blue histiocytes in bone marrow with Giemsa Wright stains.

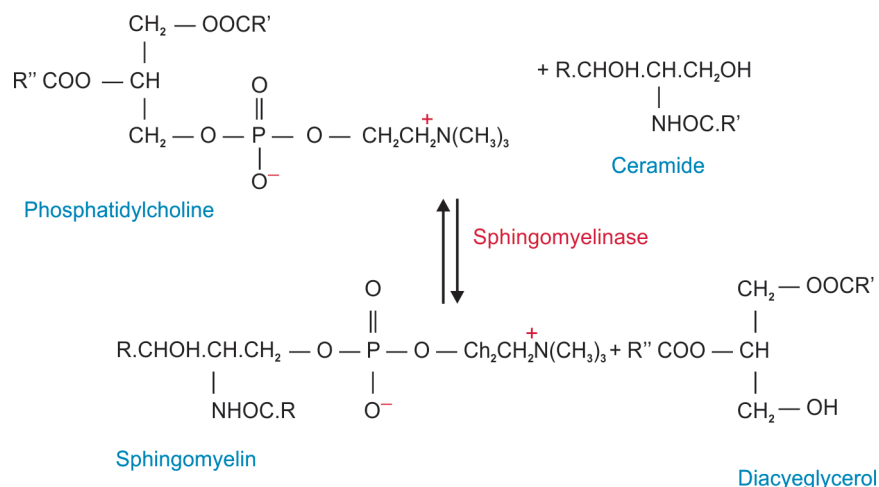
## Biochemistry

Acid sphingomyelinase (sphingomyelin phosphodiesterase) is the enzyme which degrades sphingomyelin into ceramide and phosphatidylcholine (**Fig. 2**). NP-A/B is characterized by deficiency of ASM, which results in accumulation of sphingomyelin in various tissues. The type of lipids stored in reticuloendothelial system in patients with both NP-A and NP-B is similar in all tissues



**Figure 1** Giemsa-stained bone marrow aspiration smears showing large foamy histiocytes (arrows)  
Source: Dr Ashwani Tandon, Department of Pathology, Nizam's Institute of Medical Sciences, Hyderabad.





**Figure 2** Chemical basis of acid sphingomyelinase action

with the exception of lysosphingolipids which are seen to be elevated in brains of patients with NP-A and not in NP-B. This may be the reason for non-neuronopathic presentation in patients with NP-B. In patients with NP-A/B, the enzyme activity ranges from undetectable to 5% of normal. ASM enzyme activity is measured in leukocytes or fibroblasts using artificial fluorogenic substrates. Enzyme activity is proportional to the fluorescence released. However, enzyme assay is not reliable to detect carriers of NP-A/B since there is great degree of overlap between carriers and normal individuals. The primary biochemical defect in NP-C is aberrant intracellular transport of endocytosed cholesterol. Deficiency of NPC1/NPC2 leads to accumulation of unesterified cholesterol in the late endosome/lysosomal compartments. Specific diagnosis of NP-C can be done by filipin staining of cultured fibroblasts grown in presence of low-density lipoproteins (LDL). Filipin binds to the excess unesterified cholesterol and is seen as dense birefringent granules in cytoplasm. ASM activity is normal in leukocytes. Chitotriosidase activity is a biomarker which is known to be moderately increased in NPD.

### Genetics

Niemann-Pick disease type A, type B and type C are inherited in autosomal recessive fashion. Homozygous or compound heterozygous mutations in SMPD1 result in NP-A/B whereas NP-C results from mutations in NPC1 and NPC2 genes. Risk of recurrence in next pregnancy is 25% for a couple with previous child with NPD.

The *SMPD1* gene is located at 11p15 and codes for ASM protein. Both NP-A and NP-B result from mutations in *SMPD1* gene. Hence, these diseases are called allelic disorders. More than 100 different mutations have been reported worldwide, which include missense, nonsense, frame shift and splice site mutations. The full spectrum of mutations in Indian patients is not yet known. Most of the mutations are private mutations limited to a family except in Ashkenazi Jews. NP-C is caused due to mutations in *NPC1* or *NPC2* genes, of which 95% of patients have mutations in *NPC1*. The *NPC1* gene has been mapped to 18q11 whereas *NPC2* gene has been mapped to 14q24, is about 13.5 kb in length and has 5 exons. More than 200 mutations have been reported in NP-C, mostly missense mutations scattered throughout the gene.

### CLINICAL FEATURES

Acid sphingomyelinase deficiency results in a spectrum of phenotypes ranging from classic NPD type A with early infantile

onset and neurologic involvement to the mild NPD type B with later onset and only visceral involvement. Patients with NPD type C present with manifestations ranging from visceral involvement to neuropsychiatric presentation.

### Classic Niemann-Pick Disease Type A

Patients commonly present with abdominal distension at 3–4 months age, due to hepatosplenomegaly. Other presenting complaints can be feeding problems, failure to thrive, gastrointestinal complaints (e.g., constipation, diarrhea and vomiting), recurrent respiratory infections and irritability. There is progressive increase in size of liver and spleen leading to massive hepatosplenomegaly (**Fig. 3A**). Neurological examination may be normal at the time of presentation except for hypotonia. However, as the disease progresses, there is progressive hypotonia and loss of deep tendon reflexes. Psychomotor development does not progress beyond the 1-year level for any domain and there may be loss of milestones attained. Fundus examination may reveal cherry red spot in most patients (**Fig. 3B**). Neurologic deterioration is relentless, and most children do not survive beyond 2–3 years of age.

### Niemann-Pick Disease Type B

The onset of symptoms is much later and many of the patients live into adulthood. Typically patients present with abdominal distension with mild to severe hepatosplenomegaly. Significant splenomegaly may result in hypersplenism with secondary thrombocytopenia. Pulmonary involvement is seen ranging from limitation of activity to oxygen dependence. Up to one-third of individuals with NPD-B have a cherry red spot in retina. Failure to gain height and delayed skeletal maturation may lead to significant short stature in adulthood.

### Niemann-Pick Disease Type C

Patients present with varied clinical features depending on age of onset and it may take a long time until diagnosis is established. Clinical features based on age at presentation are listed in **Table 1**. The typical finding associated with NP-C is impaired vertical gaze, which is an early manifestation. Vertical supranuclear gaze palsy first manifests as increased latency in initiation of vertical saccades, after which saccadic velocity gradually slows and is eventually lost. In late stages of the illness, horizontal saccades are also impaired. In addition, there may be



**Table 1** Clinical features of Niemann-Pick disease type C according to age of presentation

Age of presentation	Clinical features
Perinatal	Fetal ascites detected on antenatal sonography Severe neonatal liver disease with jaundice and persistent ascites
Infantile	Hypotonia, delayed psychomotor development Hepatosplenomegaly
Childhood	Clumsiness, frequent falls progressing to ataxia Vertical supranuclear gaze palsy (VSGP) Dystonia, dysarthria Partial and/or generalized seizures
Adolescent/adult	Slowly progressive neurologic deterioration Dementia, psychosis, psychiatric illness Ataxia, VSGP may be present

extrapyramidal and psychiatric symptoms. Hence, a high degree of suspicion is needed to diagnose the condition.

### APPROACH TO DIAGNOSIS

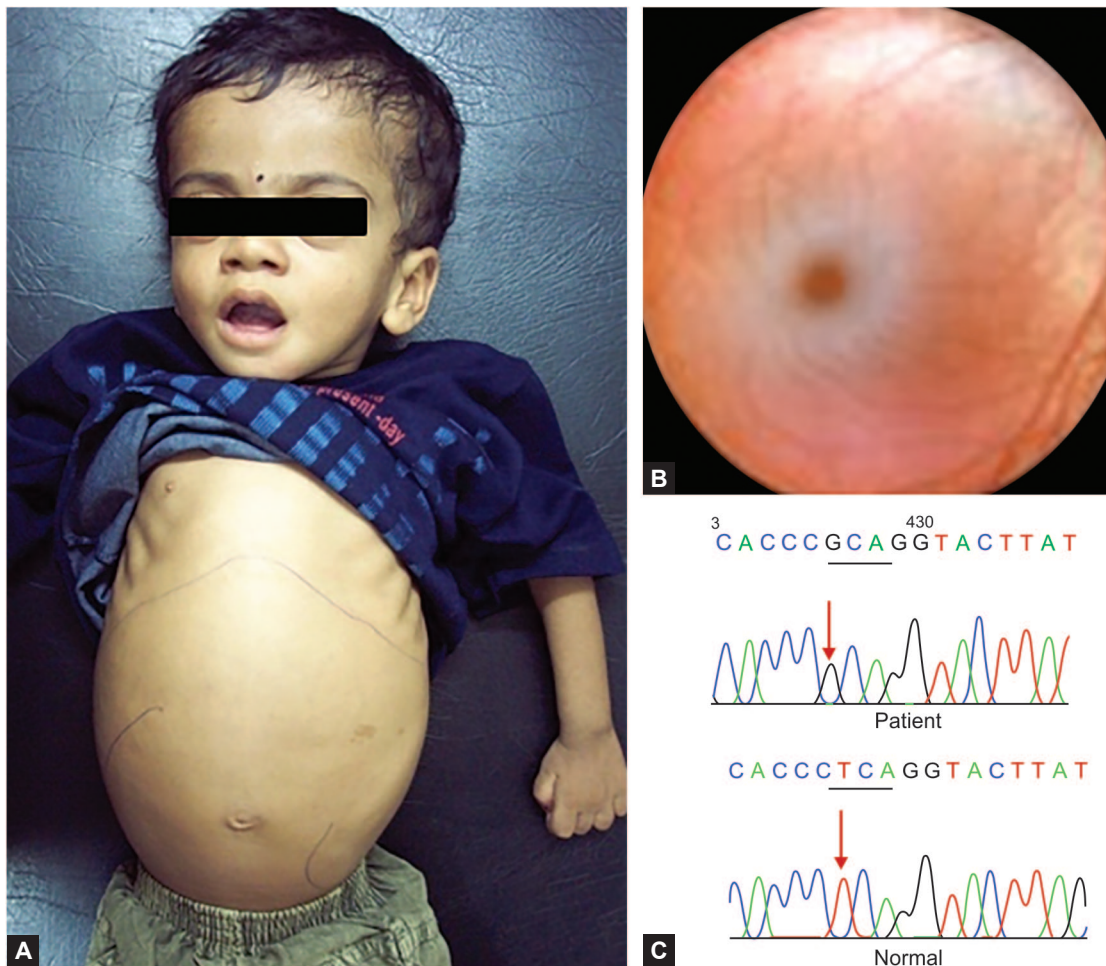
The approach to diagnosis of NPD is similar to any other storage disorder. Presence of hepatosplenomegaly with or without

neuronal involvement should raise the suspicion for NPD, especially once infective and hematological causes have been ruled out. Presence of cherry red spot on fundus examination is a very important clue. Estimation of ASM enzyme is helpful in making a confirmed diagnosis of NP-A/B. Mutation analysis of *SMPD1* gene helps to identify the mutation and confirms the diagnosis (**Fig. 3C**). In addition, mutation analysis helps in accurate carrier detection and prenatal diagnosis.

The diagnosis of NP-C is difficult due to varied clinical features and needs high degree of suspicion. The diagnosis can be confirmed by sequencing of *NPC1* and *NPC2* genes for identification of mutations. Differential diagnosis for various manifestations of the NPD is listed in **Table 2**.

### MANAGEMENT

The management of patients with NPD is multidisciplinary since various organs are involved. The extent of disease in NP-A needs to be established by complete neurological and ophthalmological evaluation followed by complete blood counts and liver function tests. In addition, NP-B patients have to be evaluated by chest X-ray, pulmonary function tests and liver biopsy when indicated. Although there is no curative treatment for NP-A, supportive treatment like treatment of seizures, dietary advice and occupational therapy can be helpful. NP-B patients will need treatment for hypersplenism,



**Figures 3A to C** (A) Affected patient showing coarse facies and hepatosplenomegaly; (B) Cherry red spot; (C) Sequence chromatogram depicting exon 2 of *SMPD1* showing homozygous c.1262T>G mutation (arrows)

**Table 2** Differential diagnosis for different presentations of Niemann-Pick disease

<i>Niemann-Pick disease type A/B</i>	
Hepatosplenomegaly	Gaucher disease, Sandhoff disease, Wolman disease, mucopolysaccharidoses and oligosaccharidoses
Interstitial lung disease	Environmental exposures, connective tissue diseases and infections
Cherry red spot	GM1 gangliosidosis, Sandhoff disease, Tay-Sachs disease, sialidosis, galactosialidosis, mucopolipidoses
<i>Niemann-Pick disease type C</i>	
Severe neonatal jaundice	Biliary atresia, congenital infections, $\alpha$ -1 antitrypsin deficiency, tyrosinemia
Splenomegaly	Storage diseases, infections, hematologic malignancies, histiocytosis
Vertical supranuclear gaze palsy	GM2 gangliosidosis, mitochondrial diseases, glycine encephalopathy, maple syrup urine disease, dorsal midbrain syndrome
Dystonia	Idiopathic torsion dystonia, dopa responsive dystonia, Wilson's disease, amino and organic acidopathies (e.g., glutaric aciduria type 1), GM2 gangliosidosis
Dementia	Pseudodementia (depressive disorder), neuronal ceroid lipofuscinoses, subacute sclerosing panencephalitis, HIV encephalopathy

use of supplemental oxygen or steroids for pulmonary involvement and surveillance for liver failure. Bone marrow transplantation (BMT) has shown variable results. It holds promise in NP-B patients since neurologic involvement is not corrected by BMT in NP-A patients. However, morbidity and mortality associated with BMT limit its use. Trials are underway for enzyme replacement therapy and gene therapy for NP-A/B.

Treatment of NP-C is primarily supportive and includes anticonvulsants for treatment of seizures, symptomatic treatment of dystonia, and cataplexy, physical therapy, speech therapy and dietary advice. Liver and bone marrow transplant have not been successful. Several new therapies under investigation include inhibition of glycosphingolipid synthesis by N-butyldeoxynojirimycin, use of miglustat for stabilization of NPC protein, and neurosteroid replacement therapy with allopregnanolone.

## PREVENTION

Niemann-Pick disease is not curable. Hence, the best strategy is to prevent birth of children with disease. Primary prevention to avoid the birth of first affected child in a family can be done if all the couples can be screened for mutations in *NPD* genes and offered prenatal diagnosis where both parents are carriers for disease causing mutations. This strategy is possible in genetic isolates like Ashkenazi Jews where a few mutations account for all cases of NPD. However, in other populations, secondary prevention can be done by prenatal diagnosis in families where a proband with NPD has been identified. Confirmed diagnosis in proband based on enzyme analysis and/or mutation analysis is a prerequisite for prenatal diagnosis. Prenatal diagnosis can be done by chorionic villus biopsy (11–13 weeks gestation) or amniocentesis (16–18 weeks gestation) followed by enzyme analysis and/or mutation analysis. Genetic testing is more accurate. The couple can opt for termination of pregnancy if the fetus is found to be affected. Expanded family screening can also be offered to these families to prevent birth of a child with NPD in siblings of parents.

## IN A NUTSHELL

1. Niemann-Pick disease is a lysosomal storage disorder characterized by accumulation of sphingolipids in various tissues.
2. Niemann-Pick disease type A is neuronopathic form caused due to deficiency of ASM resulting from mutations in *SMPD1* gene. NPD type B is an allelic disorder with only visceral involvement.
3. Niemann-Pick disease type C is a cholesterol trafficking defect resulting from mutations in *NPC1* and *NPC2* genes.
4. Patients with NPD commonly present as storage disorder with or without neurologic involvement.
5. The gold standard for diagnosis of NP-A/B is ASM enzyme assay whereas NP-C is diagnosed by filipin staining of fibroblasts grown with LDL.
6. Mutation analysis helps in confirmation of diagnosis, accurate carrier detection and prenatal diagnosis.
7. There is no cure for NPD and management is mainly supportive.
8. Prevention can be done by carrier screening in inbred populations or secondary prevention by prenatal diagnosis using enzyme assay/mutation analysis.

## MORE ON THIS TOPIC

- Boustany Rose-Mary, Mousallem T. Sphingolipid disorders and the neuronal ceroid lipofuscinoses or batten disease. In: Rimoin DL, Connor JM, Pyeritz RE, Korf B. Emery and Rimoin's Principles and Practice of Medical Genetics. 5<sup>th</sup> ed. USA: Elsevier Churchill Livingstone; 2007. pp. 2456-9.
- McGovern MM, Desnick RJ. Lipidoses (lysosomal storage disorders). In: Kliegman RM, Stanton BF, St Geme JW, Schor NF, Behrman RE. Nelson Textbook of Pediatrics. 19<sup>th</sup> ed. Philadelphia: Elsevier Churchill Livingstone; 2011. Chap 80.4.
- Nussbaum RL, McInnes RR, Williard HF. The molecular, biochemical and cellular basis of genetic disease. Thompson & Thompson's Genetics in Medicine. 7<sup>th</sup> ed. USA: Elsevier Saunders; 2007. pp. 345-92.
- Schuchman E, Desnick R. Niemann Pick disease types A and B: acid sphingomyelinase deficiencies. In: Scriver CR, Sly WS, Childs BA, et al. The Metabolic and Molecular Bases of Inherited Disease. 8<sup>th</sup> ed; 2001. pp. 3589-610.
- Turnpenny PD, Ellard S. Biochemical genetics. Emery's Elements of Medical Genetics. 13<sup>th</sup> ed. USA: Elsevier Churchill Livingstone; 2009. pp. 158-76.

## Chapter 3.12

# Fabry Disease

Ratna Dua Puri

Anderson Fabry disease (OMIM No. 301500) is an X-linked lysosomal storage disorder with a frequency of about 1 in 40,000 males. The disease manifests due to deficiency of enzyme  $\alpha$ -galactosidase A ( $\alpha$ -gal A) as a result of mutations in the *GLA* gene. Heterozygous females have intermediate levels of enzyme activity and can manifest milder manifestations of the disease. The disease phenotype in patients is due to the accumulation of the glycosphingolipid substrate, globotriaosylceramide (Gb3) in the lysosomes as a consequence of  $\alpha$ -gal A deficiency.

### PATHOPHYSIOLOGY

The glycosphingolipid primarily deposits in the lysosomes of the walls of small arteries, epithelial cells of cornea, glomeruli and renal tubules, cardiac muscles, ganglion and perineural cells of the autonomic nervous system and small unmyelinated nerves. Heterogenous clinical manifestations of Fabry disease are as a result of this widespread, progressive Gb3 accumulation in various organ systems.

### CLINICAL MANIFESTATIONS

Clinical manifestations are varied and multiple organ systems are involved. Young patients present with the classical phenotype, whereas those with greater residual enzyme activity present later, with milder manifestations or an organ-specific variant phenotype. Manifestations are typically more severe in affected males than carrier females. However, a small number of carrier females can develop severe symptoms indistinguishable from males, though at a later age. Female phenotype is classically due to skewed X inactivation or rarely due to 45X or an X-autosome translocation with disruption of the  $\alpha$ -galactosidase (*GLA*) gene at the breakpoints.

Though the phenotypic presentations of Fabry disease are always thought of as those in childhood, adolescence and adulthood, they essentially represent a continuum of phenotype due to increasing Gb3 deposition with time. Patients present with two major phenotypic manifestations, the severe classic phenotype and the variant/atypical forms.

#### Severe Classic Phenotype

Typical onset is in childhood or adolescence with clinical manifestations related to the autonomic and peripheral nervous system as well as vascular cutaneous and eye lesions. This includes the pain crisis, angiokeratomas, temperature intolerance, hypohidrosis and eye lesions. Renal, cardiac and cerebrovascular presentations manifest late in the third to fifth decade of life.

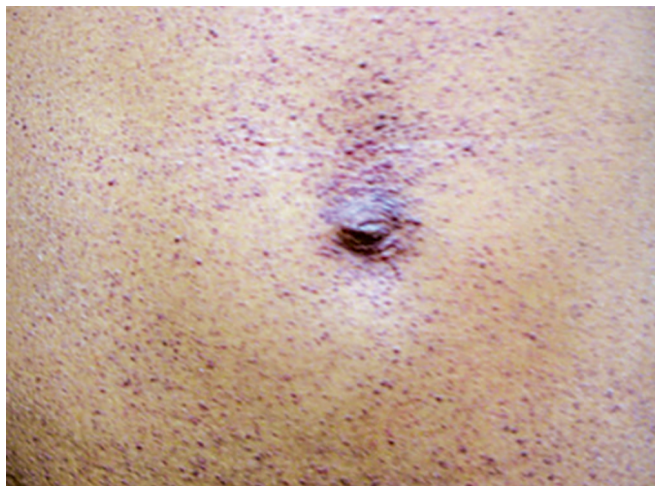
#### Pain

With an onset in childhood or adolescence, the *episodic Fabry crisis* is a hallmark of onset of clinical symptoms. It is an agonizing, burning pain in the palms and soles that radiates to the extremities and other parts of the body. The pain can be triggered by fever, emotion, stress, exercise, rapid changes in temperature and humidity and is extremely debilitating. It lasts from minutes to days. Misdiagnosis as rheumatic fever, neuralgia or neurosis is due to the accompanying fever and elevated erythrocyte sedimentation rate. Abdominal and flank pain mimics appendicitis or renal colic. The crisis decreases in frequency and severity with increasing age. Though an important and constant phenotype, pain may be absent in 10–20% patients.

The *constant discomfort* in some patients is burning and tingling paresthesias of hands and feet. These acroparesthesias are an attenuated crisis and many patients modify lifestyle to cope with the discomfort.

#### Skin

The typical lesions are angiokeratomas that manifest between 9 years and 13 years of age and are one of the earliest manifestations of the disease. They are raised, purplish-red, non-blanching lesions present on the hips, back, thighs, buttocks, penis and scrotum, as well as the oral mucosa and conjunctiva (**Fig. 1**). One-third female carriers also manifest these lesions. Other dermatological manifestations include hypohidrosis and unexplained fever due to intolerance to rising temperature.



**Figure 1** Angiokeratomas in a child with Fabry disease  
Source: Dr Madhulika Kabra, AIIMS, New Delhi.

#### Eye Manifestations

Involvement of the cornea, lens, conjunctiva and retina are reported. The characteristic spiral streaks in the corneal epithelium, *cornea verticillata* are seen as a corneal opacity on slit-lamp examination. It is present in over 90% patients, including heterozygous women and is pathognomonic of Fabry disease. Lenticular involvement as *Fabry cataract* is present in 30% affected males. The corneal and lens changes do not interfere with vision. Dilatation and tortuosity of the retinal and conjunctival vessels may be present.

#### Renal Involvement

Proteinuria/microalbuminuria can be present in adolescence without significant renal disease. The impaired glomerular filtration rate and tubulopathy are seen in the third decade in the classical presentation of the disease. Chronic kidney disease is the main cause of premature death in untreated patients by the fifth decade of life. Females are typically less severely affected.

#### Cardiac Disease

In patients with classical presentation, this presents by middle age. The earliest changes include a short PR interval, bradycardia, valvular insufficiencies and diastolic dysfunction. Conduction system abnormalities include ST segment abnormalities, T wave inversion and dysrhythmias. Rhythm abnormalities may lead to fatal arrhythmias. Hypertrophic cardiomyopathy in the absence of long-standing hypertension and left outflow obstruction should alert the clinician to a diagnosis of Fabry disease. In different studies, 3–12% patients with unexplained cardiac left ventricular hypertrophy have Fabry disease. Angina, variant angina and



myocardial infarction can occur due to pathology in the coronary vascular bed. Raynaud's phenomenon is also commonly reported in Fabry patients. Cardiac events are the most common cause of premature death in patients undergoing dialysis or transplantation for end-stage renal disease.

### Cerebrovascular Manifestations

The phenotype is due to the vascular complications of the central nervous system and is seen in about 13% of Fabry patients. Central nervous system (CNS) symptoms occur in the third decade in males and fourth decade in females. The presentations are transient ischemic attack, seizures, hemiplegia, aphasia, labyrinthine disorders, cerebral hemorrhage and cryptogenic stroke.

### Gastrointestinal Lesions

These include abdominal pain, diarrhea and vomiting.

### Miscellaneous

Sensorineural hearing loss, dyslipidemia, depression, anxiety and other psychological manifestations are reported.

### Variant Phenotypes

These are the atypical presentations without the characteristic skin lesions, pain crisis and sweating abnormalities. They present between the third and fifth decades of life with cardiac, renal or cerebrovascular manifestations. **Table 1** summarizes the different phenotypic manifestations in Fabry disease patients.

### Time to Diagnosis

The natural history studies show a long period to diagnosis from onset of initial symptoms. In children with median age at onset of symptoms was 9 years and diagnosis was made at 23 years of age and 13 and 32 respectively in women. A high index of suspicion is essential for early diagnosis and timely intervention to prevent progression to end-stage organ damage.

### Survival Data

Survival data prior to availability of enzyme replacement therapy (ERT) is reported to be 57 years for males and 72 years for females in a study of 96 Dutch Fabry patients.

## DIAGNOSIS

### Clinical

The diagnosis can be clinically suspected in classical Fabry patients by the history of acroparesthesias and associated angiokeratomas

and corneal dystrophy. In childhood, recurrent unexplained fever with pain in hands and feet should alert the astute clinician to the diagnosis. In suspected heterozygous females, slit lamp and examination for angiokeratomas in the trunk, breasts, back and posterolateral thighs are important. Adult onset phenotypes include renal sufficiency of unknown etiology, cryptogenic stroke and unexplained left ventricular hypertrophy. There is extreme heterogeneity of presentation and a Fabry patient may present with a single symptom or a combination of different organ involvements.

### Estimation of Enzyme Activity

Classically affected males will have no detectable or less than 1%  $\alpha$ -gal A levels measured in plasma, leukocytes or dried blood spots. Males with atypical phenotypes have residual activity more than 1% measured in plasma or isolated leukocytes. If enzyme levels are markedly decreased in heterozygous females, it is diagnostic of their carrier status. Conversely, normal enzyme levels in carrier females are reported.

### Gb3Cer, Globotriaosylceramide/GL3

It is the main glycosphingolipid that accumulates. GL3 levels in blood or urine have been used for diagnosis and assessment of disease burden.

### Mutation Analysis

Patients with Fabry disease harbor mutations in the *GLA* gene. These are mostly point changes though deletions and insertions are also reported. Clear genotype-phenotype correlation is not present. However, mutations causing complete loss of function of the gene are associated with the classical phenotype, whereas amino acid substitutions with some resultant enzyme activity present with the variant phenotypes. Identification of the mutation is a useful, additional confirmation of the enzymatic and clinical diagnosis in the male and is also important to identify female carriers. Knowledge of the familial mutation is important for predictive testing for at-risk family members and also for prenatal diagnosis.

A scheme for baseline and follow-up evaluation is suggested in **Table 2**.

## MANAGEMENT

Management of patients with Fabry disease is multidisciplinary (**Fig. 2**).

### Enzyme Replacement Therapy

Definitive management with two recombinant, commercially available enzymes, agalsidase alpha (Replagal®, Shire Human

**Table 1** Clinical manifestations in Fabry disease

Manifestation	Classical Fabry	Cardiac variant	Renal variant	Cerebrovascular variant
Age of onset	4–8 years	6th–8th decade	Third decade	Third decade
Acroparesthesia	++	+	+/-	–
Angiokeratoma	++	–	–	–
Temperature variation intolerance	++	–	–	–
Hypohidrosis	++	–	+/-	–
Unexplained fever	++	–	–	–
GI symptoms	++	–	–	–
Corneal/lenticular opacities	+	–	–	–
Cryptogenic stroke/TIA	+	–	–	+
Proteinuria/albuminuria	Early +	Mild +	+/ESRD	–
ESRD	+	–	+	–
Conduction abnormalities	+	++	–	–
LVH	+	++/cardiomyopathy	+	–

Abbreviations: GI, gastrointestinal; ESRD, end-stage renal disease; LVH, left ventricular hypertrophy; TIA, transient ischemic attack.



Genetic Therapies, Inc.) and agalsidase beta (Fabrazyme®, Genzyme Corp.) is available since 2001. The enzyme is administered as an intravenous infusion once every 2 weeks and is taken up by the vascular endothelial and the parenchymal cells into the lysosomes. The recommended dose for agalsidase alpha is 0.2 mg/kg/2 weeks and that for agalsidase beta is 1 mg/kg/2 weeks.

The drug is shown to decrease the accumulated cellular GL3. Clinical benefits in the classical phenotype include improvement in peripheral neuropathy and hypohidrosis. Renal disease benefits are better if treatment is initiated at less advanced renal dysfunction as lost renal function is not recovered and progression of disease cannot be halted. It is uncertain if ERT reduces the incidence of stroke in treated patients. In addition to delaying the progression of renal disease, therapy also reduces the risk of major cardiac, CNS and renal events by 60%.

### Supportive Management

Symptomatic management with angiotensin converting enzyme/angiotensin II receptor blocker (ACE/ARB) inhibitors is recommended to manage proteinuria and protect renal function. Hypertension, if present, is to be managed appropriately. Antiplatelet drugs, statins for dyslipidemia, stroke prophylaxis are other important supportive modalities. Cardiac pacing can be done if AV blocks are present. Drugs used for the management of the painful crisis, pain and constant discomfort include diphenylhydantoin, carbamazepine and gabapentin.

### Genetic Counseling and Prenatal Diagnosis

Fabry disease is an X-linked disorder with major manifestations in males. However, some female carriers can have clinical manifestations of the disease. Once a diagnosis is established in a male member, it is important to counsel the parents/family members

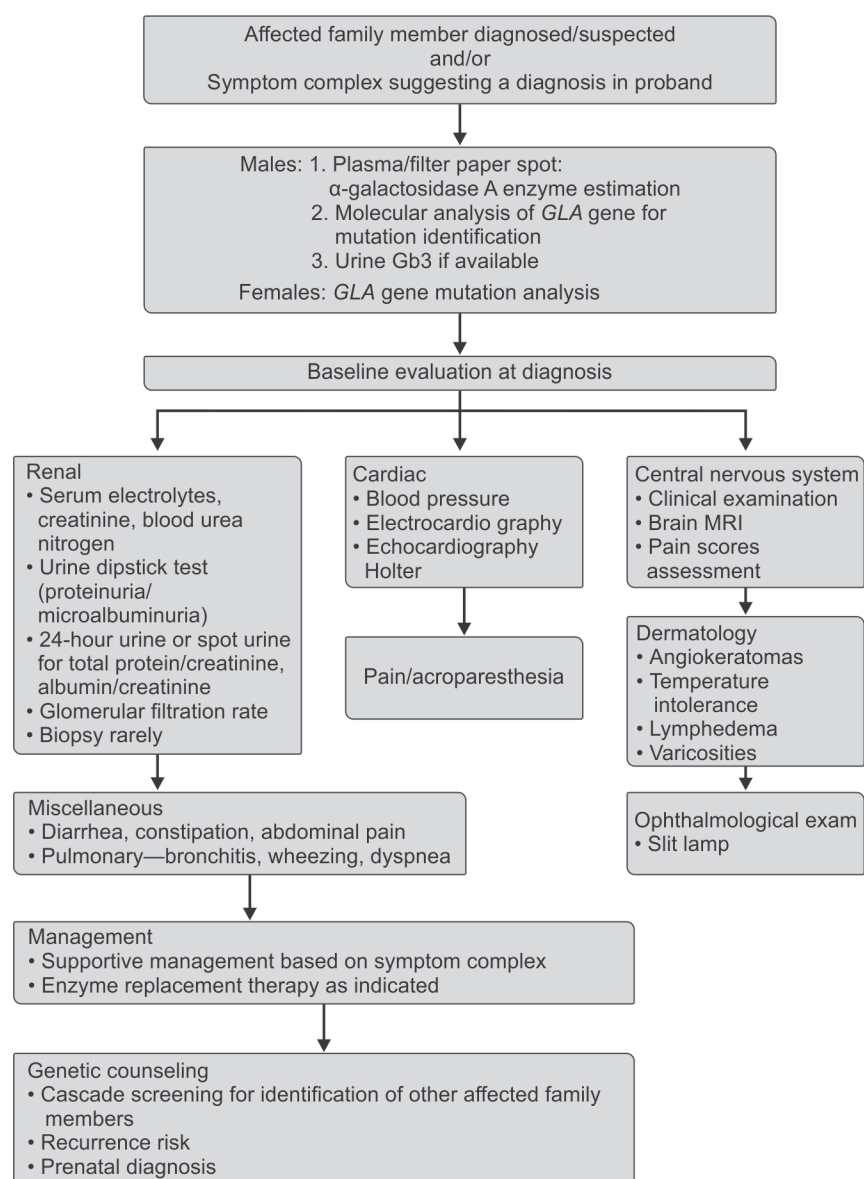
about the disease and its implication. Availability of ERT should be discussed. The limitation of cost of therapy and options available to the family are important concerns. Screening of at-risk family members to identify early any affected persons is extremely helpful. Prevention in subsequent pregnancies by chorionic villus sampling after 10 completed weeks of gestation is discussed with the families.

### IN A NUTSHELL

1. Fabry disease is an X-linked lysosomal storage disorder due to deficiency of enzyme  $\alpha$ -gal A as a result of mutations in the GLA gene.
2. Heterozygous females have intermediate levels of enzyme activity and can manifest milder manifestations of the disease.
3. The disease phenotype is due to the accumulation of the glycosphingolipid substrate, Gb3 in the lysosomes.
4. The glycosphingolipid primarily deposits in the lysosomes of the walls of small arteries, epithelial cells of cornea, glomeruli and renal tubules, cardiac muscles, ganglion and perineural cells of the autonomic nervous system and small unmyelinated nerves.
5. Clinical manifestations are varied and multiple organ systems are involved. Young patients present with the classical phenotype, whereas those with greater residual enzyme activity present later with milder manifestations or an organ specific variant phenotype.
6. The diagnosis can be clinically suspected in classical Fabry patients by the history of acroparesthesias and associated angiokeratomas and corneal dystrophy.
7. Classically affected males will have no detectable or less than 1%  $\alpha$ -gal A levels measured in plasma, leukocytes or dried blood spots.
8. Definitive management with two recombinant, commercially available enzymes, agalsidase alpha and agalsidase beta is available since 2001.

**Table 2** Baseline and follow-up evaluation in Fabry disease

Organ system		Features	Timeline
Neurological	History	Acroparesthesia, hypohidrosis, heat and cold intolerance, fatigue, stroke-related symptoms, transient ischemic attack, seizures	Baseline and every 6 months
	Examination	Stroke, hemianesthesia, hemiplegia, aphasia	Baseline and every 6 months
	Investigations	Brain MRI  Stroke risk factors: Serum lipids Factor V Leiden, serum homocysteine, protein C and S, antithrombin III, lupus anticoagulant, anticardiolipin antibody	Baseline and at onset of any central nervous system event Annually Once at baseline
Renal	Urine examination	Protein, casts, red cells and birefringent lipid globules 24-hour urine or spot urine for total protein/creatinine, albumin/creatinine, creatinine clearance	Baseline and thereafter: Three monthly if chronic kidney disease (CKD) 1 or 2 and >1 g/day proteinuria or CKD4 Six monthly if CKD3
	Blood	Serum electrolytes, creatinine, blood urea nitrogen	Every 12 months if CKD1 or 2 and <1 g/day proteinuria
Cardiac	History	Resting bradycardia, palpitations, exertional dyspnea, angina, myocardial infarction	Baseline and every 6 months
Miscellaneous			At baseline and then as clinically indicated
Audiometry			Every visit
Ophthalmological		Blood pressure	Baseline and then every other year till 35 years of age. Yearly thereafter
Pulmonary		ECG, echocardiography	
Gastrointestinal			
Skeletal			



**Figure 2** Diagnosis and management of fabry disease: possible protocol for India

## MORE ON THIS TOPIC

Gal A, Hughes DA, Winchester B. Towards a consensus in the laboratory diagnosis of Fabry disease—recommendations of an European expert group. *J Inherit Metab Dis*. 2011;34:509–14.

Mehta A, Hughes DA. Fabry Disease. In: Pagon RA, Adam MP, Ardinger HH, Bird TD, Dolan CR, Fong CT, Smith RJH, Stephens K. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from <http://www.ncbi.nlm.nih.gov/books/NBK1292/>. Accessed August, 2014.

Rombach SM, Smid BE, Bouwman MG, et al. Long-term enzyme replacement therapy for Fabry disease: effectiveness on kidney, heart and brain. *Orphanet J Rare Dis*. 2013;8:47.

Rombach SM, Smid BE, Linthorst GE, et al. Natural course of Fabry disease and the effectiveness of enzyme replacement therapy: a systematic review and meta-analysis: Effectiveness of ERT in different disease stages. *J Inherit Metab Dis*. 2014 (in press).

Zarate YA, Hopkin RJ. Fabry's Disease. *The Lancet*. 2008;372:1427–35.

## Chapter 3.13

# Defects of Carbohydrate Metabolism

Kausik Mandal

Defects of carbohydrate metabolism can be classified in two broad categories: (1) diabetes: includes type 1 and type 2 diabetes; and (2) inborn errors of carbohydrate metabolism. Diabetes is a collection of disorders leading to high blood glucose. The etiology of diabetes ranges from environmental causes, genetic predispositions to pure single gene disorders like lipotrophic diabetes (BSCL2). It will be discussed along with other endocrine

disorders in Section 44. This chapter will deal with classification and clinical implications of inborn errors of carbohydrate metabolism.

### CLASSIFICATION

Classifying inborn errors of carbohydrate metabolism is difficult; an exhaustive list will overlap with disorders within and outside the pathways involved in metabolism of various carbohydrates and a precise list will miss out on many disorders related to various carbohydrates. The various important disorders are summarized in **Table 1**, and some of the relatively common disorders are discussed below.

### Glucose Transport Defects

Glucose transporter proteins are found in various target tissues. These proteins facilitate glucose diffusion across plasma membrane. To date more than 14 such proteins have been identified. Some of the important ones and their disorders are described below:

**Table 1** Classification of inborn errors of carbohydrate metabolism

Broad categories	Types of disorders under each category	Subtypes/features	Special features
Disorders of monosaccharide metabolism	Glucose-galactose malabsorption	This is a rare autosomal recessive disorder, single gene disorder ( <i>SLC5A1</i> gene)	Newborns present with profuse watery diarrhea; which stops on dietary restriction of glucose and galactose; later on might develop nephrocalcinosis
	Glucose transport defects	More than 14	GLUT10 defect is also called arterial tortuosity syndrome
	Disorders of galactose metabolism	Galactokinase deficiency	High galactose in blood, but no mental retardation
		Galactose-1-phosphate uridyl transferase deficiency	Also known as GALT deficiency/ galactosemia
		UDP galactose-4-epimerase deficiency	Also known as epimerase deficiency
	Disorders of fructose metabolism	Essential fructosuria	A benign autosomal recessive condition; increased intermittent excretion of fructose in urine
Hereditary fructose intolerance		In contrast to essential fructosuria, this condition needs prompt diagnosis	
Gluconeogenic disorders	Fructose 1,6-bisphosphatase deficiency	Autosomal recessive disorder due to mutation in the <i>FBP1</i> gene	Excellent prognosis if diagnosed within time
	Phosphoenolpyruvate carboxykinase deficiency	Two forms: PCK1 and PCK2	Hypoglycemia
	Pyruvate carboxylase deficiency	<i>PC</i> gene	Three clinical forms: Type A, B and C
	Deficiencies of pyruvate dehydrogenase complex	PDHC is an enzyme complex; encompasses various disorders	Extreme variability in clinical expression; these children do not present with hypoglycemia
Disaccharidase deficiencies	Lactase deficiency	Congenital lactase deficiency is due to mutation in the <i>LCT</i> gene	Acquired deficiency is also described
	Sucrase-isomaltase deficiency	Found in Eskimos	Management is sacrosidase (Sucraid) enzyme and a diet with limited sucrose
Disorders of pentose metabolism	Transaldolase deficiency	Autosomal recessive condition arising from mutation in the <i>TALDO1</i> gene located at 11p	Great phenotypic variability, ranging from hydrops fetalis to slowly progressing cirrhosis of liver
	Ribose-5-phosphate isomerase deficiency	Mutation in <i>RPIA</i> gene at 2p	Extremely rare; developmental delay and epilepsy are features
	Essential pentosuria	Autosomal recessive condition due to mutation in the <i>DCXR</i> gene at 17q	Benign disorder; requires no treatment
Congenital disorders of N-linked glycosylation	Many types	Briefly discussed in this chapter	
Glycogen storage disorders	Many types	Discussed in the subsequent chapter	

Abbreviations: UDP, uridine diphosphate; PCK, phosphoenolpyruvate carboxykinase; PDHC, pyruvate dehydrogenase complex.

### Glucose Transporter 1 Deficiency Syndrome

**Etiology** Glucose transporter 1 (GLUT1) deficiency syndrome is normally inherited in autosomal dominant fashion due to de novo mutation in the *SLC2A1* gene (located at 1p); autosomal recessive inheritance has also been described. GLUT1 protein is localized in the blood-brain barrier.

**Features** Children with GLUT1 defects present with severe seizure disorder, developmental delay, spasticity, ataxia and gradually developing microcephaly. Sometimes these children might have atypical childhood absence epilepsy and paroxysmal movement disorders.

**Diagnosis** Low cerebrospinal fluid (CSF) glucose relative to blood glucose and low CSF lactate is virtually diagnostic of this disorder.

**Management** A ketogenic diet partially or completely ameliorates the accompanying seizure disorder.

### GLUT2 Defect/Fanconi-Bickel Syndrome

**Etiology** Fanconi-Bickel syndrome is a rare but well-defined autosomal recessive clinical entity characterized by proximal renal tubular dysfunction and hepatorenal glycogen accumulation. Homozygous or compound heterozygous mutation in the *SLC2A2* gene (located on 3q) causes defect in GLUT2 transporter protein, resulting in defective monosaccharide transport across the membranes. Though also classified under glycogen storage disorder (GSD), use of the term GSD type XI is discouraged for this disorder.

**Features** These children might have a doll-like face and present with hypotonia, short stature, rickets and hepatomegaly (**Fig. 1**).

**Diagnosis** Laboratory features suggest renal rickets (low calcium and phosphorus, high alkaline phosphatase and normal vitamin D levels), proximal tubular defects (low urinary specific gravity, glycosuria, bicarbonaturia, phosphaturia and proteinuria), deranged liver function [abnormal prothrombin time (PT) and activated partial thromboplastin time (aPTT), hypercholesterolemia and hypogammaglobulinemia] and early morning hypoglycemia with postprandial hyperglycemia.

**Management** Management issues are guided toward prevention of early morning hypoglycemia and management of renal rickets.

### Disorders of Galactose Metabolism

Disorders of galactose metabolism give rise to increased galactose in blood. Galactosemia however refers to galactose-1-phosphate uridyl transferase deficiency. The major pathway for the metabolism of galactose is described as the Leloir pathway (**Fig. 2**). The three principal enzymes and the defects in the galactose metabolism pathway are designated as: galactokinase deficiency, galactose-1-phosphate uridyltransferase deficiency (GALT deficiency/galactosemia) and UDP-galactose-4-epimerase (GALE) deficiency (epimerase deficiency).

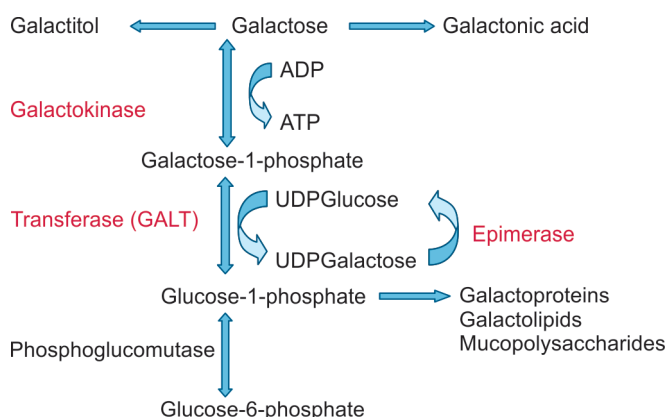
All the three enzyme deficiencies can be picked up during newborn screening by identifying increased amount of galactose or galactose-1-phosphate in dried blood spot (Guthrie card), provided the baby is on breastfeed or formula containing lactose. The specific enzyme defect is identified by enzyme assay in erythrocytes (blood needs to be drawn in heparin before the baby receives any blood transfusion). Multiplexing for detection of all the three enzymes can be done by methods using tandem mass spectrometry (MS/MS).

### Galactokinase Deficiency

**Etiology** This is an autosomal recessive disorder due to mutation in the *GALK1* gene (located on 17q). Due to galactokinase deficiency, galactitol and galactonic acid are produced following diversion of



**Figure 1** Child with Fanconi-Bickel syndrome with doll-like facies, short stature, hypotonia, rickets and hepatomegaly



**Figure 2** Metabolism of galactose/the Leloir pathway

galactose into secondary pathways. Accumulation of galactitol is the likely cause of cataract and sometimes cerebral edema.

**Features** Children suffering from galactokinase deficiency present with cataract; they might also develop pseudotumor cerebri. They however do not have mental retardation, jaundice or hepatomegaly as found in GALT deficiency.

**Diagnosis** Diagnosis is aided by a very high galactose in blood (may be as high as 100 mg/dL) after a lactose containing diet. Confirmation is by galactokinase enzyme activity in erythrocytes; this enzyme is very unstable at room temperature and special precautions need to be taken before ordering such tests.

**Management** Early treatment with lactose free diet and removal of galactose from diet prevents progression of cataract.

### Galactosemia (Galactose-1-phosphate Uridyltransferase Deficiency)

**Etiology** Galactosemia is an autosomal recessive condition caused by homozygous or compound heterozygous mutation in the *GALT* gene (located at 9p). As per the underlying mutation, residual erythrocyte GALT enzyme activity, levels of galactose metabolites (e.g., erythrocyte galactose-1-phosphate and urine galactitol), clinical manifestations and outcome, galactosemia can be described under three subcategories: classic galactosemia, clinical variant galactosemia and biochemical variant galactosemia.



**Features** Babies with classic galactosemia develop life-threatening events including feeding problems, hypoglycemia, hepatocellular damage, bleeding diathesis, jaundice and failure to thrive soon after starting breastfeeding or formula containing lactose. Sepsis with gram-negative organisms (notably *Escherichia coli*) may culminate in septic shock and death if these babies remain untreated. Infants, who survive the neonatal period, may develop severe brain damage if not started on lactose-free diet. If lactose-free diet is started in the first 3–10 days of life, the symptoms resolve rapidly and prognosis remains favorable for liver failure.

Even with early and adequate management, the long-term outcome in case of classic galactosemia can be unsatisfactory; there may be speech defects, poor intellectual function, neurologic deficits (tremor, dystonia and ataxia), growth failure, premature ovarian insufficiency and cataracts.

Clinical variant galactosemia has near identical manifestations as the classical variety and probably a favorable long-term outcome with early and adequate treatment.

**Diagnosis** In classic galactosemia, erythrocyte GALT enzyme activity is absent or barely detectable. Erythrocyte galactose-1-phosphate may be very high and usually is more than 10 mg/dL in the newborn period. When the patient is on a lactose-free diet, the level is more than and equal to 1 mg/dL (normal level of erythrocyte galactose-1-phosphate is <1 mg/dL). Plasma-free galactose is also very high and is usually more than 10 mg/dL.

**Management** Prevention of primary manifestations: Any newborn who is *screen-positive* during newborn screening or have clinical symptoms and biochemical parameters positive for galactosemia should be put on immediate dietary intervention while sample is sent for definitive diagnosis. If a baby is found to have classic galactosemia restriction of galactose intake should be continued and all milk products need to be replaced with lactose-free formulas. While growing up, they should be cautious to avoid casein or whey-containing foods and medicines containing lactose and galactose.

**Treatment of manifestations** Childhood speech problems including dysarthria require expert speech therapy. Developmental assessment and continued care is needed for developmental delay. Special education is required for school going children. Hormone replacement therapy may be required for delayed puberty and/or primary or secondary amenorrhea in females. Sometimes cataract surgery may be required.

**Prevention of secondary complications** Calcium and vitamin supplements help to prevent osteoporosis.

**Family evaluation** Evaluation of at-risk siblings at the earliest is required to prevent complications. Mutation testing in the affected baby and prenatal testing should be offered to the family.

### UDP Galactose-4-Epimerase Deficiency (Epimerase Deficiency)

**Etiology** This is an autosomal recessive condition due to mutation in the *GALE* gene (at 1p).

**Features and diagnosis** UDP-galactose 4-epimerase deficiency is categorized into severe and benign forms. Severe form is very rare (only few cases reported), and should be considered in individuals with liver disease, failure to thrive, who have elevated erythrocyte galactose-1-phosphate concentrations but normal erythrocyte GALT enzyme activity. The benign form is more common and is mostly identified during newborn screening.

**Management** The severe form requires dietary restriction like classic galactosemia. The outcome is uncertain. The benign form probably does not require much intervention.

### Disorders of Fructose Metabolism

Fructose is found abundantly in fruits, honey and various vegetables. Fructose in combination with glucose forms sucrose, which is a disaccharide. Liver is the major organ for fructose metabolism (**Fig. 3**). Here fructose is phosphorylated to fructose-1-phosphate (F-1-P) in presence of the enzyme fructokinase. Fructokinase is not present in muscle and adipose tissue; in these tissues, enzyme hexokinase converts fructose to fructose-6-phosphate.

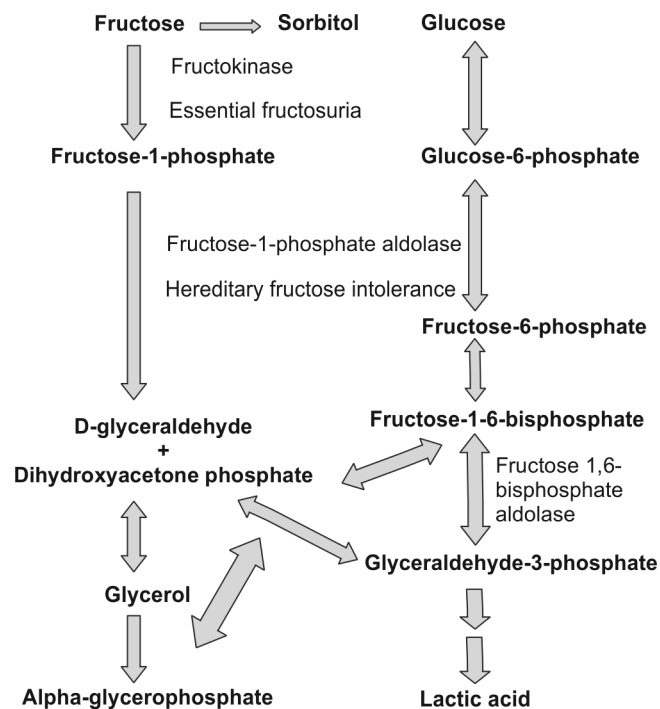


Figure 3 Fructose metabolism

### Hereditary Fructose Intolerance

Hereditary fructose intolerance (HFI) is a condition with devastating outcome if it remains undiagnosed. This condition is also referred to as fructosemia.

**Etiology** The underlying defect is deficiency of liver F-1-P aldolase (aldolase B). This condition is inherited in autosomal recessive fashion due to mutation in the *ALDOB* gene (at 9q).

**Features** HFI becomes apparent during infancy when sucrose and fructose-containing food are introduced while weaning. Children may present with recurrent vomiting, abdominal pain and hypoglycemia, which might be fatal at times. Continued exposure to fructose will result in growth failure, liver damage and renal tubulopathy. Some children might develop aversion to sweets and fruits as a compensatory mechanism to avoid symptoms; they might get diagnosed late during the course. Rarely, some might have a milder course and get diagnosed in adolescent or adulthood.

**Diagnosis** Peripheral blood cannot be used for enzyme assay since the enzyme is not present in leukocytes or red blood cells. Enzyme assay needs to be done in liver biopsy specimen or in intestinal mucosa. Enzyme activity is usually less than 10% of normal when F-1-P is used as the substrate, and is between 10% and 50% of normal when fructose 1,6-bisphosphate is used as the substrate. Diagnosis is aided by clinical symptoms and large amounts of fructose in urine. Most such children might also show a gross generalized aminoaciduria.

A fructose tolerance test can be done with caution for diagnosis. Administration of fructose, orally or parenterally, causes fall in the blood glucose (due to inhibition of glycogenolysis by F-1-P), fall in serum inorganic phosphate (due to its increased utilization during formation of F-1-P), rise in serum uric acid (arising from rapid degradation of purine) and lactic acidosis.

**Differential diagnosis** HFI may biochemically resemble tyrosinemia since there may be elevation of blood tyrosine and methionine in view of liver damage. The generalized aminoaciduria and hypoglycemia may resemble that found in galactosemia patients.

**Management** Prompt recognition and avoidance of fructose and sorbitol from diet has been shown to reverse liver and renal damage. Overall outcome including neurological function is found to be good in children, who are adequately managed.

## Gluconeogenic Disorders

There are various metabolic processes which interplay for the maintenance of glucose homeostasis in our body. During fasting, glucose is derived from breakdown of glycogen (glycogenolysis) or conversion of lactate and certain amino acids like glutamate, aspartate and alanine to glucose (gluconeogenesis). Gluconeogenesis primarily takes place in the liver and kidneys (**Fig. 4**). The overall process is partly controlled by the endocrine system. In cases of key enzyme deficiencies, there is hypoglycemia and lactic acidosis.

### Fructose 1,6-Bisphosphatase Deficiency

**Etiology** This is an autosomal recessive gluconeogenic disorder arising from mutation in the *FBP1* gene (located on 9q).

**Features** Children suffering from this disorder, present during infancy with hypoglycemia, lactic acidosis and ketosis following a trivial infection and/or fasting (**Fig. 5**). They may have periods of hyperventilation. Sometimes, manifestations are delayed and present action may resemble ketotic hypoglycemia. There may be hepatomegaly; but liver and kidney functions are normal.

**Diagnosis** The clinical picture along with detection of metabolites in urine by gas chromatography-mass spectrometry (GCMS), helps in diagnosis of the disorder. The enzyme assay needs to be done in liver tissue; so mutation analysis is a preferred method for confirmation of diagnosis. In view of hypoglycemia and hepatomegaly, this disorder is often confused with GSD type I; however, these children do not have the typical doll-like facies associated with GSD I.

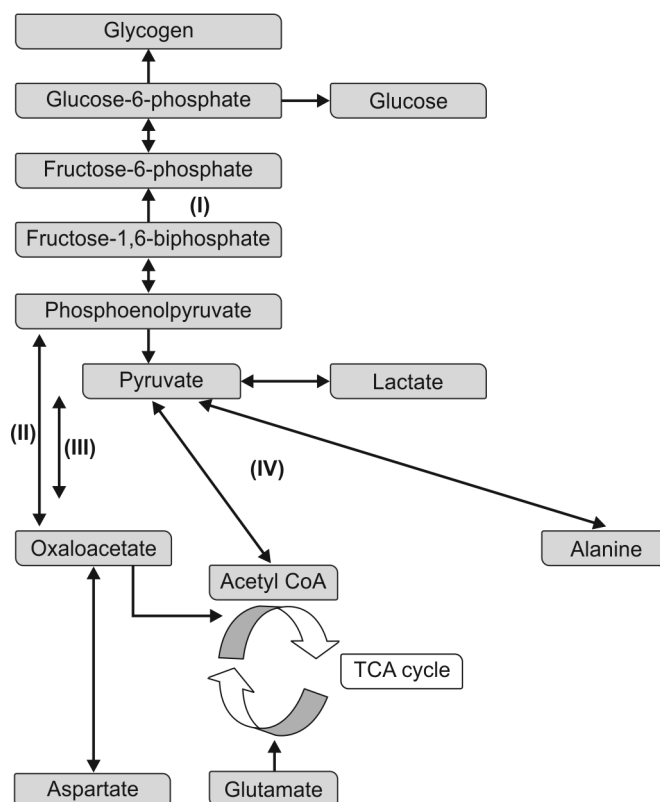
**Management** At times, undiagnosed, children may die in the neonatal period or early infancy; however, once recognized in time, most will have excellent outcome. Management consists of frequent feeding and avoidance of long periods of fasting. Avoidance of fructose and sorbitol in food and use of folic acid has been suggested.

### Pyruvate Carboxylase Deficiency

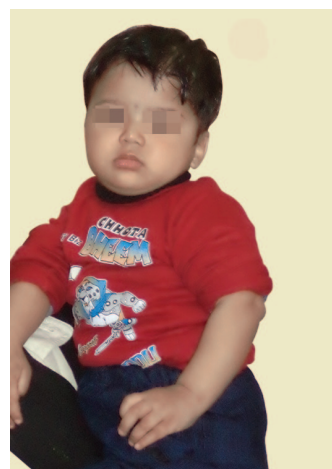
**Etiology** Pyruvate carboxylase deficiency is inherited in autosomal recessive fashion. The putative gene is located on 11q.

**Features** Affected children generally present in the neonatal period with metabolic acidosis due to increased lactic acid, hypotonia, hyporeflexia, refusal to feed and failure to thrive. Death might occur within first few months. Children surviving the neonatal period may present with seizures, hypotonia, metabolic acidosis and growth failure. Three clinical forms have been described: type A (infantile or North American form), type B (neonatal or French form) and type C (benign form). Genotype-phenotype correlation has been established.

**Diagnosis** Laboratory findings include metabolic acidosis with lactic acidosis, ketonemia and a near normal lactate/pyruvate ratio (exception is type B). There may be concomitant hypoglycemia,



**Figure 4** Gluconeogenesis. The positions of various enzymes/enzyme complex shown in Roman numerals are (I) fructose 1,6-bisphosphatase, (II) phosphoenolpyruvate carboxykinase, (III) pyruvate carboxylase, (IV) pyruvate dehydrogenase complex



**Figure 5** A normal looking 1-year-old child with fructose 1,6-bisphosphatase deficiency. He presented with episodic hypoglycemia, lactic acidosis and ketonuria, following trivial infections. He had hepatomegaly. Diagnosis is confirmed after mutation testing of the *FBP1* gene

Source: Dr Shubha R Phadke, SGPGIMS, Lucknow.

hyperammonemia, citrullinemia and hyperlysinemia. Such disorders are suspected when a baby with metabolic acidosis is being evaluated using arterial blood gas, serum lactate, ammonia, blood sugar and metabolic screen by tandem mass spectrometry and/or GCMS.

Low enzyme activity has been demonstrated in liver, leukocytes and skin fibroblasts. Enzyme activity in cultured amniocytes

has been used for prenatal testing in at-risk families. Definitive diagnosis is by mutation testing.

**Management** Supportive treatment is required to correct metabolic acidosis, dehydration and hypoglycemia. Peritoneal dialysis to reverse metabolic derangement has been tried. Biotin and thiamine have also been used in some patients. Ketogenic diet as a treatment for epilepsy should be avoided. Overall outcome remains poor even with all supportive measures.

### Deficiencies of Pyruvate Dehydrogenase Complex (PDHC)

As the name suggests, PDHC is an enzyme complex with three major enzymes (E1, pyruvate dehydrogenase or pyruvate decarboxylase; E2, dihydrolipoyl transacetylase; and E3, dihydrolipoyl dehydrogenase), and five coenzymes. Pyruvate dehydrogenase is composed of four subunits, two E1 alpha and two E1 beta. The alpha subunit is X-linked encoded by *PDHA1* gene located on Xp.

There is extreme variability in clinical expression in view of underlying biochemical and genetic heterogeneity. These children might have lactic acidosis, but they do not have hypoglycemia, unlike other disorders of gluconeogenesis. Patients with neonatal PDHC deficiency generally die within first few months of life. Most other children have neurological manifestations ranging from developmental delay, seizures, microcephaly and ataxia. In view of complexity and variability of this enzyme system, diagnosis and pinpointing the basic defect by enzyme assay remains difficult.

Treatment with ketogenic diet low is recommended; however, overall outcome remains unfavorable. Somewhat favorable outcome has been reported in patients with dihydrolipoyl dehydrogenase deficiency, who are treated with lipoic acid treatment and diet low in branched chain amino acids.

### Disaccharidase Deficiencies

The major carbohydrates in our diet are starch (which is broken down to maltose, maltotriose, isomaltose and alpha-limit dextrins), lactose and sucrose. Deficiency of disaccharidases causes accumulation of undigested disaccharides leading to bacterial overgrowth.

#### Etiology

Acquired deficiencies are common due to following acute intestinal infections, which causes damage to the brush border of the small intestine. They are mostly transient and resolve with time. There can be inherited deficiencies due to mutation in certain genes.

#### Lactase Deficiency

Lactase deficiency is found to happen in two different clinical settings with mutation in two different genes which lie near one another. *Congenital lactase deficiency* presenting in early infancy is found commonly in Finnish population. It is inherited in autosomal recessive pattern due to mutation in the *LCT* gene (lactase gene) located at 2q. The *adult onset form* called lactase non-persistence is probably inherited in autosomal dominant fashion, found commonly in Mediterranean, African-American and Asian population. With time it has been perceived that the disease is due to noncoding sequence variations in *MCM6* gene; located upstream of the lactase gene (at 2q).

#### Sucrase-Isomaltase Deficiency

This disorder is inherited in autosomal recessive pattern due to mutation in the *SF* gene located on 3q.

#### Features of Disaccharidase Deficiency

The symptoms of disaccharidase deficiency are abdominal pain, flatulence, diarrhea and perianal redness. Stools are acidic, foamy and watery. Following milk feeds, babies with congenital lactase deficiency present with diarrhea, dehydration, acidosis and weight loss.

### Diagnosis

Disaccharidase deficiencies are diagnosed using a challenge test, where there is a flat blood glucose curve with increased breath hydrogen concentration, after ingestion of the suspected disaccharide.  $^{13}\text{C}$ -sucrose labeled breath test is useful for sucrase-isomaltase deficiency.

Definitive diagnosis can be done by enzyme assay in small bowel biopsy specimen or by mutation testing of the putative gene.

### Management

Management of lactase deficiency is avoidance of lactose in diet. Lactose-free infant formulas are readily available these days. It is, however, important to differentiate the acquired causes, where lactose-free formula need not be continued for long.

### Disorders of Pentose Metabolism

Hexose monophosphate pathway is an alternative pathway of glucose metabolism, which caters to around 10% of the total glucose metabolized in our body. This shunt leads to formation of pentoses and provides nicotinamide adenine dinucleotide phosphate (NADPH). The important disorder, glucose-6-phosphate dehydrogenase (G6PD) deficiency, is linked to this pathway. It, however, is not generally described under carbohydrate metabolism; and more commonly described under hemolytic anemia. The abnormalities related to pentose metabolism are very rare and only described as few case reports.

### Congenital Disorders of N-Linked Glycosylation

#### Etiology

Many proteins undergo post-translational modification. Glycosylation is addition of oligosaccharides or glycans on these proteins. These glycans are of two types designated as per their linkage to the protein, O-linked and N-linked. N-linked refers to those bound to the amide group of asparagine.

Congenital disorders of N-linked glycosylation, also called the CGDs are a group of disorders caused by deficiency of various enzymes (around 42 different enzymes) in the N-linked synthetic pathway. They are genetically heterogenous, most inherited as autosomal recessive fashion; some are X-linked. These days nomenclature includes the word CDG linked to the gene involved; this makes description easier than the old nomenclature with numerical and alphabetical system.

#### Features

As glycosylated proteins have widespread distribution, most such disorders have multisystem manifestations. Most disorders begin in infancy, manifesting as severe developmental delay and hypotonia with multiple organ system involvement. In the other end of the spectrum, there are children presenting with protein-losing enteropathy with normal development. Only few individuals are described in each type; making understanding of each phenotype difficult.

PMM2-CDG (*CDG-Ia*) is the most common type reported; it has a highly variable presentation and clinical course. The clinical progression is divided into infantile multisystem stage, late-infantile and childhood ataxia-intellectual disability stage, and adult stable disability stage. The classical diagnostic clue of *inverted nipples* and *abnormal fat distribution* (**Figs 6A and B**) may not be present in many children. The typical neurological features are slow-rolling vertical and horizontal eye movements with slow head movement in neonatal period along with hyporeflexia and hypotonia. There can be alternating internal strabismus, seizures, stroke-like episodes, stupor and coma. Some might present with intracranial hemorrhage. Various changes are described in neuroimaging ranging from myelination defects to atrophic changes.



## Diagnosis

The diagnostic test for most types of CDGs is transferrin isoform analysis, mostly done by isoelectric focusing of serum transferrin to determine the defect in sialylated N-linked oligosaccharides linked with serum transferrin. Other methods including capillary electrophoresis have also been used. Exact enzymatic defect is difficult to be determined; molecular testing by gene panels has been more readily used for definitive diagnosis and prenatal testing.

## Management

Most infants and children with all types of CDG require nutritional supplements [except MPI-CDG (*CDG-Ib*)]. Many may require nasogastric tube or gastrostomy tube feedings. Supportive therapies for gastroesophageal reflux, developmental delays, ocular findings, stroke-like episodes, orthopedic issues, etc. are required. For MPI-CDG (*CDG-Ib*), mannose is given as 1 g/kg/day in five divided oral doses. It is found to normalize hypoproteinemia and coagulation defects; it also improves the protein-losing enteropathy and hypoglycemia associated with MPI-CDG.

Acetaminophen and other agents metabolized by the liver need to be avoided.

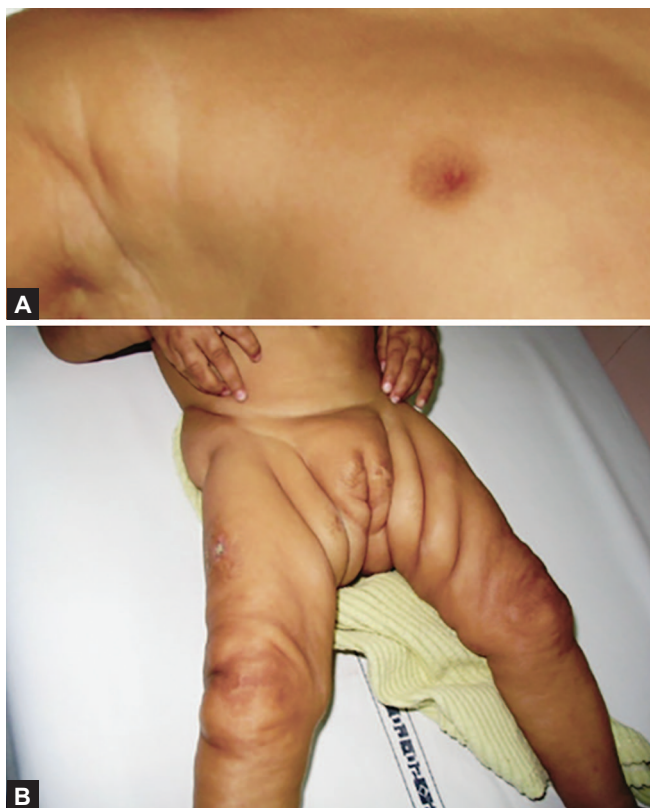
Care should be taken about coagulation status before surgery in view of increased risk of bleeding and deep venous thrombosis.

## Glycogen Storage Disorders

Glycogen is the principle storage form of carbohydrate in our body. GSDs are a group of disorders that affect glycogen metabolism. The glycogen is of abnormal quality, quantity or both. These disorders are described in the subsequent chapter.

### IN A NUTSHELL

1. Though disorders of carbohydrate metabolism are rare, they need to be suspected in certain clinical settings with hypoglycemia and lactic acidosis.
2. Galactosemia is being incorporated in newborn screening program. A timely intervention might minimize neurological disabilities in the affected babies.
3. Some of the disorders like fructose 1,6-bisphosphatase deficiency and HFI have very good prognosis, if recognized and treated in time. Most of them require avoiding certain foods and refraining from fasting states.
4. Some disorders like essential fructosuria are benign disorders; they only require reassurance.
5. Most disorders are autosomal recessive conditions. They are prone to recur in the family. The recurrence risk is 25% for autosomal recessive and X-linked recessive disorders.
6. A definitive diagnosis by enzyme assay and/or mutation testing in the affected child is a priority.
7. Various metabolites in blood and urine can be tested by tandem mass spectrometry (MS/MS) and GCMS; these methods can be used as screening tests for difficult to recognize metabolic disorders.
8. When there is diagnostic dilemma, testing for gene panels for specific group of disorders or exome sequencing might help in finding the putative gene.



**Figures 6A and B** (A) Inverted nipple; (B) Abnormal fat distribution in a child with congenital disorders of N-linked glycosylation (CDG)

Source: Contributed by Dr Ratna Dua Puri.

### MORE ON THIS TOPIC

- Dhanya Lakshmi N, Phadke SR. Fructose-1,6-bisphosphatase deficiency: a treatable cause of recurrent hypoglycemia. *Genet Clin.* 2014;7:3-5.
- Ekbote AV, Mandal K, Agarwal I, et al. Fanconi-Bickel syndrome: mutation in an Indian patient. *Indian J Pediatr.* 2011;79:810-2.
- Krishnani PS, Chen Y. Disorders of carbohydrate metabolism. Emery and Rimoin's Principles and Practice of Medical Genetics. USA: Elsevier; 2013. pp. 1-36 in online version.
- Mandal K, Aneja S, Seth A, Khan A. Berardinelli-Seip congenital lipodystrophy. *Indian Pediatr.* 2006;43:440-5.
- Valle D, Vogelstein B, Kinzler KW, et al. The online metabolic and molecular bases of inherited disease (online version of The Metabolic and Molecular Bases of Inherited Disease by Scriver and coworkers). Chapters 67-76. From: [www.ommbid.mhmedical.com](http://www.ommbid.mhmedical.com). Accessed August 1, 2014.



## Chapter 3.14

# Glycogen Storage Diseases

Priya S Kishnani, Stephanie Austin

Glycogen storage diseases (GSDs) are caused by the inability to synthesize or metabolize stored glycogen. In some GSDs, there is an accumulation of normally structured glycogen while in others the structure of glycogen is abnormal. GSDs are categorized either chronologically by discovery or by the type of tissue involved, which primarily includes liver, muscle and cardiac tissue. To date, over twelve glycogen metabolism disorders have been catalogued. Hepatic GSDs include types I, III, IV, VI, IX and XI. Muscle GSDs include types II, III, V, VII and IX. Hepatic glycogenoses cause hepatomegaly and fasting hypoglycemia, whereas the muscle glycogenoses can cause muscle weakness and cramps during exercise. Progressive limb-girdle muscle weakness occurs in some patients, especially those with Pompe disease (GSD II).

The phenotypic expression of the gene defects involved in GSDs greatly varies and both the age of onset of symptoms and the rate of progression can be different for the same enzymatic defect. Symptoms can either be correlated with the degree of residual enzyme activity or with different mutations in the genes. With the exception of hepatic phosphorylase kinase deficiency and lysosomal-associated membrane protein 2 (LAMP2) deficiency, which are inherited as X-linked recessive traits, all of these disorders are inherited as autosomal recessive traits.

Glycogen storage diseases are most often diagnosed at a young age due to the early onset of symptoms. Treatment for GSDs affecting the liver often involves maintaining glucose levels by regulating the release of glucose into the bloodstream. Treatment for GSDs that affect muscles often involves avoiding muscle weakness by limiting exercise or increasing protein intake. Early treatment is imperative to reducing the severity of the symptoms of GSDs.

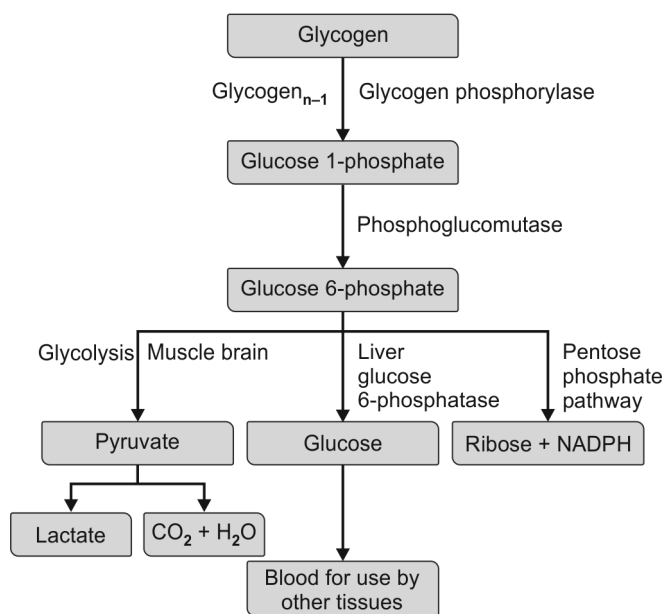
## ETIOLOGY

Glycogen storage diseases are genetic disorders. The majority of GSDs are due to autosomal recessive inheritance, with the exception of a few forms that are due to X-linked inheritance (hepatic phosphorylase kinase deficiency and LAMP2 deficiency). The genetic mutations that result in each GSD cause a defect in a particular enzyme that affects glycogen metabolism.

## PATHOGENESIS

Normal glycogen metabolism is shown in **Figure 1**. A schematic diagram showing different GSDs and their pathways is shown in **Figure 2**. GSD type I has two biochemical subtypes: GSD Ia and GSD Ib, each derived from deficiencies in particular components of the glucose-6-phosphatase complex. The defects in both type Ia and type Ib lead to inadequate hepatic conversion of glucose-6-phosphate to glucose through normal glycogenolysis and gluconeogenesis and make affected individuals susceptible to fasting hypoglycemia. GSD II will be discussed in Chapter 3.15 on Pompe disease.

Glycogen storage disease type III is due to a deficiency of the debrancher enzyme, necessary to cleave the 1,6 linkages in the outer branches of the glycogen molecule, resulting in the accumulation of glycogen with short branch points (limit dextrin) because of incomplete glycogenolysis. In type IIIa, many patients develop a progressive myopathy due to the deficiency of both liver and muscle debrancher enzyme. Type IIIb, in which



**Figure 1** Normal glycogen metabolism

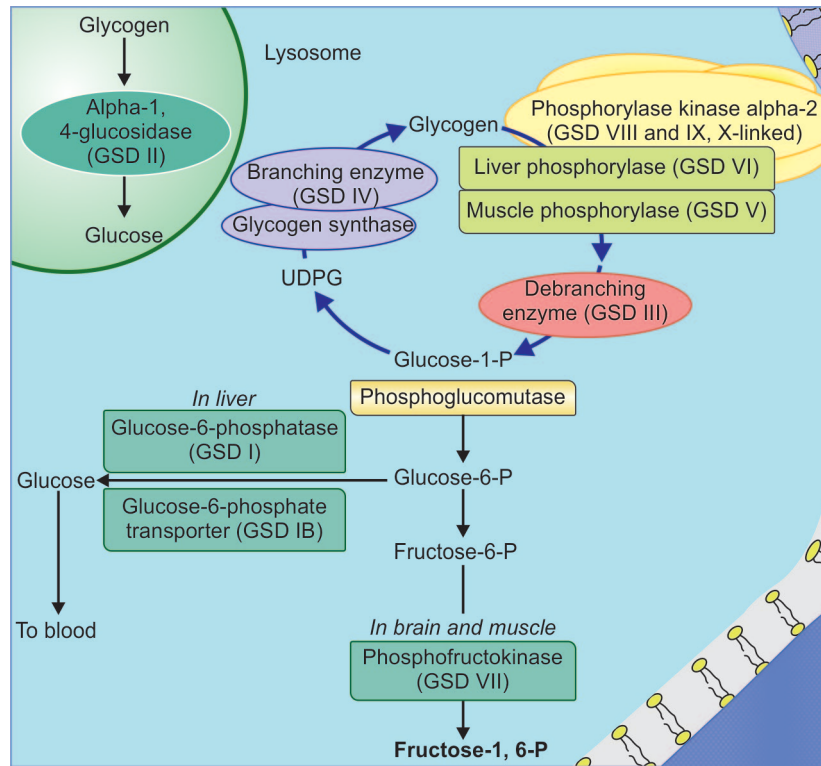
the deficiency is only in the liver, is less common. Patients have fasting hypoglycemia, but unlike patients with GSD I, infants with debrancher deficiency can tolerate longer fasts due to active phosphorylase and intact gluconeogenesis. When the feeding times are spaced many hours apart or when the child is unable to feed because of illness, hypoglycemia can occur.

Glycogen storage disease type IV, Andersen's disease, is the most variable of the GSDs. The deficiency of the brancher enzyme produces amylopectin, an abnormal glycogen with few branch points. GSD type V, McArdle's disease, is one of the most common GSDs. It is caused by a deficiency of myophosphorylase. This enzyme is necessary for the cleavage of glucose-1-phosphate from glycogen. Lack of production of glucose-1-phosphate impairs energy production through the glycolysis pathway, leading to muscle weakness and cramping. GSD type VI is caused by a deficiency of hepatic phosphorylase, which is regulated by a complex system of activators. Phosphorylase kinase activates this enzyme and is, in turn, activated by other enzymes such as hepatic cAMP-dependent protein kinase.

Glycogen storage diseases type VII, Tauri's disease, is caused by a deficiency of the muscle isozyme of phosphofructokinase. GSD IX, which is also one of the most common GSDs, is caused by deficiency of phosphorylase b kinase (PhK). PhK activates liver and muscle glycogen phosphorylase and is composed of four copies each of four subunits and the most common subtype of liver PhK deficiency, which affects about 75% of patients, is inherited in an X-linked manner.

## CLINICAL FEATURES

Patients with GSD I type Ia may present in the first few months of life with hypoglycemia, lactic acidosis, and hepatomegaly. There may be typical *doll-like facies* (**Fig. 3**). Because none of the glycogens can be converted directly to glucose, hypoglycemia occurs soon after the last meal and can cause hypoglycemic seizures. The resulting excess glucose-6-phosphate is shunted through the Embden-Meyerhof pathway, causing excessive production of lactic acid, lipid synthesis and hyperuricemia. The pathways for gluconeogenesis also become activated, adding to the production of these intermediary metabolites. Other manifestations include



**Figure 2** Different glycogen storage diseases and their pathways



**Figure 3** A child with glycogen storage disease type I. Note hepatomegaly and chubby appearance

impaired platelet function, recurrent renal disease, pancreatitis, and hepatic adenomas. Type 1b disease also causes impaired neutrophil function with risk for recurrent infections and inflammatory bowel disease.

The clinical spectrum for patients with GSD type III is broad, with some infants resembling type I disease and some patients presenting later in life. Hepatomegaly, elevated liver enzymes (Aspartate transaminase, Alanine transaminase) and hyperlipidemia are seen in patients with GSD IIIa and IIIb. Patients with GSD IIIa usually do not experience clinical symptoms of myopathy until the third or fourth decade of life. Cirrhosis, portal hypertension, hepatocellular carcinoma, and liver failure may occur and be progressive. Patients can also develop

widespread myopathy including weakness of the proximal and distal small muscles of the hand. In addition, some patients have abnormal nerve conduction studies. Patients with GSD IIIa may develop cardiac hypertrophy, and are at risk for life-threatening arrhythmias. Cardiac manifestations are extremely variable; there is no correlation between extent of involvement of liver, heart and skeletal muscle.

The classic presentation of GSD type IV includes failure to thrive, hepatosplenomegaly, progressive cirrhosis of the liver, and death in childhood. Other presentations include an infantile form sharing characteristics of infantile Pompe disease, such as childhood progressive myopathy and cardiomyopathy, and an adult-onset form involving polyglucosan body disease, which affects both the central and peripheral nervous system. In patients with progressive liver presentation, liver enzymes are elevated. Additionally, in late stages, synthetic function decreases to 1–10% of normal function. Hypoglycemia can be a feature in cases with progressive liver cirrhosis. Biopsy material from involved tissue shows Periodic Acid-Schiff (PAS)-positive inclusions and characteristic fibrillar aggregates of amylopectin.

Most patients with GSD type V present in childhood with muscle fatigue, cramps on routine exercise, and myoglobinuria with strenuous exercise. Patients with myophosphorylase deficiency often demonstrate a *second-wind phenomenon*. Attributed to increased oxidative capacity, this anomaly is caused by increased glucose infusion during exercise. The blood creatine kinase (CK) is usually elevated, especially when the patient is symptomatic.

Clinical presentation in GSD type VI is variable, ranging from mild to severe. Hepatomegaly and growth retardation mark the childhood clinical course. Hypoglycemia, hyperlipidemia, mild to moderate elevations of serum transaminase values, and hyperketosis are typical laboratory findings. Hepatomegaly usually improves as the patient ages, although those with a more severe presentation have presented with significant hepatomegaly, recurrent severe hypoglycemia and postprandial lactic acidosis.

In patients with GSD type VII, glycolysis is impaired, causing fatigue, cramps from exercise and myoglobinuria. Patients rarely present with infantile hypotonia or progressive myopathy.

A common symptom of patients with GSD type IX is liver PhK deficiency which is more often seen in males, although some female carriers may exhibit symptoms. Children with liver PhK deficiency usually present in the first 2 years of life with short stature and abdominal distention from moderate to marked hepatomegaly, all of which usually improve by adolescence. The clinical severity varies considerably and some patients can be very involved with significant liver disease. This is usually seen in patients with the gamma variant form of the disease. Symptoms include hyperketotic hypoglycemia, hypotonia, mild gross motor delays, and liver fibrosis. Some patients can have progressive liver cirrhosis and liver failure. In rare cases, presentation includes liver adenoma and renal tubular acidosis.

Muscle-specific PhK deficiency is a rarely reported X-linked condition with a clinical presentation ranging from exercise intolerance, with myoglobinuria and muscle cramping, and progressive muscle weakness presenting from childhood to adulthood, to a virtually asymptomatic condition. Serum CK may be normal.

## DIFFERENTIAL DIAGNOSES

Due to the broad spectrum of GSDs, when diagnosing patients with GSDs, it is often difficult to differentiate between certain types of GSDs. The clinical features of GSD I and GSD III are often similar. Hypoglycemia, which can be present in both types; however, it is often more severe in GSD type I. GSD III can also be distinguished from GSD I early in childhood by measuring liver enzyme, plasma CK concentrations, and plasma ketones (these are increased in GSD III as compared to GSD I). Patients with GSD I have a lactic acidosis, hyperuricemia and much higher levels of serum triglycerides and cholesterol as compared to GSD III. Patients with GSD VI and GSD IX have several similar clinical features as well, that makes it difficult to distinguish between both types. Checking for activity of phosphorylase and phosphorylase kinase can be used to diagnose either GSD VI or IX.

Another gluconeogenesis disorder that has several clinical features similar to GSD I, Fructose 1-6-bisphosphatase deficiency, has biochemical abnormalities that are similar to those in GSD I. Unlike GSD I, however, when glucagon administration is performed in the fed state, it elicits a brisk glycemic response. In patients with GSDs that affect muscle, there are other muscular disorders that must be considered as well, such as Duchenne muscular dystrophy, and secondary muscular disorders such as polymyositis.

## Approach to Diagnosis

Glycogen storage disease type Ia usually has an earlier presentation with hepatomegaly, hypoglycemia, lactic acidosis, hyperuricemia and deranged lipid profile with hypertriglyceridemia. GSD Ib additionally has neutropenia and frequent infections. Diagnosis can be confirmed by enzyme assay in liver biopsy (not available in India) or mutation analysis. Diagnosis of GSD type III is suspected in infants and children with fasting hypoglycemia and hepatomegaly and in older patients with progressive myopathy. Glucagon increases blood glucose after a carbohydrate meal but not after fasting. The liver biopsy shows typical glycogen storage and liver tissue can be assayed for the debrancher enzyme. Confirmation of a GSD IIIa diagnosis requires demonstration of enzyme deficiency in liver and muscle. Mutation analysis is available. Mutations in exon 3 at amino acid codon 6, [c.18\_19delGA (p.Gln6HisfsX20) and c.16C > T (p.Gln6X)], in combination with another mutation, are indicative of IIIb. The gene is located on chromosome 1p21.

Diagnosis of GSD type IV can be made by assaying the enzyme in a variety of tissues, including leukocytes, fibroblasts and amniocytes. Mutations in the gene *GBE1*, located on chromosome 3p14, are known to cause GSD type IV.

The ischemic exercise test can be useful for identifying patients with GSD type V; however, it is not specific to McArdle disease. Muscle biopsy shows subsarcolemmal lakes of PAS-positive material that is diastase positive. Myophosphorylase enzyme activity can be assayed in muscle tissue and demonstrated by histochemical stains on frozen sections from muscle biopsy. Genetic testing is available and is best to confirm diagnosis. The gene is located on chromosome 11q13.

The diagnostic approach for GSD type VII is similar to that used in McArdle disease. Muscle biopsy shows glycogen storage and the ischemic exercise test is positive. An enzyme analysis is necessary for a definitive diagnosis. The gene is located on chromosome 1q32.

Patients with GSD type IX can be diagnosed by deficient PhK activity in liver, erythrocytes or leukocytes. Genetic testing is also available. At diagnosis, individuals with liver PhK deficiency usually have elevated liver transaminases, and mildly elevated triglycerides and cholesterol. Liver glycogen content is markedly elevated in this GSD, similar to GSD III. The structure of glycogen is, however, abnormal in GSD III with an altered ratio of glucose-1-phosphate to glucose.

The relationship between the cognitive impairment and PhK deficiency is unclear. Electromyography and plasma lactate levels on forearm ischemic exercise tests are usually normal in these patients. Muscle biopsies show subsarcolemmal glycogen accumulation and marked reduction of PhK activity. Mutations causing muscle-specific PhK deficiency have been found in the gene encoding the alpha-subunit of PhK in muscle (PHKA1). Mutations causing liver-specific PhK deficiency are found in genes encoding both the alpha-subunit (PHKA2) and the gamma-subunit (PHKG2). Autosomal recessive PhK deficiency in both muscle and liver is linked to mutations in the gene encoding the beta-subunit (PhKB).

## MANAGEMENT

Treatment for GSD type I involves continuous nocturnal nasogastric feedings or uncooked cornstarch and should begin as soon as the diagnosis is suspected to maintain normal blood glucose levels and to prevent long-term complications. Nocturnal meals, in certain cases, may replace these nasogastric feedings. A number of enteral formulas and glucose polymers, such as uncooked cornstarch, can be used. Since infants may not adequately digest the starch, they may need to be given pancreatic enzymes. Older children should receive frequent daytime feedings of complex carbohydrates in addition to cornstarch to help maintain euglycemia and promote growth. Additionally, fructose and galactose intake should be restricted. Due to their high intake of carbohydrates, patients with GSD I should generally maintain a low-fat diet. The diet often needs supplementation with vitamins, specifically vitamin D, calcium and iron when there is a possibility of anemia. Secondary problems, such as hyperuricemia, hyperlipidemia and hepatic adenomas must be monitored and treated appropriately. In studies involving patients with small hepatic adenomas, percutaneous ethanol injection or transcatheter arterial embolization have been used as treatments. Liver transplantation or pre-emptive simultaneous liver plus kidney transplantation is required for some patients. Patients with GSD Ib have neutropenia and are at risk for life-threatening bacterial infections; these patients benefit from treatment with granulocyte colony-stimulating factor, but their spleen size, bone density and blood counts should be monitored.

Management of GSD type II, both infantile and late onset Pompe disease, has been greatly improved with the advent of enzyme replacement therapy using  $\alpha$ -glucosidase alfa and its approval for human use in 2006.



Glycogen storage diseases type III can be managed by cornstarch intake and a high protein diet. The latter is extremely useful due to intact gluconeogenesis. A ketogenic diet has also been shown to improve cardiomyopathy. Unlike GSD I, these patients do not have to restrict intake of sucrose and fructose. Frequent daytime meals rich in complex carbohydrates and proteins are usually sufficient to prevent hypoglycemia.

For patients with GSD type IV, there is no treatment except liver transplantation for those with progressive cirrhosis. This does not prevent nonhepatic complications of this disease.

Patients diagnosed with GSD type V can lessen symptoms and the chance of developing rhabdomyolysis by avoiding strenuous exercise. Exercise tolerance may be increased by fat and carbohydrate-rich meals as well as creatine and vitamin B<sub>6</sub> supplements taken prior to exercise.

Patients with GSD type VI can be managed with a high-carbohydrate and protein diet and frequent feeding to prevent hypoglycemia. There is no specific management other than avoidance of strenuous exercise for patients with GSD type VII. The use of a ketogenic diet has proven effective in some cases. Unlike in McArdle disease, eating before exercising worsens intolerance in Tauri disease.

Hypoglycemia in patients diagnosed with GSD type IX can be prevented by frequent daytime meals that are high in complex carbohydrates and protein. Growth may be improved by carbohydrate and protein supplementation, presumably by reducing the demand for gluconeogenesis and increasing insulin secretion. Individuals with muscle PhK deficiency may benefit from physical therapy and nutritional consult to optimize glucose concentrations based on level of activity. Malignant hyperthermia precautions should be taken.

## PREVENTION

Since GSDs are genetic disorders, there are no prevention measures that can be taken. In a known family history, prenatal diagnosis is possible allowing for treatment decision including not continuing an affected pregnancy. However, early diagnosis and treatment can greatly reduce the effects of GSDs on children.

## IN A NUTSHELL

1. Glycogen storage diseases are caused by the inability to synthesize or metabolize stored glycogen.
2. Glycogen storage diseases are categorized either chronologically by discovery or by the type of tissue involved, which primarily includes liver, muscle and cardiac tissue.
3. To date, over twelve glycogen metabolism disorders have been catalogued. Hepatic GSDs include types I, III, IV, VI, IX and XI. Muscle GSDs include types II, III, V, VII and IX. Hepatic glycogenoses cause hepatomegaly and fasting hypoglycemia, whereas the muscle glycogenoses can cause muscle weakness and cramps during exercise.
4. Glycogen storage diseases are most often diagnosed at a young age due to the early onset of symptoms.
5. Treatment for GSDs affecting the liver often involves maintaining glucose levels by regulating the release of glucose into the bloodstream. Treatment for GSDs that affect muscles often involves avoiding muscles weakness by limiting exercise or increasing protein intake.

## MORE ON THIS TOPIC

- Chou JY, Jun HS, Mansfield BC. Glycogen storage disease type I and G6Pase- $\beta$  deficiency: etiology and therapy. *Nat Rev Endocrinol*. 2010;6:676-88.
- Chou JY, Mansfield BC. Gene therapy for type I glycogen storage diseases. *Curr Gene Ther*. 2007;7:79-88.
- Heller S, Worona L, Consuelo A. Nutritional therapy for glycogen storage diseases. *J Pediatr Gastroenterol Nutr*. 2008;47:S15-21.
- Hicks J, Wartchow E, Mierau G. Glycogen storage diseases: a brief review and update on clinical features, genetic abnormalities, pathologic features and treatment. *Ultrastruct Pathol*. 2011;35:183-96.
- Oldfors A, DiMauro S. New insights in the field of muscle glycogenoses. *Curr Opin Neurol*. 2013;26:544-53.
- Ozen H. Glycogen storage diseases: new perspectives. *World J Gastroenterol*. 2007;13:2541-53.
- Quinlivan R, Buckley J, James M, et al. McArdle disease: a clinical review. *J Neurol Neurosurg Psychiatry*. 2010;81:1182-8.
- Shin YS. Glycogen storage disease: clinical, biochemical and molecular heterogeneity. *Semin Pediatr Neurol*. 2006;13:115-20.



## Chapter 3.15

# Pompe Disease

Mari Mori, Priya S Kishnani

Pompe disease (glycogen storage disease type II or acid maltase deficiency) is caused by a deficiency of acid alpha-glucosidase (GAA), leading to the deposition of glycogen predominantly in skeletal, smooth and cardiac muscles. GAA deficiency results in glycogen accumulation in lysosomes of all tissues, leading to progressive muscle destruction. It can present at various ages with variable symptoms. Advent of enzyme replacement therapy (ERT) with alglucosidase alfa has changed the natural history of the disease.

The disease is broadly categorized as infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD). IOPD is further divided into two groups—*classic* and *atypical* (or *nonclassic*). Classic IOPD is characterized by generalized muscle weakness, hypotonia and hypertrophic cardiomyopathy. Atypical IOPD is characterized by slower progression, less severe to no cardiac involvement, and survival past 2 years of age. In IOPD, skin fibroblast GAA enzyme activity is below 1% of normal levels. LOPD is characterized by progressive muscle weakness with onset as early as age 1 year to as late as the sixth decade. Cardiac involvement, while more typical for classic IOPD, can be seen across the disease continuum. The cause of death in LOPD is typically respiratory failure.

Outcome of ERT is impacted by age and stage of the disease at treatment initiation, amongst other factors such as muscle fiber type, underlying mutation and defective autophagy. In this chapter, the new emerging natural history, limitations of ERT and pharmacologic and nonpharmacologic treatment approaches are reviewed. Multidisciplinary approach holds a key to an improved quality of life for patients with Pompe disease.

## EPIDEMIOLOGY

The prevalence of Pompe disease was previously estimated to be 1 in 40,000 livebirths, with varying prevalence depending on ethnicity. Founder effects in Taiwanese, Chinese and African population have been reported. New data from newborn screening (NBS) in Taiwan has shown an estimated prevalence of 1 in 18,108 across the disease spectrum.

## ETIOLOGY

Pompe disease is inherited in an autosomal recessive manner. The disease is caused by mutations in the GAA gene encoding GAA. The gene has been mapped on chromosome 17q21-q23. A founder mutation is found in the Chinese population causing IOPD, p.Asp645Glu; a common mutation found in African Americans is known, p.Arg854X; and a common mutation is known among Europeans, p.Gly309Arg. Genotype-phenotype correlation exists to some extent.

## PATHOGENESIS

Acid alpha-glucosidase digests glycogen to glucose. The enzyme is synthesized in the endoplasmic reticulum-Golgi complex and is transported to the lysosomes. It is a glycoprotein and goes through various modifications in the process. GAA activity is decreased in all tissues of patients with Pompe disease. Fibroblasts from IOPD have less than 1% residual activity, while those from LOPD have 1–40% residual activity.

Genotypes overall correlate with expression and activity of GAA. Over 200 disease causing mutations have been discovered and are available on the website: <http://cluster15.erasmusmc.nl/klgn/pompe/mutations.html>. The splice site mutation c.-32-13T > G is the most common mutation found in LOPD. It allows production of some normal protein leading to a less severe phenotype. The c.525delT and exon 18 deletion mutations are the most common mutations in the IOPD patients. Certain mutations correlate with cross-reactive immunological material (CRIM) status. CRIM-positive indicates detectable GAA protein, whereas CRIM-negative denotes absence of GAA protein (processed and unprocessed). The p.Arg854X stop mutation is a common mutation found in CRIM-negative patients. The majority of CRIM-negative patients are homozygous or compound heterozygous for nonsense, frame shift or exon-level deletions. In contrast, CRIM-positive patients have missense mutations, in-frame deletions or other milder mutations.

Muscle biopsy specimens show vacuolar myopathy. Both free and lysosomal glycogen accumulate in most tissues. Electron microscopy shows glycogen in lysosomal sacs, as well as in cytoplasm. It is important to recognize that histology may appear normal in LOPD depending on the site of biopsy. Enzyme testing is recommended when there is a strong clinical suspicion, as biopsy results can be reported as normal in LOPD. In these cases, positive acid phosphatase stain can be useful in making the diagnosis.

Compromised autophagy is evidenced both in humans and murine models. Autophagy debris build-up in muscle correlates with a decrease in muscle strength, mitochondrial dysfunction and muscular atrophy. Earlier treatment leads to less autophagic build-up.

## CLINICAL FEATURES

The severity of the Pompe disease reflects the residual activity of the acid alpha-glucosidase enzyme. The phenotype is also influenced by environment, diet, exercise and other genetic elements.

Infantile onset Pompe disease is the severe end of the spectrum of Pompe disease. Infants can manifest at birth or in the first few days to weeks of life with generalized hypotonia (**Figs 1A and B**) and muscle weakness. Classic IOPD is characterized by hypertrophic cardiomyopathy (**Fig. 1C**) and skeletal myopathy. Glycogen accumulation increases the muscle bulk (pseudohypertrophy), most prominent in the gastrocnemius muscles. Macroglossia is commonly seen. Infants with IOPD, if untreated, usually die before 2 years of age due to complications of cardiac and muscle weakness. Atypical IOPD present with slower progression with or without cardiac involvement. A natural history study of IOPD showed median onset of 2 months of age, diagnoses at 4.7 months, and death at 8.7 months. Central nervous system involvement in patients with IOPD includes anterior horn cells and brain stem nuclei. Treatment with ERT has changed the course of the disease. The oldest survivors are now 15 years of age. Long-term complications include persistent myopathy leading to a risk for cardiac arrhythmias, ptosis, hypernasal speech, swallowing dysfunction, poor anal sphincter tone, basilar artery aneurysm, and sensorineural hearing loss. Late-onset Pompe disease is characterized by muscle weakness manifesting from early childhood to late adulthood. Weakness predominates in truncal and proximal muscles, with lower extremities more involved than upper extremities. Respiratory muscles are also selectively affected. Respiratory insufficiency may be the presenting complaint and be associated with morning headache, exertional dyspnea, or sleep-disordered breathing. In LOPD, respiratory muscles are affected early and respiratory failure is usually the cause of death. LOPD can also present with ptosis, rigid spine syndrome, lingual weakness, and vascular complications such as basilar artery aneurysms, arrhythmias including Wolff-Parkinson-White (WPW)



**Figures 1A to C** Child with Pompe disease: Extreme floppiness. (A) Slip through appearance; (B) Ragged doll appearance; (C) Chest X-ray PA view shows presence of cardiomegaly. Source: Dr Neerja Gupta, AIIMS, New Delhi.

syndrome, intracranial aneurysms, lingual weakness, sensorineural impairment or oropharyngeal dysphagia due to bulbar weakness. Without treatment, LOPD patients tend to have an earlier mortality than the general population, with a median age of death at 55 years. LOPD patients receiving ERT tend to have stabilization of their disease process. Improvement is noted in some cases where treatment is initiated early.

## DIFFERENTIAL DIAGNOSIS

Both myopathy and cardiomyopathy can be seen in infants with cytochrome c oxidase deficiency (mitochondrial complex IV deficiency), but cardiomegaly is usually less marked than in IOPD. Autosomal dominant AMP-activated protein kinase deficiency caused by a heterozygous mutation in the *PRKAG2* gene, previously known as heart-specific phosphorylase b kinase deficiency, can present with massive cardiomegaly in infancy. Muscle weakness is usually minimal and muscle biopsy is essentially normal in this condition. Glycogen storage disease type IV due to branching enzyme (glycogen branching enzyme) deficiency can also present with infantile weakness and cardiomegaly. Danon disease, caused by either hemizygous or heterozygous mutation in the *LAMP2* gene, is another disorder that presents with cardiomyopathy.

Late-onset Pompe disease may simulate Duchenne muscular dystrophy in boys with calf pseudohypertrophy. Other metabolic myopathies of childhood include debrancher deficiency (GSD IIIa), brancher deficiency (GSD IV), and muscle phosphorylase b kinase deficiency (GSD V). GSD IV and V are often accompanied by hepatomegaly, fasting hypoglycemia, and elevated cholesterol and triglycerides. Disorders of fatty acid beta-oxidation including

carnitine uptake defect and mitochondrial respiratory chain defects also need to be considered. Lactic acidosis can be a clue to cytochrome c oxidase deficiency and other mitochondrial respiratory chain defects. LOPD is often misdiagnosed. It is important for clinicians to consider Pompe disease when diagnosing myopathic conditions.

## Approach to Diagnosis

The ACMG Practice Guidelines for Pompe disease offer a clear method for diagnosis in Pompe disease. The AANEM Consensus Treatment Recommendations for LOPD and Diagnostic criteria for LOPD (childhood and adult) also provide useful methodologies.

Infants presenting with floppy baby syndrome should be referred for a chest X-ray. A finding of massive cardiomegaly is highly suggestive of classic infantile Pompe disease and separates Pompe disease from other causes of floppy baby syndrome, such as spinal muscular atrophy type I (Werdnig-Hoffmann disease) and other metabolic or congenital myopathies. An electrocardiogram can further indicate the diagnosis, as IOPD patients typically have short PR intervals with tall QRS complexes. An echocardiogram would reveal a hypertrophic cardiomyopathy, occasionally with left ventricular outflow tract obstruction. Infantile patients will usually have high levels of creatine kinase (CK) (as high as 2,000 UI/L). CK is also elevated in other muscle diseases such as mitochondrial/respiratory chain disorders and several other glycogen storage diseases and muscular dystrophies.

Serum levels of CK, CK-MB, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase are often elevated and can be useful clues to the diagnosis of Pompe disease, though nonspecific. Urinary Glc4, the predominant hexose tetrasaccharide

(Hex4) is a good biomarker of overall disease severity, as Glc4 levels increase as the level of skeletal muscle glycogen accumulation increases. In LOPD, weakness predominates in truncal and proximal muscles. Respiratory muscles, especially the diaphragm, may also be affected. Respiratory insufficiency may be the main complaint, accompanied by morning headache, exertional dyspnea, or sleep-disordered breathing. A pulmonary function test revealing a decrease in forced vital capacity from the upright to supine position can point to LOPD. These symptoms typically trigger the initial diagnosis of either limb girdle muscular dystrophy or polymyositis. LOPD can also present with WPW syndrome, various other rhythm disturbances, and dilation of the ascending aorta. Nerve conduction may show prevalent and abnormal myotonic discharges. CK levels are usually elevated.

Confirmation of the diagnosis of Pompe disease requires demonstration of reduced acid  $\alpha$ -glucosidase activity or presence of pathogenic mutations in the *GAA* gene. Acid  $\alpha$ -glucosidase activity can be measured on fibroblasts, muscle or blood. The activity can be measured most accurately in skin fibroblast. Blood-based assays including dried blood spots, lymphocytes and leukocytes are the least invasive methods. Histology and electron microscopy from muscle biopsy can offer further diagnostic support. It is important to recognize that normal muscle biopsy does not rule out LOPD.

*GAA* gene sequencing should be used for disease confirmation as well as for classification into IOPD/LOPD based on mutation. Genotyping can identify patients with pseudodeficiency who do not manifest as clinical disease. If p.Gly576Ser and p.Glu689Lys are found *in cis*, the combination is known to manifest pseudodeficiency. Genotyping is especially useful in NBS in order to limit false positives.

## MANAGEMENT

Alglucosidase alfa was approved in 2006 as ERT for patients with Pompe disease. Studies in IOPD showed that ERT improved survival, cardiac function, and growth/motor development in the population. Early treatment was found to be important for maximum efficacy. A subset of IOPD patients experienced a clinical plateau requiring an increase in ERT dose. IOPD survivors on ERT show a new phenotype, which provides insights into the disease process. Treatment response varies based on muscle fiber type, defective autophagy, degree of disease progression at the start of treatment, CRIM status, antibody response to ERT, and enzyme uptake into skeletal muscle. It has been shown that type II muscle fibers respond less to ERT compared to type I fibers. This explains why weakness in certain muscles, especially anterior tibialis, which contains abundant type II fibers, can persist in IOPD. Defective autophagy in Pompe disease leads to accumulation of autophagosomes containing recombinant enzyme. The autophagosome accumulation prevents glycogen clearance, especially in type II fibers, leading to the weakness of the anterior tibialis and other such muscles. Early treatment of IOPD is associated with improved skeletal muscle and respiratory functions. A study on the NBS program in Taiwan showed that early treatment of IOPD identified by NBS had better response to ERT than those identified based on clinical symptoms.

Cross-reactive immunological material-negative patients tend to respond to ERT poorly due to the development of persistently high sustained antibody titers (HSAT) to the recombinant enzyme. Even in CRIM-positive patients, HSAT can develop and compromise ERT. Immunomodulation with anti-CD20 monoclonal antibody, rituximab, methotrexate and gamma globulin eliminates the antibodies against recombinant enzyme in CRIM-negative patients, alleviating negative responses in ERT. Genotype of *GAA*

can predict CRIM status so that immunomodulation can be started simultaneously with ERT. It is crucial that immunomodulation is started before antibodies are formed. In mice, oral administration of recombinant enzyme was shown to reduce autoimmune response.

In LOPD, ERT has proven to reduce disease burden with improved walking distance, stabilized pulmonary function and neuromuscular deficits. Earlier treatment will be beneficial in patients with Pompe disease across the disease spectrum. Respiratory muscle strength training is being studied in individuals with Pompe disease.

High-protein low-carbohydrate diet and aerobic exercise have shown to lead to better function of LOPD. Caution is required to prevent overexertion as it leads to muscle damage. Muscle contraction can cause stress on the lysosomes and potentially leads to rupture of lysosomes, glycogen leakage into the cytoplasm and cell damage. Muscle contraction may, on the other hand, help glycogen clearance. Studies on optimal exercise are needed. A multidisciplinary approach is the key to overall improvement of quality of life in patients with Pompe disease.

Research on new therapeutic targets and immunomodulation is underway to maximize ERT efficacy. Specifically, the addition of mannose 6-phosphate residues, glycosylation independent lysosomal targeting are strategies being used to help recombinant enzyme better target the lysosomes. Chaperone-mediated therapy is another approach that aims to enhance delivery of the recombinant enzyme to lysosomes. Up-regulation of mannose-6-phosphate receptors is another promising treatment modality. A selective beta (2)-agonist clenbuterol effectively increased skeletal muscle cation-independent mannose-6-phosphate receptor expression and subsequent ERT efficacy in Pompe knockout mice. The addition of oral albuterol in patients on ERT also showed improvement in LOPD patients who were in clinical plateau on ERT. Gene replacement therapy is also in development.

## OUTCOME

Before availability of ERT, patients with IOPD died by 2 years of age. ERT leads to increased life expectancy in most IOPD patients. In surviving IOPD patients, long-term issues are being discovered. These include residual muscle weakness, hearing loss, osteopenia, dysphagia with risk for aspiration, risk of arrhythmias and hypernasal speech. In LOPD, ERT has resulted in stabilization of the disease.

## PREVENTION

Pompe disease is inherited in an autosomal recessive pattern. The disease can potentially be prevented by way of biochemical or molecular prenatal diagnosis. Genetic counseling is vital as part of prenatal testing. Early detection of Pompe disease by NBS enables early start of ERT and better outcome.

## MORE ON THIS TOPIC

- Banugaria SG, Prater SN, Patel TT, et al. Algorithm for the early diagnosis and treatment of patients with cross reactive immunologic material-negative classic infantile pompe disease: a step towards improving the efficacy of ERT. *PLoS One*. 2013;8:e67052.
- Burton BK. Newborn screening for Pompe disease: an update, 2011. *Am J Med Genet C Semin Med Genet*. 2012;160C:8-12.
- Byrne BJ, Kishnani PS, Case LE, et al. Pompe disease: design, methodology and early findings from the Pompe Registry. *Mol Genet Metab*. 2011;103:1-11.
- Case LE, Beckemeyer AA, Kishnani PS. Infantile Pompe disease on ERT: update on clinical presentation, musculoskeletal management and exercise conditions. *Am J Med Genet C Semin Med Genet*. 2012;160C:69-79.

- Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45:319-33.
- Hirschhorn R, Reuser AJJ. Glycogen storage disease type II: acid alpha-glucosidase (acid maltase) deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D, (Eds). *The Metabolic and Molecular Basis of Inherited Disease*. 8<sup>th</sup> ed. McGraw Hill; 2001. pp. 3389-420.
- Hobson-Webb LD, Kishnani PS. How common is misdiagnosis in late-onset Pompe disease? *Muscle Nerve*. 2012;45:301-2.
- Kishnani PS, Steiner RD, Bali D, et al. Pompe disease diagnosis and management guideline. *Genet Med*. 2006;8:267-88.
- Messinger YH, Mendelsohn NJ, Rhead W, et al. Successful immune tolerance induction to enzyme replacement therapy in CRIM-negative infantile Pompe disease. *Genet Med*. 2012;14:135-42.
- Nascimbeni AC, Fanin M, Masiero E, et al. The role of autophagy in the pathogenesis of glycogen storage disease type II (GSDII). *Cell Death Differ*. 2012;19:1698-708.
- Prater SN, Banugaria SG, Dearnley SM, et al. The emerging phenotype of long-term survivors with infantile Pompe disease. *Genet Med*. 2012;14:800-10.
- Raben N, Wong A, Ralston E, Myerowitz R. Autophagy and mitochondria in Pompe disease: nothing is so new as what has long been forgotten. *Am J Med Genet C Semin Med Genet*. 2012;160C:13-21.

### IN A NUTSHELL

1. Pompe disease has aspects of glycogen storage, lysosomal storage and neuromuscular disease.
2. Clinical spectrum is wide but can be divided into two groups: IOPD and LOPD. IOPD consists of classic and atypical types. *Classic infantile Pompe disease* is currently the only term used with consensus.
3. Approval of intravenous alglucosidase alfa in 2006 as ERT changed the natural history of the disease and furthered our understanding of the disease.
4. Enzyme replacement therapy response varies based on muscle fiber type, defective autophagy, the degree of disease progression at the time of treatment initiation, CRIM status, antibody response to ERT, and insufficient enzyme uptake of skeletal muscle.
5. Investigational treatment modalities include noninvasive adjunctive therapies, immunomodulation to suppress or abrogate immune response, and new therapeutic targets.



## Chapter 3.16

# Mucopolysaccharidoses

Girisha KM

Mucopolysaccharidoses (MPSs) are a group of rare genetic disorders caused by deficiency of enzymes that catabolize glycosaminoglycans (GAGs). All are lysosomal enzymes and are coded by specific genes. They are biochemically characterized by accumulation of partially degraded GAGs in several tissues, urine and blood. Clinically, accumulation of GAGs leads to progressive cellular damage and causes multiple organ failures. The most commonly affected organs are brain, skeleton, eyes and viscera and they manifest with intellectual disability, cloudy cornea, organomegaly, coarse facies and dysostosis multiplex. Though individually rare, as a group MPSs represent common storage disorders with poor quality of life and they progress relentlessly. Early diagnosis and therapy not only help to decrease the severity of the disease, but also provide an opportunity to offer prenatal diagnosis to the affected families in their subsequent pregnancies.

## EPIDEMIOLOGY

The exact incidence of these disorders is not known, and the incidence of MPSs together is estimated to be around 3.5–4.5/100,000. The studies from India are scanty and prevalence data is not available from the community except for data from hospitals and laboratories. Our experience suggests that MPSI, MPSII and MPSIV are common varieties.

## ETIOLOGY

All MPSs are caused by mutations in specific genes. All genes encode lysosomal enzymes that are involved in degradation of GAGs (acid mucopolysaccharides). GAGs are complex carbohydrates made up of uronic acids, amino sugars and

neutral sugars. When the catabolizing enzymes are deficient, these GAGs (heparan sulfate, dermatan sulfate, chondroitin-4-sulfate, chondroitin-6-sulfate, keratan sulfate and hyaluronan, are components of proteoglycans present in cellular membranes and ground substance of connective tissue) get accumulated in tissues and excreted in urine. It is expected that mutations are spread throughout the entire gene and may be population specific. Except for Hunter syndrome (MPSII) which is an X-linked condition, all MPSs are inherited in autosomal recessive manner. **Table 1** lists all the MPSs and their causative genes. It may be noted that defects in the same gene can have varying severity of the same disease, best exemplified by MPSI.

## PATHOPHYSIOLOGY

The activity of enzyme is usually very low or absent in affected individuals. It is important to note that most of the MPSs exhibit a wide phenotypic variation, partly determined by the residual enzyme level and the mutant allele. This is best exemplified by the milder Scheie, intermediate Hurler-Scheie and severe Hurler syndromes, all caused by deficient activity of  $\alpha$ -L-iduronidase. Accumulated GAGs are responsible for the clinical, radiological and biochemical manifestations of the disease. Mental retardation is more likely when heparan sulfate catabolism is affected.

## CLINICAL FEATURES

Mucopolysaccharidoses are clinically distinct group of disorders with variable degree of growth failure, intellectual disability, coarse facial features, joint contractures, organomegaly, corneal clouding, glycosaminoglycanuria and dysostosis multiplex with onset in infancy and childhood. However, the classical subtypes may have quite distinct clinical features and often are easily recognized (**Figs 1A to C**).

*Hurler syndrome* is prototype for clinical features of MPSs presenting with three phenotypes of different severity. Similar features are shared by *Hunter syndrome* and *Sly syndrome* though *Sly syndrome* can present with hydrops fetalis. Coarse

**Table 1** Types of mucopolysaccharidoses, deficient enzymes and the genes

Type	Name	Enzyme	Gene	Glycosaminoglycans in urine
MPSI-H	Hurler syndrome	$\alpha$ -L-Iduronidase	IDUA	DS, HS
MPSI-HS	Hurler-Scheie syndrome	$\alpha$ -L-Iduronidase	IDUA	
MPSI-S (formerly MPSV)	Scheie syndrome	$\alpha$ -L-Iduronidase	IDUA	
MPSII	Hunter syndrome	Iduronate-2-sulfatase	IDS	DS, HS
MPSIII-A	Sanfilippo syndrome A	N-Sulfoglucosamine sulfohydrolase	SGSH	HS
MPSIII-B	Sanfilippo syndrome B	$\alpha$ -N-Acetylglucosaminidase	NAGLU	
MPSIII-C	Sanfilippo syndrome C	Heparan acetyl-CoA: $\alpha$ -glucosaminide-N-acetyltransferase	HGSNAT	
MPSIII-D	Sanfilippo syndrome D	N-Acetylglucosamine-6-sulfatase	GNS	
MPSIV-A	Morquio syndrome A	N-Acetylgalactosamine-6-sulfate sulfatase	GALNS	KS, CS
MPSIV-B	Morquio syndrome B	$\beta$ -Galactosidase	GLB1	KS
MPSVI	Maroteaux-Lamy syndrome	N-Acetylgalactosamine-4-sulfatase deficiency	ARSB	DS
MPSVII	Sly syndrome	$\beta$ -Glucuronidase	GUSB	DS, HS, CS
MPSIX	Natowicz syndrome	Hyaluronidase 1 deficiency	HYAL1	Unknown

Abbreviations: DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate; CS, chondroitin sulfate

facial features refer to constellation of large head with prominent forehead, flat nasal bridge, hirsutism, thick lips, large tongue and broad nasal tip. They often have noisy breathing (persistent nasal discharge). Skeletal changes include restricted joint mobility (contractures), dysostosis multiplex and short stature. In fact, the milder phenotype might present with isolated joint contractures (*Scheie syndrome*). Dysostosis multiplex (**Figs 2 and 3**) refers to the skeletal changes seen in MPSs and similar conditions (GM1 gangliosidosis and mucopolidoses): thick skull bones, widened sella turcica, broad oar-shaped ribs, bullet-shaped phalanges and metacarpals, irregular epiphyses and metaphyses, beaked or ovoid vertebral bodies (sloping of anterosuperior aspect best seen in lateral radiographic view of thoracolumbar spine) and broad diaphysis. Tapering of lower iliac wing is often evident and is a very useful radiological sign. Variable degree of intellectual disability is seen and is progressive. Other symptoms include loss of vision (pigmentary retinopathy), hearing loss, otitis media, obstructive sleep apnea, recurrent respiratory infections, hepatomegaly, splenomegaly, umbilical hernia, inguinal hernia and widely spaced teeth. Cardiac involvement results in regurgitation across valves, cardiomyopathy and arrhythmias. Hydrocephalus and spinal cord compressions can also occur. Subcutaneous nodules (pebble-like) are seen in MPSII often over back, neck and chest. Patients with severe forms of the disease usually succumb in the first or second decade of life.

Milder variants have a later age of onset (second half of first decade for MPSI-HS and second decade or beyond for MPSI-S) and intellectual functioning is better preserved (MPSI-S has almost normal intelligence).

*MPS-III* has more severe cognitive and neurological impairment than the somatic manifestations that may be very mild. Behavioral problems, developmental delay, dementia, poor social and communication skills are the predominant symptoms.

*MPS-IV* is unique in terms of skeletal involvement (with pronounced spondyloepiphyseal dysplasia, anterior-middle beaking of vertebral bodies, short ulna forming V-shaped angle

with lower end of radius and proximal pointing of metacarpals), joint laxity (striking at wrist joints), genu valgus, pectus carinatum and atlantoaxial instability (which can often lead to quadriplegia, if not fixed). Intellect is well preserved. However, corneal clouding is always seen. Milder forms of Morquio syndrome do exist and need to be carefully sought while dealing with children with skeletal dysplasia.

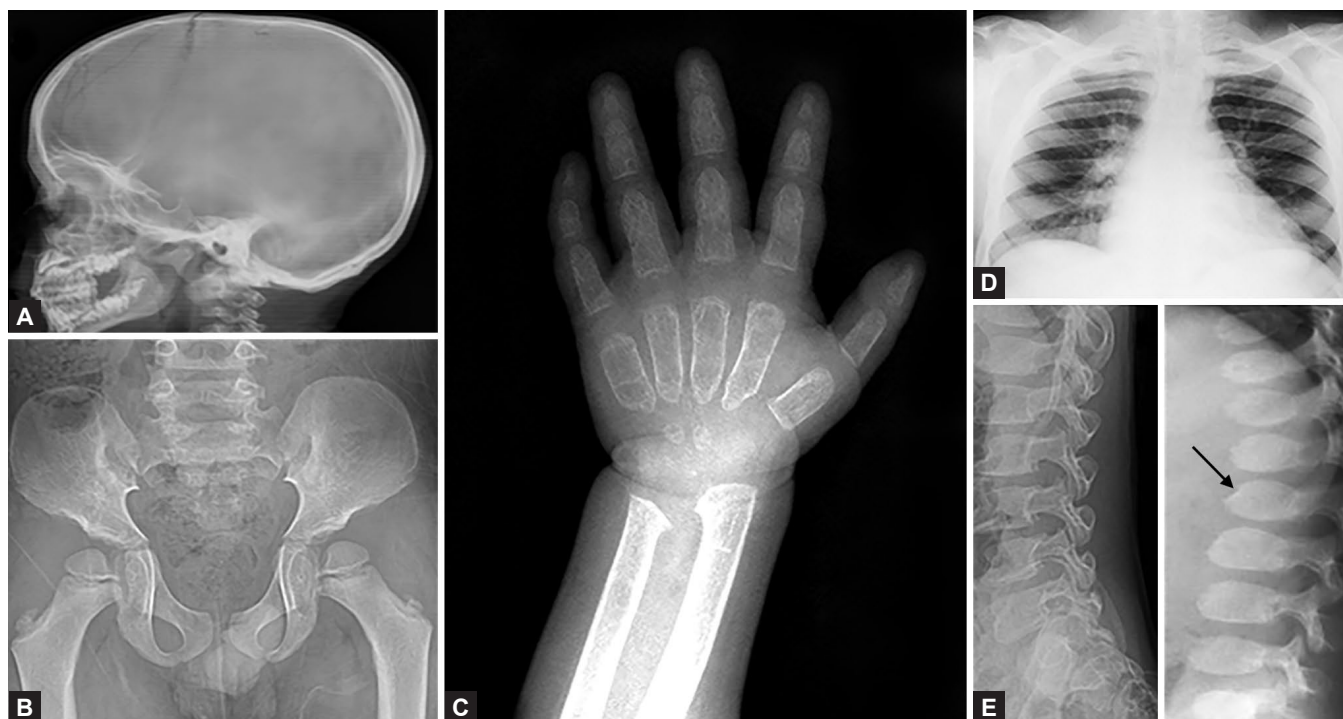
*MPS-VI* has somatic manifestations similar to that of MPSI, II and VII but differ from them in terms of preserved intellectual function. Other types of MPSs are rarely described in the literature.

## DIFFERENTIAL DIAGNOSIS

The other conditions which can have coarse facial features and dysostosis multiplex (of varying degree) are: aspartylglycosaminuria, fucosidosis, geleophysic dysplasia, GM1 gangliosidosis, mannosidosis, mucopolidoses, multiple sulfatase deficiency, sialidosis and Winchester syndrome. Coarse features may also be seen in hypothyroidism (with mild skeletal changes: epiphyseal dysgenesis and anterior beaking of vertebrae) and Coffin-Lowry syndrome. Cherry-red spots may be seen in GM1 gangliosidosis and sialidosis, whereas gum hypertrophy is commonly seen with GM1 gangliosidosis and mucopolidoses (I-cell disease). Extensive Mongolian spots also typify GM1 gangliosidosis. An elevated lysosomal enzyme in plasma is a clue for mucopolidoses. A thorough clinical, ophthalmic (for cherry-red spot in fundus) and radiographic evaluation, complemented by urine analysis for GAGs and oligosaccharides will usually help in differentiating these conditions. Final diagnosis will rest on enzyme assay or mutation testing. A referral to specialist may be warranted when the common tests do not lead to any definitive diagnosis. In consanguineous families, knowing the regions of homozygosity will provide useful differentials and may facilitate diagnosis. Of course, panels using next generation sequencing technology promise to be a cost-efficient way to test all these diseases with overlapping clinical features.



**Figures 1A to C** (A) Typical coarse facial features in a child with Hunter syndrome; (B). Mild coarsening in a 5-year-old boy with Hurler-Scheie syndrome; (C) Contractures of fingers in an adult with Hunter syndrome



**Figures 2A to E** Skeletal changes in mucopolysaccharidoses are termed dysostosis multiplex. (A) Skull shows thickened calvarium and widened sella turcica; (B) Pelvis shows straightening of lateral border of iliac bones with narrowing of lower part; (C) Metacarpals and phalanges resemble bullets (proximal narrowing of metacarpals and distal narrowing of phalanges; (D) Broad, oar-shaped ribs; (E) Beaking (flattened anterosuperior surface, arrow) of vertebrae

## APPROACH TO DIAGNOSIS

In all patients with clinical suspicion of MPS, detailed documentation of clinical findings guides one to the diagnosis. A three-generation pedigree will often help to determine the mode of inheritance. Important findings to note are intellectual disability, coarse facial features, joint contractures, corneal clouding and dysostosis multiplex.

A complete skeletal survey and urine analysis should be sought in all patients. Cloudy cornea is often detectable by simple torch light, but mild haziness and its absence should be confirmed by a slit lamp examination. Some important tips for diagnosis are: intelligence is normal in Maroteaux-Lamy syndrome, Morquio syndrome and Scheie syndrome, cornea are clear in Hunter syndrome and Sanfilippo syndrome, skin nodules are characteristic of Hunter syndrome, joint laxity and central beaking of vertebrae are seen in Morquio syndrome, and pronounced intellectual disability and behavioral problems in Sanfilippo syndrome.

Pattern of excretion of GAGs also gives a clue to the type of MPS. However, it should be noted that a spot urine test often gives false positive as well as false negative results. Enzyme assay to show the lack of activity (usually very low) and mutation analysis (sequencing of the causative gene) help to confirm the diagnosis and should be carried out in all cases. Enzyme assay is usually carried on leukocytes and rarely on cultured fibroblasts. The laboratory should always assay at least another enzyme as a control (for transport conditions). Presence of multiple sulfatase deficiency (which presents with similar phenotype) should also be sought by the laboratory performing the enzyme assay.

Presence of gum hypertrophy and cherry-red spot should be sought to consider MPS-like conditions. Carriers show a decreased activity of the enzyme, but enzyme assay is not usually the preferred method of carrier testing in clinical practice and mutations should

be confirmed in them before genetic counseling. When a sick child is first seen in the hospital, it is vital to carry out all the tests possible and preserve blood samples for DNA analysis at a later date to prevent the recurrence of the condition in the family.

## MANAGEMENT

A multidisciplinary approach is most crucial in the management of these patients and should involve the members from clinical genetics, genetic counseling, biochemistry, orthopedics, cardiology, neurology, neurosurgery, physical and occupational therapy, pulmonology, ophthalmology and otorhinolaryngology, whenever possible, considering the multisystem nature of these diseases. Early intervention can improve the life expectancy and quality of life in MPSs, which are otherwise life-threatening.

Hematopoietic stem cell therapy and enzyme replacement therapy are currently available definitive treatment options. Hematopoietic stem cell transplant if done early can halt the progression of the diseases and improve several manifestations of MPSI, MPSII, MPSVI and MPSVII. Life expectancy, quality of life, growth, respiratory symptoms, visceromegaly, joint mobility, hearing and vision improve with transplant. Hematopoietic stem cell transplant does not help to reduce the pre-existing neurological problems, skeletal and eye changes. Morbidity and mortality of transplant need to be considered against the natural history of the disease.

Enzyme replacement therapy has become available for MPS I, II and VI, and improves mobility, respiratory symptoms and organomegaly. Recently, enzyme replacement has been approved for Morquio syndrome as well. As administered enzymes do not cross blood-brain barrier, it is not effective in curing or preventing neurological manifestations. Currently, this is expensive and requires regular, lifelong administration and should be considered when hematopoietic stem cell transplant is not an option. It is often





**Figures 3A to D** Skeletal changes in Morquio syndrome are different from that seen in other mucopolysaccharidoses and are more like a spondyloepiphyseal dysplasia. (A) Atlantoaxial instability is a common complication; (B) Vertebrae show central anterior beaking; (C) Severe epiphyseal changes in head of femora; (D) Hands show V-shaped lower ends of radius and ulna (short ulna) and abnormal shaped metacarpals and phalanges

instituted before stem cell transplant and both may be combined for a better outcome. Enzyme replacement is being investigated for other MPSs too.

### OUTCOME AND COMPLICATIONS

All MPSs are progressive and affected children deteriorate gradually. The progression of the disease is difficult to predict and is complicated by the presence of a spectra of phenotype with mild to severe manifestations. If untreated, all are life-threatening and are associated with significantly low quality of life with delayed growth and development. Hydrocephalus and spinal cord compression are important neurological complications that need to be sought during follow-up visits. Other complications seen with these children include recurrent otitis media, impaired hearing, obstructive airway disease, valvular heart disease, cardiac arrhythmia, poor dental condition, carpal tunnel syndrome and progressive joint stiffness. Odontoid hypoplasia with resulting atlantoaxial instability and genu valgum need to be specifically looked for in patients with Morquio syndrome. A thorough preanesthetic evaluation is necessary for all the patients with MPSs before any surgery is contemplated.

### PREVENTION

Early diagnosis and appropriate treatment by a multidisciplinary team help to prevent the complications and decrease the morbidity of MPSs. As all of them carry a 25% risk of recurrence in the sibs of an affected child, prenatal diagnosis is an option for parents in their subsequent pregnancies. All the conditions can be diagnosed by enzyme assay in chorionic villus sample or cultured amniocytes. However, currently molecular methods are preferred over others for accurate prenatal diagnosis. The most crucial step for prenatal diagnosis is establishing a definitive diagnosis in the proband by enzyme assay and mutation testing which are now available at several centers in India. Newborn screening is now possible for most of these by high-performance liquid chromatography or tandem mass spectrometry and holds promise for early diagnosis. Early institution of therapy in the asymptomatic period can prevent progression of the disease in the child. This also helps to prevent recurrence of the condition in the family. Genetic counseling is essential for all families and extended family members, especially in view of widespread consanguineous marriages in several parts of our country.



### IN A NUTSHELL

1. Mucopolysaccharidoses represent a group of lysosomal storage disorders with defective metabolism of GAGs.
2. All of them are caused by enzyme deficiencies and have mutations in different genes.
3. Hunter syndrome is an X-linked condition and others exhibit autosomal recessive inheritance.
4. All MPSs exhibit varying degree of coarse facial features and dysostosis multiplex. Coarse features and dysostosis are seen in few other conditions as well. Morquio syndrome, however, is distinct with predominant skeletal dysplasia.
5. Multidisciplinary supportive care is currently the mainstay of therapy. Hematopoietic stem cell transplantation and enzyme replacement therapy have the potential to limit the manifestations of the disease if instituted early in select MPSs.
6. Genetic counseling is an important part of management of these conditions. Prenatal diagnosis is now possible in India either by enzyme assay or by molecular methods (preferred) for all these conditions.
7. Newborn screening and early intervention are promising new developments for these conditions.

### MORE ON THIS TOPIC

- Lachman R, Martin KW, Castro S, et al. Radiologic and neuroradiologic findings in the mucopolysaccharidoses. *J Pediatr Rehabil Med*. 2010;3:109-18.
- Muenzer J. Overview of the mucopolysaccharidoses. *Rheumatology (Oxford)*. 2011;50 Suppl 5:v4-12.
- Ohashi T. Enzyme replacement therapy for lysosomal storage diseases. *Pediatr Endocrinol Rev*. 2012;10 Suppl 1:26-34.
- Stevenson DA, Steiner RD. Skeletal abnormalities in lysosomal storage diseases. *Pediatr Endocrinol Rev*. 2013;10 Suppl 2:406-16.
- Tomatsu S, Fujii T, Fukushi M, et al. Newborn screening and diagnosis of mucopolysaccharidoses. *Mol Genet Metab*. 2013;110:42-53.
- Valayannopoulos V, Wijburg FA. Therapy for the mucopolysaccharidoses. *Rheumatology (Oxford)*. 2011;50 Suppl 5:v49-59.
- Wraith JE. Mucopolysaccharidoses and mucopolipidoses. *Handb Clin Neurol*. 2013;113:1723-9.

## Chapter 3.17

# Approach to Hypoglycemia

Meenakshi Bothra, Vandana Jain

### DEFINITION

The operational threshold for hypoglycemia is defined as the concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in literature. Operational definition of hypoglycemia in neonates is taken as blood glucose value less than 40 mg/dL (plasma glucose level less than 45 mg/dL). In older infants and children, a whole blood glucose concentration of less than 50 mg/dL (10–15% higher for serum or plasma) is considered as hypoglycemia, while in children with severe acute malnutrition (SAM), the cut-off is taken as blood glucose value of less than 54 mg/dL.

### EPIDEMIOLOGY

The estimated incidence of symptomatic hypoglycemia in newborns is 1–3/1,000 livebirths. It is more common in premature and small for gestational age (SGA) neonates. The incidence of hypoglycemia in children older than 6 months in a large urban critical care department at Philadelphia, USA was noted to be 3.4 per 10,000 births. Ketotic hypoglycemia has a frequency of 1/10,000–15,000 births.

### NORMAL GLUCOSE HOMEOSTASIS

Plasma glucose is derived from intestinal absorption of dietary carbohydrates or endogenous glucose production by either glycogenolysis or gluconeogenesis. Glucose is transported into the cellular compartment by different glucose transporters. In neonates, glucose homeostasis is regulated by a balance between glucose utilization and production, controlled by the action of insulin and the counter-regulatory hormones, like growth hormone, cortisol, glucagon and catecholamines. Normally, there is an abrupt fall in the blood glucose concentrations within 1–2 hours after birth. Over the first few days of life, with establishment of regular enteral feeding and continued maturation of hepatic gluconeogenesis, blood glucose levels further stabilize.

Plasma glucose concentrations are normally maintained within a relatively narrow range, in the fasting state with transient excursions after a meal by a network of hormones, neural signals, and substrate effects that regulate endogenous glucose production and glucose utilization. Between meals and during fasting, plasma glucose levels are maintained by endogenous glucose production, hepatic glycogenolysis, and hepatic (and to a small extent, renal) gluconeogenesis. Hepatic glycogen stores are usually sufficient to maintain plasma glucose levels for approximately 8 hours. This time period can be shorter if glucose demand is increased by exercise or if glycogen stores are depleted by starvation. Among the factors regulating blood glucose level, insulin plays a dominant role. As plasma glucose level decreases, insulin secretion decreases. This results in decrease in glucose utilization in peripheral tissues, increase in hepatic glycogenolysis and gluconeogenesis, and increase in lipolysis and proteolysis. Among the counter-regulatory hormones, glucagon, which stimulates hepatic glycogenolysis, is the most important, and is the second defense against hypoglycemia. Epinephrine, which stimulates hepatic glycogenolysis and gluconeogenesis is the third defense against hypoglycemia.

## ETIOLOGY

### Transient Hypoglycemia

The important causes of transient hypoglycemia in neonates are listed in **Box 1**. In the preterm and SGA babies, there are inadequate stores of glycogen, protein, and fat needed to provide the substrates required to generate energy. In addition, their enzyme systems for gluconeogenesis may not be fully developed. Transient hypoglycemia usually resolves within 48–72 hours after birth. Transient hyperinsulinemic hypoglycemia (lasting for weeks to months) is occasionally seen in asphyxiated, SGA and premature newborns.

#### BOX 1 Etiology of transient hypoglycemia in neonates

- Prematurity
- Small for gestational age
- Infant of diabetic mother
- Discordant twin
- Birth asphyxia
- Infant of toxemic mother.

Maternal gestational or insulin-dependent diabetes mellitus represents one of the most common conditions responsible for transient hypoglycemia in neonates. It is also the most common cause of hypoglycemia posing significant risk of permanent brain damage. These babies are usually born large for date and plethoric, and may have other metabolic abnormalities like hypocalcemia and hypomagnesemia. The most plausible explanation for hypoglycemia in these neonates is the Pederson's maternal hyperglycemia, fetal hyperinsulinemia hypothesis. The high insulin, low glucagon and low epinephrine levels in these babies inhibit the endogenous glucose production, thus predisposing them to hypoglycemia. Babies born to diabetic mothers with good glycemic control are less likely to develop neonatal hypoglycemia.

### Persistent/Recurrent Hypoglycemia

The causes of persistent hypoglycemia in infancy are listed in **Box 2**.

#### Endocrine Causes

Hyperinsulinism is the most common cause of persistent hypoglycemia in early infancy. Hyperinsulinemic infants may be macrosomic at birth. In these babies, plasma insulin concentration is inappropriately elevated at the time of documented hypoglycemia. The age at which a baby becomes symptomatic depends on the degree of hyperinsulinemia, with severely affected babies becoming hypoglycemic immediately after birth and the less severely affected ones manifesting later (up to the age of 18 months). The hyperinsulinemic babies who are less severely affected may manifest with hypoglycemia within 4–8 hours of fasting.

*Persistent hyperinsulinemic hypoglycemia of infancy* It is a heterogeneous group of disorders, previously known by different names like nesidioblastosis and congenital hyperinsulinism. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) can be due to either diffuse or focal  $\beta$ -cell hyperplasia, of which, the focal type has a better prognosis. Both autosomal recessive and dominant forms of PHHI have been described. The autosomal recessive form is much more common in the Arabic and Ashkenazi Jewish population, probably due to the high rates of consanguinity. Mutations in the genes encoding for the pancreatic K-ATP channel, glutamate dehydrogenase (GDH), glucokinase (GCK), L-3-hydroxyacyl-coenzyme A dehydrogenase (HADH), hepatocyte nuclear factor 4 $\alpha$  (HNF4 $\alpha$ ), monocarboxylate transporter (MCT1)

**BOX 2 Etiology of persistent hypoglycemia in infancy and childhood**

- Endocrine causes
  - Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)
  - Panhypopituitarism, isolated growth hormone deficiency
  - Adrenocorticotrophic hormone deficiency, Addison disease
  - Epinephrine deficiency
- Glycogenolysis and gluconeogenesis disorders
  - Glycogen storage diseases (GSD) types 1, 3, 6, 9, 0
  - Fructose-1,6-diphosphatase deficiency
  - Pyruvate carboxylase deficiency
  - Galactosemia
  - Hereditary fructose intolerance
- Fatty acid oxidation disorders
  - Primary or secondary carnitine deficiency
  - Carnitine palmitoyltransferase-1 or 2 deficiency
  - Carnitine translocase deficiency
  - Very long-, long-, medium-, short-chain acyl CoA dehydrogenase deficiency
- Amino acid and organic acid disorders
  - Maple syrup urine disease
  - Propionic acidemia
  - Methylmalonic acidemia
  - Tyrosinosis
  - Glutaric aciduria
- Systemic disorders
  - Sepsis, shock
  - Neoplasms secreting insulin-like growth factor II
  - Malnutrition, malabsorption, diarrhea
  - Burns, postsurgical
  - Pseudohypoglycemia (leukocytosis, polycythemia)
  - Excessive insulin therapy in type 1 diabetes mellitus
  - Factitious
  - Falciparum malaria

and uncoupling protein 2 (UCP2) as shown in **Figure 1**. Out of the above, mutations in the genes coding for SUR or KIR6.2 that prevent K-ATP channel from being open, result in increased insulin secretion, are the most common and the genes responsible are *ABCC8* and *KCNJ11* on chromosome 11p15.1. One form of autosomal dominant PHHI is due to an activating mutation in GCK. The common mutations associated with hyperinsulinemia have been shown in **Figure 1**.

Hyperinsulinemic hypoglycemia is also seen in 50% of patients with *Beckwith-Wiedemann syndrome*, which is caused by mutations in the chromosome 11p15.5 region close to the genes for insulin, *SUR*, *KIR6.2*, and insulin-like growth factor 2 (IGF-2). These babies also have omphalocele, gigantism, macroglossia, microcephaly, and visceromegaly with or without hemihypertrophy. Hyperinsulinemia in these babies is due to diffuse pancreatic islet cell hyperplasia. These children are predisposed to develop certain tumors like Wilms tumor, hepatoblastoma, adrenal carcinoma, gonadoblastoma and rhabdomyosarcoma.

Hyperinsulinemic hypoglycemia presenting in children above 5 years of age is usually due to *islet cell adenomas*, which may be associated with hyperparathyroidism and pituitary tumors, as a part of multiple endocrine neoplasia type 1 (MEN 1, Wermer syndrome). Prolonged fasting for 24–36 hours usually provokes hypoglycemia in these patients.

Hypoglycemia is seen in about 20% of patients with *panhypopituitarism* and combined or isolated adrenocorticotrophic hormone (ACTH) or growth hormone deficiency. Male babies with panhypopituitarism may have micropallus due to coexistent gonadotropin deficiency. Cholestatic jaundice is commonly seen among these babies.

Hypoglycemia can also be seen in children with *adrenal insufficiency*, as seen in congenital adrenal hyperplasia (CAH), bilateral adrenal hemorrhage, familial glucocorticoid deficiency, adrenal hypoplasia or congenital absence of the adrenal glands. Depending on the underlying adrenal disorder, some of these babies may have associated hyperpigmentation, dyselectrolytemia, hypertension, salt wasting or ambiguous genitalia.

### Metabolic Causes

Inborn errors in glycogen synthesis or breakdown, gluconeogenesis and fatty acid oxidation can present with hypoglycemia. Several hours of fasting are needed for hypoglycemia to manifest. These disorders usually present in later infancy when feeding interval has increased and the infant has started sleeping through the night, or during intercurrent illness with reduced oral intake. Some of the major inborn errors of metabolism presenting with hypoglycemia are discussed briefly in the following section.

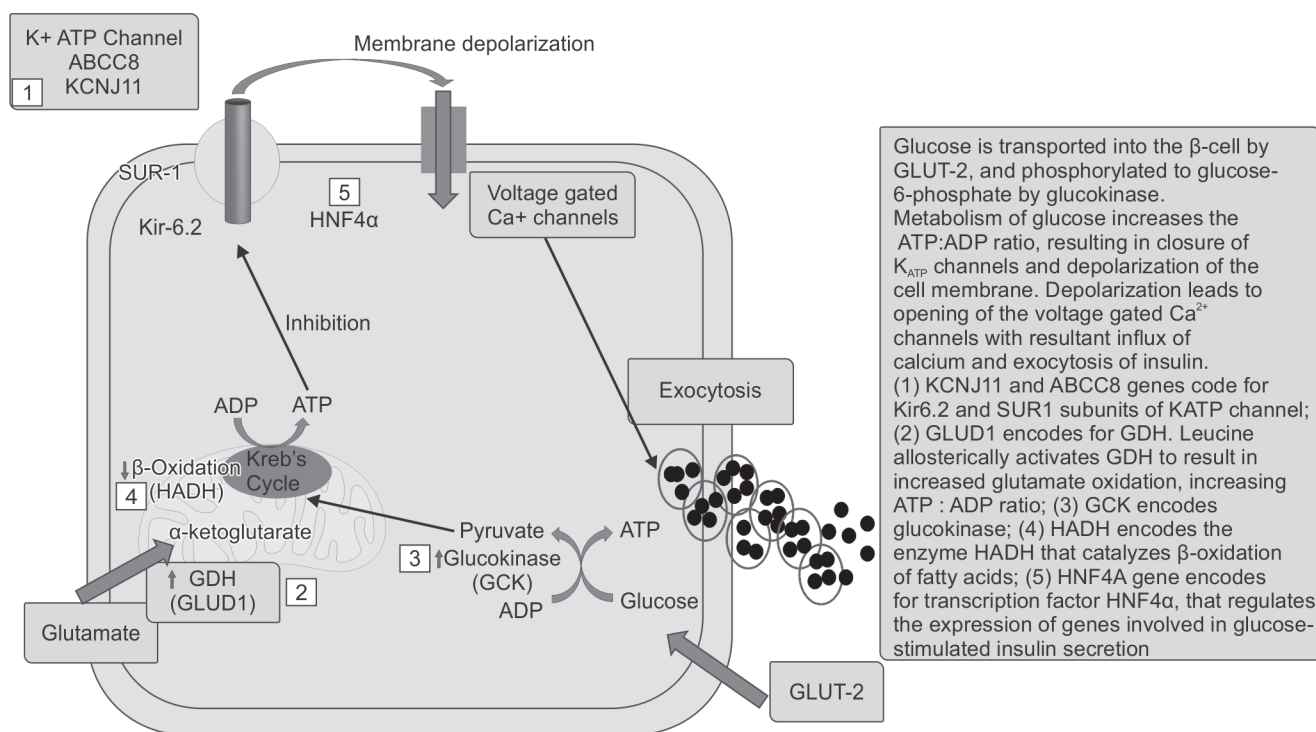
**Ketotic hypoglycemia** It is the most common form of childhood hypoglycemia and usually presents with episodes of hypoglycemia in early morning, between 18 months and 5 years of age. It usually undergoes spontaneous remission by the age of 8–9 years. Hypoglycemic episodes occur during periods of intercurrent illness when food intake is limited. Ketotic hypoglycemia may be due to a defect in any of the steps involved in protein catabolism, oxidative deamination of amino acids, transamination, alanine synthesis or alanine efflux from muscle. These children are usually smaller than other children of their age, and may have a history of transient neonatal hypoglycemia. These children have been found to have markedly reduced plasma alanine (a major gluconeogenesis precursor) concentrations after an overnight fast. In branched chain ketonuria (maple syrup urine disease) also, hypoglycemia is due to limited availability of alanine.

**Glycogen storage disease (GSD)** Type I (most common), III and VI may present with fasting hypoglycemia. These babies may have lethargy or hypoglycemic seizures early in the morning due to relatively longer intervals between feeding at night. These children usually have growth failure and hepatomegaly due to excessive deposition of glycogen in liver.

**Defects in fatty acid or carnitine metabolism** These may be associated with fasting hypoglycemia, as fatty acids are substrates for gluconeogenesis. Fasting hypoglycemia with hepatomegaly, cardiomyopathy and hypotonia is seen in long- and medium-chain fatty acid coenzyme-A dehydrogenase deficiency (LCAD and MCAD). Patients with acyl CoA dehydrogenase deficiency may present with a Reye-like syndrome, hypotonia, seizures and a characteristic acrid odor. Hypoglycemia without ketonuria can also be seen as an adverse effect of sodium valproate, which can also lead to a Reye-like syndrome.

**Galactosemia** is caused by the deficiency of the enzyme galactose-1-phosphate uridyl transferase (GALT). Deficiency of UDP-galactose-4-epimerase also has a similar presentation. Affected infants present with vomiting, diarrhea, jaundice and hepatomegaly in addition to hypoglycemia. *E. coli* sepsis commonly occurs in affected infants. Cataracts, liver dysfunction, renal tubular defects, intellectual impairment and ovarian failure are other clinical manifestations. Diagnosis is suspected by presence of non-glucose-reducing substance in urine and confirmed by assay for GALT and epimerase enzymes. Management consists of dietary galactose restriction.

**Hereditary fructose intolerance** is caused by deficiency of the enzyme fructose-1-phosphate aldolase and manifests only after inclusion of fructose in the diet. In infants fed with fructose or sucrose containing formulae, there is acute postprandial hypoglycemia along with vomiting and abdominal distension. The



**Figure 1** Regulation of insulin secretion by pancreatic  $\beta$ -cell, and mutations associated with persistent hyperinsulinemic hypoglycemia of infancy (PHHI)  
 Abbreviations: GDH, glutamate dehydrogenase, HADH, hydroxyacyl-coenzyme A dehydrogenase; HNF4 $\alpha$ , hepatocyte nuclear factor 4 $\alpha$ ; MCT1, monocarboxylate transporter.

hypoglycemia is caused by an acute inhibition of glycogenolysis and gluconeogenesis by the accumulation of fructose-1-phosphate. As the affected children become symptomatic after eating sweet food items (containing fructose or sucrose), they gradually develop aversion to sweets.

**Phosphoenol pyruvate carboxykinase deficiency** This rate-limiting gluconeogenic enzyme deficiency is associated with severe fasting hypoglycemia soon after birth. There is fatty infiltration of organs like liver, due to increased synthesis of acetyl CoA, which becomes available for fatty acid synthesis.

**Glucose transporter 1 and 2 deficiency** Those with glucose transporter 1 (GLUT 1) deficiency may present with seizures and are found to have low cerebrospinal fluid (CSF) glucose and lactate concentrations, despite normal plasma glucose, while those with GLUT-2 deficiency may present with hypoglycemia due to defective release of glucose from liver and its impaired tubular reabsorption, hepatomegaly, galactose intolerance and renal tubular dysfunction (Fanconi-Bickel syndrome).

### Systemic Disorders

In *severe sepsis*, especially in neonates or *severely malnourished* babies, hypoglycemia is seen due to impaired gluconeogenesis as well as diminished caloric intake. Polycythemia (hematocrit >65%) is also one of the important causes of hypoglycemia among neonates. In tropical countries, *falciparum malaria* is also an important cause of hypoglycemia.

## CLINICAL FEATURES

A detailed history including the age at onset, birth weight, temporal relation of hypoglycemia to meals, history of maternal diabetes, parental consanguinity, family history of unexplained infant deaths

or siblings with similar presentation should be enquired. Most of the babies presenting in the 1st week of life have the transient form of neonatal hypoglycemia, as discussed earlier. A large for date baby, born to a nondiabetic mother suggests hyperinsulinemic hypoglycemia of infancy. Hypoglycemia occurring shortly after meals is commonly seen in galactosemia or hereditary fructose intolerance, while symptoms due to hypoglycemia occurring 6 hours or more after meals points toward an underlying disorder of gluconeogenesis or autosomal dominant forms of hyperinsulinemic hypoglycemia. Hypoglycemia only on prolonged fasting (usually for 24–36 hours) is seen in fatty acid oxidation defects. Enquiry should also be made about the ingestion of toxins like alcohol or salicylate and inadvertent or deliberate ingestion of oral hypoglycemic drugs or use of excessive insulin in a known diabetic or nondiabetic child. Possibility of errors in dispensing or administering medicines should also be considered.

Symptoms and signs due to hypoglycemia per se, seen especially in older children have been mentioned in **Box 3**. However, in the neonatal period and infancy, there can be some atypical features like jitteriness or tremors, apathy, cyanosis, convulsions, apnea or lethargy. Characteristic clinical features of some of the earlier

### BOX 3 Clinical features of hypoglycemia

#### Features of sympathetic overactivity

- Due to release of adrenaline
- Usually seen with rapid decline in blood glucose
- Anxiety, perspiration, palpitations, pallor and tremulousness.

#### Neuroglycopenic symptoms

- Due to decreased cerebral glucose utilization
- Seen with slow decline in blood glucose or in prolonged hypoglycemia
- Headache, mental confusion and visual disturbances.



described disorders and associated abnormalities have already been mentioned in the etiology section.

On physical examination, presence of hepatomegaly points towards the possibility of an underlying glycogenolytic or gluconeogenic enzyme deficiency. The presence of a microphallus (in males) and neonatal jaundice may be clues to the presence of hypopituitarism in neonates and infants, while short stature or a subnormal growth velocity may be a useful clue in older children.

## INVESTIGATIONS

The first step in determining the underlying etiology of hypoglycemia is the collection of *critical sample*, comprising of certain investigations on blood and urine at the time of documented hypoglycemia, which may have occurred spontaneously or had to be *provoked* by supervised fasting for several hours. The investigations done as a part of *critical sample* include simultaneous measurement of blood glucose, insulin, cortisol, ketones and free fatty acids (FFAs) in the same sample at the time of clinically manifested hypoglycemia as listed in **Table 1**. Blood ketone level estimation is not readily available, so detection of urine ketones using dipsticks can be used as a surrogate marker. The algorithmic approach that may be followed in infants and children with hypoglycemia is shown in **Flow chart 1**.

In children with PHHI, the insulin level is usually more than 5–10  $\mu\text{U/mL}$  and the insulin ( $\mu\text{U/mL}$ ): glucose (mg/dL) ratio is more than 0.4. In addition, plasma insulin-like growth factor binding protein-1 (IGFBP-1), ketones and FFA levels are low and there is no acidosis. The glycemic response to glucagon at the time of hypoglycemia shows a brisk increment in blood glucose by 40 mg/dL or more, because the glycogenolytic mechanisms are

intact. 18F-labeled L-dopa positron emission tomography (PET) scanning is highly accurate in distinguishing the focal from the diffuse form of PHHI.

C-peptide levels can be measured in cases where exogenous administration of insulin is suspected as the cause for hyperinsulinemic hypoglycemia. C-peptide will be low or absent in such cases of factitious hypoglycemia.

The presence of reducing substances in urine can be detected by Benedict's test. It helps to diagnose fructose intolerance and galactosemia. Presence of nonglucose-reducing sugar in the urine points towards galactosemia. The absence of ketonemia or ketonuria suggests hyperinsulinemia, defect in fatty acid oxidation, galactosemia or hereditary fructose intolerance as the underlying etiology.

Hypoglycemia with ketonemia and ketonuria in children between 1.5 years and 5 years is most likely to be ketotic hypoglycemia, especially if hepatomegaly is absent. In susceptible individuals, fasting usually provokes a hypoglycemic episode with ketonemia and ketonuria within 12–18 hours.

In fatty acid oxidation defects, plasma carnitine levels are low, ketones are not present in urine, but dicarboxylic aciduria is present. Fasting to induce hypoglycemia is contraindicated if a fatty acid oxidation defect is suspected. Tandem mass spectrometry (TMS), urinary gas chromatography mass spectrometry (GCMS) and molecular methods are useful in diagnosis.

In phosphoenol pyruvate carboxykinase deficiency, liver, kidney and myocardium demonstrate fatty infiltration. Atrophy of the optic nerve and visual cortex may be noted. Hypoglycemia may be profound. A supervised fasting may be used to provoke hypoglycemia. Lactate and pyruvate levels in plasma are normal,

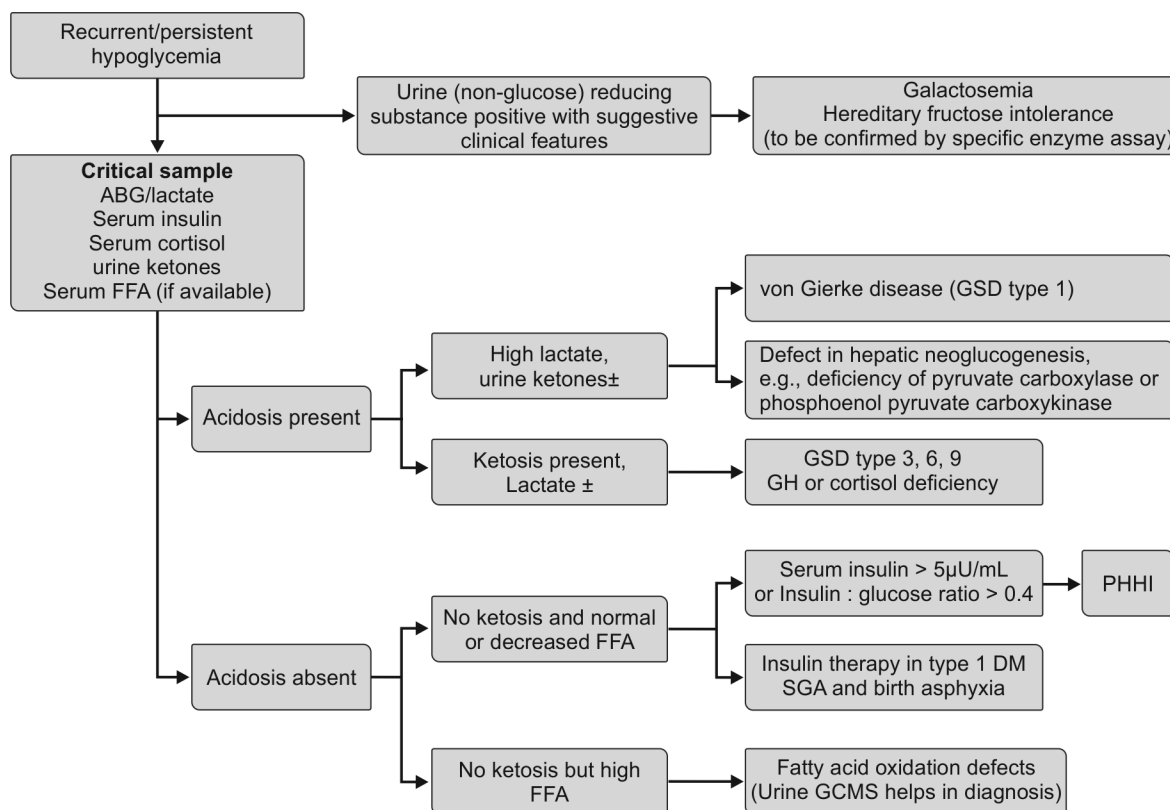
**Table 1** Investigations for determining the etiology of hypoglycemia using the critical sample

Investigation	Cut-off beyond which abnormal	Underlying disease, if abnormal
Glucose*	<40 mg/dL (newborns), <50 mg/dL (older children) <i>Glucagon challenge test:</i> Rise by $\geq 40$ mg/dL, 30 min after giving glucagon 50 $\mu\text{g}$ /kg (maximum 1 mg) IV or IM	Confirmation of hypoglycemia  Hyperinsulinemic state with adequate hepatic glycogen stores and intact glycogenolytic enzymes
Insulin*	Plasma insulin $> 2$ $\mu\text{U/mL}$ or Insulin ( $\mu\text{U/mL}$ ): glucose (mg/dL) $> 0.4$ Plasma insulin $> 100$ $\mu\text{U/mL}$	Endogenous hyperinsulinemia  Suspect factitious cause (exogenous insulin injection)
Cortisol*	<10 $\mu\text{g/dL}$	Adrenal insufficiency or pituitary disease or both
Ketones* (urine ketones may be used as surrogate if blood ketones unavailable)	Plasma $\beta$ -hydroxybutyrate: $< 2.0$ mmol/L and/or urine ketones absent Plasma $\beta$ -hydroxybutyrate: $> 2.0$ mmol/L and/or urine ketones present	Hyperinsulinemia or fatty acid oxidation defect  Inborn error of glycogen metabolism, or defective gluconeogenesis
Free fatty acids <sup>#</sup>	Plasma-free fatty acids $< 1.5$ mmol/L	Hyperinsulinemia
Growth hormone <sup>#</sup>	$< 5$ ng/mL	Adrenal insufficiency or pituitary disease or both
Thyroxine/TSH <sup>#</sup>	Low free thyroxine in the setting of a low or inappropriately normal TSH level	Hypopituitarism
Lactate <sup>#</sup>	$> 1.6$ mmol/L or 14.4 mg/dL	Organic acidemias, GSD type 1, fructose-1,6-diphosphatase deficiency
Uric acid <sup>#</sup>	$> 5$ –7 mg/dL	von Gierke disease (GSD type 1)
Ammonia <sup>#</sup>	$> 100$ –200 $\mu\text{m}$	Activating mutation of glutamate dehydrogenase

Note: \*To be done in all cases of undiagnosed persistent/recurrent hypoglycemia.

#May be done depending on the clinical scenario and/or availability.

Abbreviations: TSH, thyroid-stimulating hormone; GSD, glycogen storage disease.

**Flow chart 1** An algorithmic approach to persistent/recurrent hypoglycemia in infants and children

but a mild metabolic acidosis may be present. Confirmatory diagnosis requires enzymatic determination in liver biopsy material.

If hepatomegaly is present along with hypoglycemia, glycogen storage disease is suspected. One should investigate for the presence of hyperlipidemia, acidosis, hyperuricemia and response to glucagon in the fed and fasted states. Definitive diagnosis may require liver biopsy with estimation of the enzyme activity or molecular diagnosis.

Adrenal insufficiency is a close mimicker of ketotic hypoglycemia. So, plasma cortisol levels should be determined at the time of documented hypoglycemia, which if low, should be followed by definitive tests of pituitary-adrenal function.

## TREATMENT

The treatment comprises of:

- The management of hypoglycemic episode, and
- Treatment based on the underlying etiology of hypoglycemia.

### Treatment of Acute Symptomatic Neonatal or Infantile Hypoglycemia

This includes intravenous (IV) administration of 2 mL/kg of 10% dextrose, followed by a continuous infusion of glucose at 6–8 mg/kg/min, adjusting the rate to maintain blood glucose levels in the normal range and gradually decreasing and stopping the IV fluids, if the child remains euglycemic. Asymptomatic babies may be offered a feed and the blood glucose rechecked after 30–60 minutes. If the blood glucose becomes normal, frequent feeding along with blood glucose monitoring is continued. The management of persistent neonatal or infantile hypoglycemia includes increasing the rate of

IV glucose infusion to 10–15 mg/kg/min and titrating the rate of infusion according to the blood glucose values. A central venous access should be established in these infants as it helps in ensuring uninterrupted infusion. Also, dextrose solutions of strength more than 12.5% should not be infused through peripheral lines. If the baby is tolerating feeds, attempts should be made to gradually decrease IV glucose infusion and start baby on oral/orogastric/nasogastric fortified feeds.

Hypoglycemia may recur in 10–15% of infants after adequate treatment. Recurrence is more common if there is disruption in the glucose infusion due to mechanical causes, or IV fluids are extravasated or discontinued too rapidly before oral feeds are tolerated.

### Treating Hyperinsulinemia

If hyperinsulinemia is present, medical management with diazoxide (5–15 mg/kg/day in 2–3 divided doses) and somatostatin analogs like octreotide is tried first. An adequate trial of diazoxide is considered as its use in maximal dose for at least 5 days. The adverse effects of diazoxide include hirsutism, edema, nausea, hyperuricemia, electrolyte disturbances, advanced bone age and hypotension with prolonged use. Addition of thiazide with diazoxide helps in reducing edema and dyselectrolytemia. Octreotide is used as the second-line therapy in infants who do not respond to or tolerate diazoxide. This is administered subcutaneously every 6–12 hourly in doses of 5–25 µg/kg/day. Adverse effects include poor growth due to inhibition of growth hormone release, pain at the injection site, vomiting, diarrhea and hepatic dysfunction. There are anecdotal reports on the use of calcium channel blockers. The target blood glucose level in these babies is between 50 mg/dL and 100 mg/dL. Hyperglycemia is to be avoided as it will further stimulate insulin secretion and would lead to rebound

hypoglycemia. Long-term medical therapy without pancreatic resection may be tried if blood glucose is maintained in the normal range, because some children have a spontaneous resolution of the hyperinsulinemic hypoglycemia. However, this approach should be balanced against the risk of hypoglycemia-induced central nervous system (CNS) injury and the toxicity of drugs. In infants who are refractory to medical management, subtotal or focal pancreatectomy may be needed. Total pancreatectomy is not advocated, owing to the risks of surgery, permanent diabetes mellitus and exocrine pancreatic insufficiency.

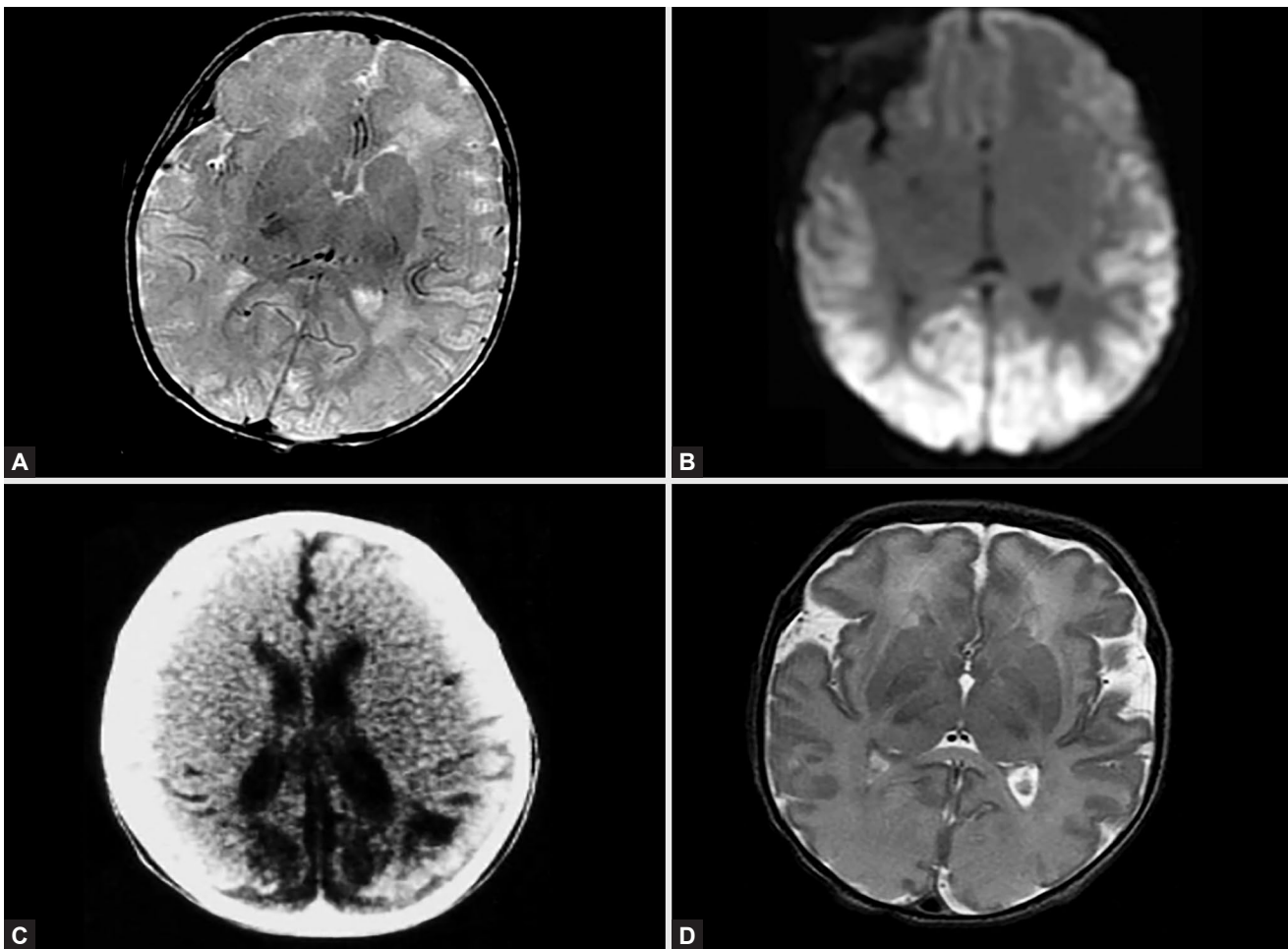
### Ketotic Hypoglycemia

The treatment of ketotic hypoglycemia consists of frequent feedings with a high-protein and carbohydrate diet. During intercurrent illnesses, urinary ketones (which usually precede hypoglycemia) should be monitored. In the presence of ketonuria, if the child is accepting orally, liquids of high carbohydrate content should be offered to the child. However, if the oral intake is poor, IV fluids should be started. In children with fatty acid oxidation defects, carnitine supplementation has been found to be beneficial. In phosphoenol pyruvate carboxykinase deficiency, avoidance of periods of fasting through frequent feedings rich in carbohydrate should be helpful, because glycogen synthesis and breakdown are intact. In infants and children with glycogen storage diseases as

the underlying cause of hypoglycemia, frequent feeds including nocturnal feeds is recommended. Use of cornstarch feeds help in maintaining blood glucose for longer periods of time and decreasing episodes of hypoglycemia.

### PROGNOSIS

The prognosis is good in asymptomatic neonates with hypoglycemia of short duration, if the child has not incurred any CNS insult due to hypoglycemia. The regions of brain commonly affected by hypoglycemia are parieto-occipital region, hippocampus, caudate nucleus and putamen. The common changes seen on neuroimaging in children with hypoglycemia have been illustrated in **Figures 2A to D**. Prolonged, recurrent and severe symptomatic hypoglycemia is associated with long-term neurologic sequelae and intellectual disability, visual deficits, motor deficits manifesting as spasticity or ataxia, seizure disorder and even microcephaly. In a study done at a tertiary care center in south India, neonatal hypoglycemia was found to be the most common etiology of remote symptomatic infantile onset epilepsy. Babies with symptomatic hypoglycemia have a poorer prognosis than those with asymptomatic hypoglycemia. In babies with hypoglycemia related to inborn errors of metabolism, survival depends on the severity of the underlying defect.



**Figures 2A to D** Magnetic resonance imaging (MRI) brain showing changes due to hypoglycemic brain injury. (A) Abnormal signal intensity in parieto-occipital region; (B) Restricted diffusion on DWI in occipital region; (C) Loss of cerebral cortex and white matter; (D) Loss of differentiation between gray and white matter

### IN A NUTSHELL

1. Hypoglycemia is defined as blood glucose value less than 40 mg/dL in neonates, less than 50 mg/dL in older infants and children and less than 54 mg/dL in children with severe acute malnutrition.
2. Hyperinsulinism is the most common cause of persistent hypoglycemia in early infancy, for which the most common underlying etiology is persistent hyperinsulinemic hypoglycemia of infancy, while in older children, ketotic hypoglycemia is most common.
3. Collection of *critical sample* (blood glucose, insulin, cortisol, FFAs and urinary ketones) at the time of documented hypoglycemia helps in determining the underlying etiology.
4. The treatment comprises of management of hypoglycemic episodes, changes in the dietary pattern and use of drugs based on the underlying etiology.
5. Prolonged, recurrent and severe symptomatic hypoglycemia is associated with long-term neurologic sequelae. Hence, early detection and prompt management is essential.

### MORE ON THIS TOPIC

Hypoglycemia in the Newborn. AIIMS NICU Protocol 2014.

Kliegman R, Stanton B, Joseph W, et al. Nelson Textbook of Pediatrics. 19<sup>th</sup> ed. Philadelphia: Elsevier; 2011.

Mohamed Z, Arya VB, Hussain K. Hyperinsulinaemic hypoglycaemia: genetic mechanisms, diagnosis and management. J Clin Res Pediatr Endocrinol. 2012;4:169-81.

Udani V, Munot P, Ursekar M, Gupta S. Neonatal hypoglycemic brain injury—a common cause of infantile-onset remote symptomatic epilepsy. Indian Pediatr. 2009;46:127-32.

Hay WW Jr, Raju TNK, Higgins RD, et al. Knowledge gaps and research needs for understanding and treating neonatal hypoglycemia: workshop report from Eunice Kennedy Shriver National Institute of Child Health and Human Development. J Pediatr. 2009;155:612-7.



## Chapter 3.18

# Porphyrias

Meenal Agarwal, Shubha R Phadke

Porphyrias are a rare group of disorders with pain in abdomen as the commonest manifestation in many of them. Abdominal pain mimics many surgical and medical conditions and diagnosis is often delayed or never made. As the acute attacks can be life-threatening, timely diagnosis is important. In addition to the clinical features similar to many common disorders, other symptomatology, mode of inheritance, intermittent presentations and decreased penetrance make this group of genetic metabolic disorders stand out.

Porphyrias are a group of eight inherited disorders of heme synthesis, each caused by deficiency of a specific enzyme in heme synthesis pathway. Porphyrins are organic compounds with four modified pyrrole rings. These pyrrole rings are interconnected through methane rings between their  $\alpha$ -carbon atoms. Porphyrins containing ferrous ion in the center are called heme and heme containing proteins are called hemoproteins. Examples of hemoproteins are oxygen carrying molecules (hemoglobin, myoglobin), cytochromes P450 which are involved in the metabolism of many drugs, cytochromes b and c are involved in oxidative phosphorylation, catalase, peroxidase and endothelial nitric oxide synthase. Hence, it is also called pigment of life. Block in the synthesis of heme causes accumulation of its precursors as well as deficiency of necessary heme-containing products.

### HEME SYNTHESIS PATHWAY

Synthesis of heme occurs in every human cell. However, 85% of it is synthesized in erythroid precursor cells in bone marrow to be incorporated in hemoglobin (**Fig. 1**). About 15–29% of heme is synthesized in the hepatocytes in the form of various cytochromes and other enzymes including catalase and peroxidase. The enzymes, their properties and a brief description of the type of porphyria associated are described in **Table 1**.

### Regulation of Heme Synthesis

Regulation of heme synthesis is controlled in liver mainly by negative feedback regulation by heme. In erythroid cells, control mechanisms are different as erythroid precursors have their own erythroid-specific enzymes for first four reactions [separate gene for 5-aminolevulinic acid synthase (ALAS), and separate transcripts for next three enzymes]. In erythroid precursors, ALAS2 is active during erythroid differentiation. Also heme synthesis is regulated by the level of iron transport. It is important to understand the physiological regulatory factors which control heme synthesis, because in most types of acute porphyria, the neurovisceral attacks are precipitated by recognizable events. In hepatocytes, the first enzyme of the pathway (ALAS1) is the rate-limiting enzyme. Fifty percent of reduced activity of enzymes in hepatocytes is sufficient to carry out the normal metabolic functions. The factors or events which use heme protein induce ALAS, and, hence, result in accumulation in heme precursors in various tissues and are thought to be precipitating factors for acute attacks. These factors include fasting or caloric restrictions, drugs inducing cytochrome P450 systems, alcohol, estrogen use in females, etc.

### CLASSIFICATION

There are several ways by which these disorders can be classified. One approach is to classify them according to the organ in which heme precursors mainly accumulate, i.e., hepatic or erythrocytic.

However, clinically useful classification is based on signs and symptoms. Most hepatic porphyrias [except porphyria cutanea tarda (PCT)] are associated with neurovisceral attacks, and most erythrocytic porphyrias have cutaneous manifestations as the predominant feature. PCT is a hepatic porphyria and mainly presents with cutaneous manifestations. Two other hepatic porphyrias, namely hereditary coproporphyria (HCP) and variegate porphyria (VP) may present with both neurovisceral and cutaneous symptoms.

### Acute Porphyrias

This group includes four hepatic porphyrias, i.e., acute intermittent porphyria (AIP), HCP, VP and rare aminolevulinic acid dehydratase deficient porphyria (ALADP). The symptomatic porphyrias are more common in females and pan-ethnic in distribution. The combined prevalence is around 5 in 100,000 with highest prevalence in Sweden (1 in 10,000). Each of these four acute hepatic porphyrias is caused by deficiency of distinct enzyme in heme biosynthesis pathway (**Table 1**), but clinical signs and symptoms are the same. Most people affected with the disorder develop symptoms in second or third decade and rarely after menopause. Only less than 10% of affected people suffer recurrent attacks (reduced penetrance). Because of reduced penetrance and nonspecific symptoms, high suspicion is to be kept in mind to make a diagnosis.

### PATHOGENESIS

In cutaneous porphyrias, porphyrins accumulate in bone marrow and skin. In skin, these accumulated porphyrins absorb light and convert to their ground state by transferring their energy to other molecules like membrane lipids, nucleic acid and other proteins and is the cause of photosensitivity. The causes of neurovisceral attacks are less clear. The pathogenic mechanisms which have been proposed include deficiency of enzyme/protein containing heme or accumulation of heme precursors. The accumulation of heme precursors are thought to be neurotoxic.

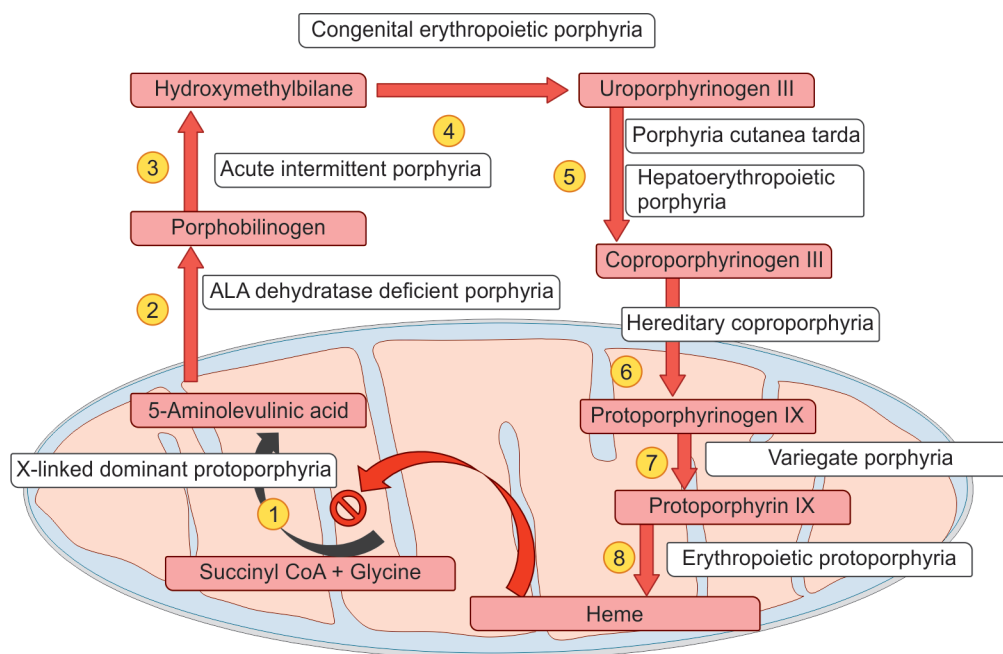
### CLINICAL FEATURES

#### Acute Porphyrias: Neurovisceral Attacks

Clinical symptoms are nonspecific, mimic other medical acute conditions and highly variable in the same individual or different members of the same family. None of symptoms is specific to acute porphyria but few suggested features which may point toward the diagnosis are—recurrent nonspecific neurovisceral symptoms not associated with inflammatory reaction, women of reproductive age group, presence of family history, dark-colored urine, proximal muscle weakness during attack, cyclical symptoms associated with luteal phase of menstrual cycle, antecedent history of fasting, intercurrent illness and exposure to drugs which are known to precipitate acute attacks. The neurovisceral attacks classically present in the form of recurrent abdominal pain with or without vomiting, muscle paralysis and psychiatric symptoms. Severity of symptoms may range from mild to severe requiring ventilatory support and, if untreated, may lead to death. Systemic signs of infection or inflammation, like tenderness and leukocytosis are absent. Biochemical investigations are essential to make a definite diagnosis. The summary of clinical symptoms is presented in **Table 2**.

#### Cutaneous Signs and Symptoms

Cutaneous signs may be divided into two categories: (i) blistering type, and (ii) nonblistering type. The porphyrias which present with cutaneous signs and symptoms include congenital erythropoietic porphyria (CEP), hepatoerythropoietic porphyria (HEP), VP,



**Figure 1** Steps in biosynthesis of heme. There are eight enzymes in this pathway. Four reactions are cytosolic (2nd, 3rd, 4th and 5th) and four are mitochondrial. Each enzyme is coded by an autosomal gene except first enzyme  $\delta$ -aminolevulinic acid synthase which has two isoforms coded by two different genes: (i) housekeeping gene ALAS1; and (ii) erythroid-specific ALAS2. Every enzyme deficiency is associated with separate class of porphyria which is illustrated in the figure. Second, third and fourth enzymes have different housekeeping and erythroid-specific transcripts, mainly formed by alternate promoters or splicing. Out of all the genes in hemesynthetic pathway, only ALAS2 is situated on X chromosome. Numbers written inside yellow circles represent sequential reactions and enzymes responsible for each step are as follows: 1. 5-aminolevulinic synthase, 2. 5-aminolevulinic dehydratase, 3. hydroxymethylbilane synthase, 4. uroporphyrinogen III synthase, 5. uroporphyrinogen decarboxylase, 6. coproporphyrinogen oxidase, 7. protoporphyrinogen oxidase, 8. ferrochelatase.

Source: Adapted from the book chapter "Inherited Porphyrias" in Emery and Rimoin's Principles and Practice of Medical Genetics, 5<sup>th</sup> ed. Volume 3, 2006.

erythropoietic protoporphyria (EPP), PCT and rare HCP. Blistering type of lesions include friability, edema and vesicle formation in sun-exposed parts, mainly dorsum of hands. Later on, they may present with hypertrichosis, abnormal pigmentation, skin scarring and mutilation of fingers. Nonblistering type of cutaneous photosensitivity is mainly characteristic of EPP, which mainly presents with burning pain as soon as skin is exposed to sun, sometimes described like prick of a hot needle. EPP is generally not associated with blister formation.

## LABORATORY INVESTIGATIONS

### Acute Porphyrias

Laboratory investigations should begin as soon as there is suspicion of porphyria. In case of acute porphyria, first screening investigation is measurement of urine porphobilinogen (PBG) level which should immediately be done in any patient with nonspecific neurovisceral symptoms with or without cutaneous symptoms. Increased urinary PBG level (20–200 mg/dL) can detect acute porphyria with high sensitivity and specificity. Urine PBG levels are much higher and last for longer time in cases of AIP in comparison to VP and HCP. The cases which can be missed are ALA dehydratase-deficient acute porphyria [normal PBG with high aminolevulinic acid (ALA) level in urine] and patients who have already received hemin therapy. Apart from this, blood electrolytes level, blood glucose, liver function test and kidney function tests should also be done. Urine, plasma and fecal samples should be preserved for second line of investigations before treatment is started.

Once the diagnosis is confirmed by raised PBG levels in urine, treatment should start immediately as treatment protocol is similar in all acute porphyrias. Later, second line investigations can be performed which differentiate between different types

of porphyrias. These second line investigations include plasma fluorescence spectrum, high performance liquid chromatography and mass spectrometry, quantitative measurement of 5-ALA and porphyrins levels in urine, relative concentration of different porphyrins in plasma and stool, enzyme assay in erythrocytes and mutation analysis. The differentiation of different acute porphyrias needs to be done on the basis of biochemical investigations including porphyrins in urine and stools, plasma fluorescence peak, enzyme activity and molecular testing. VP has a characteristic peak plasma fluorescence emission at 624–627 nm and HCP has high stool coproporphyrin III.

### Genetic Mutation Analysis in Acute Porphyrias

All acute porphyrias except ALADP are inherited in an autosomal dominant manner (Table 1). ALADP is inherited in an autosomal recessive manner. Most molecular defects are family-specific and identification of molecular defect is essential to provide prenatal diagnosis or presymptomatic diagnosis. However, most patients (80–90%) who carry the mutation are clinically asymptomatic, and hence, prenatal diagnosis is usually not offered.

### Laboratory Investigations in Cutaneous Porphyrias

In porphyrias presenting with predominantly cutaneous symptoms with acute neurovisceral attacks, the first step is to analyze urine porphyrin levels. If urinary PBG levels are increased and neurovisceral symptoms are present, then a diagnosis HCP or VP should be considered and further differentiation can be done on the basis of biochemical tests. VP can readily be identified on the basis of peak plasma fluorescence emission at 624–627 nm. If neurovisceral attacks are absent and cutaneous symptoms are in

**Table 1** Characteristics of enzymes of heme synthesis pathway

S. No.	Name of enzyme	Characteristics of enzyme	Disorder caused by deficiency of enzyme	Genetics
1.	ALA synthase	<ul style="list-style-type: none"> <li>Mitochondrial enzyme</li> <li>Rate-limiting step in heme synthetic pathway in hepatocytes</li> <li>Two isoforms</li> </ul>	<ul style="list-style-type: none"> <li>X-linked sideroblastic anemia</li> <li>Rare variety of X-linked ALAS-deficient EPP</li> </ul>	<ul style="list-style-type: none"> <li>Loss of function mutation: X-linked sideroblastic anemia</li> <li>Gain of function mutation: X-linked erythropoietic protoporphyria</li> </ul>
2.	ALA dehydratase or PBG synthase	<ul style="list-style-type: none"> <li>Occurs in cytoplasm</li> <li>Converts ALA to PBG, cyclic pyrrole</li> <li>Two alternative forms, housekeeping and erythroid specific by using alternate splicing</li> </ul>	ALA dehydratase deficient rare autosomal recessive porphyria	<ul style="list-style-type: none"> <li>ALAD, situated on 9p32</li> <li>Autosomal recessive inheritance</li> </ul>
3.	HMB synthase or PBG deaminase or uroporphyrinogen I synthase	<ul style="list-style-type: none"> <li>Occurs in cytoplasm</li> <li>Converts four molecules of PBG to HMB by deamination</li> <li>Two alternative forms, housekeeping and erythroid specific by alternate splicing</li> </ul>	Acute intermittent porphyria	<ul style="list-style-type: none"> <li>HMBS gene, situated on 11q23.3</li> <li>Autosomal dominant inheritance</li> <li>Reduced penetrance (&lt;10%)</li> <li>&gt;300 mutations reported, mostly private. Mutation detection is important for presymptomatic testing for family members</li> </ul>
4.	Uroporphyrinogen III synthase	<ul style="list-style-type: none"> <li>Occurs in cytoplasm</li> <li>Converts HMB to uroporphyrinogen III</li> </ul>	Congenital erythropoietic porphyria	<ul style="list-style-type: none"> <li>UROD gene</li> <li>Autosomal recessive</li> </ul>
5.	Uroporphyrinogen III decarboxylase (URO decarboxylase)	<ul style="list-style-type: none"> <li>Occurs in cytoplasm</li> <li>No tissue-specific isoform</li> <li>Converts uroporphyrinogen III to coproporphyrinogen III</li> </ul>	<ul style="list-style-type: none"> <li>Porphyria cutanea tarda</li> <li>Most common porphyria with prevalence of 1:25,000 (acquired or heterozygous autosomal dominant)</li> <li>HEP, homozygous dominant form</li> </ul>	<ul style="list-style-type: none"> <li>Acquired form is more common (80% of the cases, type I if sporadic, type III if familial), no mutation in specific gene in acquired form</li> <li>Genetic forms due to mutation in UROD gene are found in 20% of the cases, type II)</li> </ul>
6.	Coproporphyrinogen III oxidase (COPRO oxidase)	<ul style="list-style-type: none"> <li>Mitochondrial enzyme</li> <li>Converts coproporphyrinogen III to protoporphyrinogen IX</li> </ul>	<ul style="list-style-type: none"> <li>Heterozygous mutation: HCP</li> <li>Homozygous mutation: Harder porphyria</li> </ul>	<ul style="list-style-type: none"> <li>CPOX gene, autosomal dominant</li> <li>Recessive forms are also known</li> </ul>
7.	Protoporphyrinogen IX oxidase	<ul style="list-style-type: none"> <li>Mitochondrial enzyme</li> <li>Converts protoporphyrinogen IX to protoporphyrin IX</li> </ul>	Variegate porphyria (VP)	<ul style="list-style-type: none"> <li>PPOX gene</li> <li>Autosomal dominant inheritance</li> </ul>
8.	Ferrochelatase or Heme synthase	<ul style="list-style-type: none"> <li>Mitochondrial enzyme</li> <li>Insertion of ferrous iron to form heme</li> </ul>	Erythropoietic porphyria (EPP)	<ul style="list-style-type: none"> <li>FECH gene</li> <li>Autosomal dominant with reduced penetrance</li> </ul>

**Abbreviations:** PBG, porphobilinogen; HMB, hydroxymethylbilane; ALA, aminolevulinic acid; EPP, erythropoietic porphyria or protoporphyria or erythropoietic protoporphyria; CEP, congenital erythropoietic porphyria; PCT, porphyria cutanea tarda; HEP, hepatoerythropoietic porphyria; HCP, hereditary coproporphyria; VP, variegate porphyria.

**Table 2** Clinical signs and symptoms in acute porphyrias

Abdominal pain	Usually the most common presenting symptom. Diffuse, generalized, often cramp, associated with nausea/vomiting/diarrhea/distension of abdomen, lasts from hours to days. Inflammatory signs like fever, peritoneal irritation and leukocytosis are usually absent
Central nervous system	Present in 40–60% of cases, may be variable from minor behavioral changes to acute psychiatric symptoms like agitation, confusion, hallucinations and depression. Seizures can also occur as neurologic manifestation or due to hyponatremia. Sometimes blindness, pyramidal signs, cerebellar signs and altered consciousness may also occur
Peripheral neuropathy	Mostly motor in early stages present with limb weakness. Later on, it may be associated with pain or sensory loss in extremities. Recovery from limb paralysis is slow and often incomplete. Sometimes may progress to bulbar or respiratory muscle paralysis and can be life-threatening
Others	Cardiac arrhythmias and sudden death, chronic arterial hypertension, renal insufficiency, liver cirrhosis and hepatocellular carcinoma
Cutaneous signs	Chronic blistering lesion in sun-exposed areas

**BOX 1 Treatment of acute porphyrias***Acute Management*

1. Hospitalization
2. Identify the precipitating event for the attacks (calorie restriction, drugs, day of menstrual cycle)
3. Stop all medications which can precipitate an acute attack of porphyria (list of unsafe drugs is available on site—[www.drugs-porphyria.org](http://www.drugs-porphyria.org))
4. Adequate calorie intake (total parenteral nutrition may be required in some cases)
5. 10% or 25% dextrose solution intravenously, 3–4 g/day (initial treatment for mild attacks)
6. Infusion of hemin preparation (hemin, heme albumin or heme arginate) is the most effective therapy in acute attacks which is given in a dose of 3–4 mg/kg/day over 10–15 min once daily at least for 4 days and may be prolonged on the basis of clinical presentation
7. Correct electrolyte imbalance (especially hyponatremia and hypomagnesemia)
8. Pain: opiates, aspirin
9. Nausea, vomiting: promethazine, chlorpromazine, ondansetron
10. Seizures: correct electrolyte imbalance and use antiepileptic drugs like gabapentin or lamotrigine
11. Symptomatic hypertension and tachycardia:  $\beta$ -adrenergic blockers (propranolol, atenolol, labetalol)
12. Constipation: bulk laxatives, lactulose
13. Close monitoring for nutrition, neurological signs, electrolyte imbalance, pulmonary function test and bladder distension
14. Respiratory muscle weakness: ventilator support in intensive care unit
15. Kidney failure: management of hypertension, dialysis, consider kidney transplantation.

*Surveillance and Chronic Management*

1. Stop smoking and alcohol consumption
2. Carry medical alert cards for diagnosis, medical records, list of harmful or safe drugs and emergency treatment.
3. Limb weakness: physiotherapy
4. For cyclical attacks in females: gonadotropin releasing hormone (GnRh) analogues with add back estradiol after 6 months (low dose combined oral contraceptive pills may be tried but they sometimes can precipitate attacks), weekly hemin infusion can be considered
5. Avoid prolonged fasting with adequate carbohydrate intake
6. For chronic psychiatric symptoms: education, psychological support, neuroleptics and antidepressant if required
7. For iron overload in patients receiving frequent hemin transfusion: iron chelators
8. Periodic renal function assessment
9. Surveillance for liver cell carcinoma (frequent imaging after 50 years of age). Kidney and/or liver transplantation in last stages
10. Early severe attacks: consider liver transplantation
11. Genetic counseling and education of family members.

the form of blisters, then first investigation is plasma fluorescence spectrum. Once VP is excluded, second test is estimation of fecal porphyrins. In porphyria cutanea tarda, isocoproporphyrins and 7-carboxylporphyrins are secreted in large quantity. If cutaneous symptoms are nonblistering painful variety, then measurement of protoporphyrin IX in erythrocytes is a sensitive measure for EPP. Enzyme assay and mutation analysis are final investigations in differentiating cutaneous porphyria.

**TREATMENT****Acute Porphyria**

Management of acute porphyria should begin as soon as screening test (urine PBG levels) is found to be positive. Management can be discussed under two separate subheadings: (i) acute management, and (ii) chronic management. Steps are summarized in **Box 1**.

**Treatment for Cutaneous Porphyria**

For cutaneous porphyria, there are some general management rules including protection of sun exposure and trauma, application of sunscreen lotion and treatment of secondary infection of skin lesions. For PCT, frequent phlebotomy and chloroquine or hydroxychloroquine is the mainstay of therapy. However, in cases of CEP, treatment of hemolytic anemia, hydroxyurea and  $\pm$  splenectomy have important role in management, and bone marrow transplantation is considered to be curative. In VP and HCP, avoidance of harmful drugs and acute management is important as described under the heading of acute porphyria above. In cases of EPP, use of  $\beta$ -carotene is the treatment of choice.

**IN A NUTSHELL**

1. Porphyrias are a group of eight inherited disorders of heme synthesis and classified as acute (hepatic) or cutaneous.
2. Pain in abdomen is the most common visceral symptom of porphyrias. Seizures and cutaneous manifestations are other presentations depending on the subtype.
3. Acute porphyrias include four hepatic porphyrias, i.e., acute AIP, HCP, VP and rare ALADP.
4. The porphyrias which present with cutaneous signs and symptoms include CEP, HEP, VP, EPP, PCT and rare HCP.
5. PCT is a hepatic porphyria and mainly presents with cutaneous manifestations. VP and HCP may present with both neurovisceral and cutaneous symptoms.
6. Increased urinary PBG level (20–200 mg/dL) can detect acute porphyria with high sensitivity and specificity.
7. Management should start as soon as the diagnosis is made.

**MORE ON THIS TOPIC**

- Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and management. *Blood*. 2012;120:4496–504.
- Bonkovsky HL, Guo JT, Hou W, et al. Porphyrin and heme metabolism and the porphyrias. *Compr Physiol*. 2013;3:365–401.
- Puy H, Gouya L, Deybach JC. Porphyrias. *Lancet*. 2010;375:924–37.



## Chapter 3.19

# Newborn Screening

Seema Kapoor, Madhulika Kabra

Newborn screening (NBS) refers to screening of the newborn shortly after birth for potentially fatal disorders that are treatable but inapparent. Since there are no prototypic symptoms of inborn errors of metabolism (IEM), clinical diagnosis at birth is difficult. NBS is a coordinated comprehensive system with multiple components including education, screening (specimen collection, transportation and testing), follow-up of abnormal and unsatisfactory test results, confirmatory testing and diagnosis, treatment and periodic outcome evaluation, quality assurance and program evaluation, validity of testing systems, efficiency of follow-up and intervention, and assessments of long-term benefits to individuals, families and society.

## TEST AND DISEASE CHARACTERISTICS

### Test Characteristics

The test should be able to provide a value to decide whether the screening test is positive. This value is above a designated cut-off—placed generally beyond 99.9th percentile or below 0.11th percentile—depending on whether it is a high or a low marker. The cut-off is arbitrary and as in all physiologic parameters has a wide dispersion across the central value. Though it is set to increase the sensitivity, i.e., not to miss any case, this may also lead to a few false positives. Thus, for each screened positive result, a second analytical test is required for confirmation. The technology for the confirmatory test should be different from that used for the screening test. Each infant called back for retesting is labeled as *recall*. If there is a suspicion of a technical error, the test is repeated on the same filter paper sample punched from a different site (*repunch*) before recall. A recall may be associated with significantly parental anxiety and should be asked only if absolutely essential.

### Disease Characteristics

The disorders commonly screened are endocrine disorders like congenital hypothyroidism (CH) and IEM but also include nongenetic targets like hearing testing. These screening programs are often run by state or national governing bodies in developed countries with the goal of screening all infants born in their jurisdiction. Other disorders where this has been used are congenital infection like toxoplasmosis and inherited immune deficiency disorder like severe combined immunodeficiency. Disorders to be included in the screening program differ from country to country. For most developed countries, initial targets for screening were phenylketonuria and congenital hypothyroidism, but now include congenital adrenal hyperplasia (CAH), cystic fibrosis, galactosemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, biotinidase deficiency, hemoglobinopathies (sickle cell disease) and nongenetic targets such as hearing and intrauterine infections. The recent introduction of pulse oximetry to this program has an added value of screening for critical congenital heart disease.

### Criteria for Disease Selection

It may not be economically and ethically viable to screen for a complete range of disorders for which diagnostic modalities are available. Wilson and Jungner have outlined specific criteria (**Box 1**) that can serve as a template to decide what disorders to include in the screening at a national platform.

### BOX 1 Wilson and Jungner criteria for disease screening

- The condition sought should be an important health problem
- There should be an accepted treatment for patients with recognized disease
- Facilities for diagnosis and treatment should be available
- There should be a recognizable latent or early symptomatic stage
- There should be a suitable test or examination
- The test should be acceptable to the population
- The natural history of the condition, including development from latent to declared disease, should be adequately understood
- There should be an agreed policy on whom to treat as patients
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
- Case-finding should be a continuing process and not a *once and for all* project.

## CORE AND EXPANDED PANEL

*Core panel* indicates the basic minimum set of disorders for which screening should be advocated at a national level. Since all countries chose the set of disorders to be initiated in their domain based on epidemiologic prevalence and resources, the panel across the world is not uniform. This distinction not only outlines the group to be tested but also the differences in technology for the set of disorders included in each category. The term *expanded newborn screening* emerged after the introduction of tandem mass spectrometry (MS/MS) into the newborn screening program, which can handle simultaneous screening of multiple analytes from the same drop of blood.

### Diseases Included in the Core Panel of All Countries

#### Congenital Hypothyroidism

This disorder serves as a template to introduce NBS in any country. It is the commonest cause of preventable mental retardation, but therapy is easily and economically available to even the least affording. Both thyroid stimulating hormone (TSH) and tetraiodothyronine (T4) can be used for an ideal screening test as the former identifies the primary hypothyroidism and T4 identifies both primary and secondary hypothyroidism. The ideal time to collect samples is between 72 hours and 7 days of life. The treatment if initiated within the first 2 weeks, it is associated with a normal outcome in all domains of development. Since it is a screening test, it is always important to confirm this by doing a venous sample for estimating free triiodothyronine (T3), free T4 and TSH. It is important to mention here that central hypothyroidism, which is due to defects in the hypothalamo-pituitary axis, is reflected in the low levels of TSH and will not be picked up while using TSH as a primary approach.

#### Congenital Adrenal Hyperplasia

This group of disorders involving deficiency of 21 $\alpha$ -hydroxylase causes either genital ambiguity in a female child or a salt-wasting type of presentation, often mistaken as sepsis in the neonatal period in a male infant. The variety presenting later in life is called the nonclassical CAH and can be missed in newborn screening. This is also included in the core panel of many countries. The analyte tested for it is 17-hydroxyprogesterone (17-OHP). Since this analyte is prone to elevations due to stress and parturition, it needs to be adjusted for both gestational age and weight. Significant elevations of 17-OHP early in life may not indicate CAH and the magnitude of elevations does not correspond with true positivity. A second

tier testing using residual blood spots obtained on filter paper for steroid profiling for confirmation delineates levels of cortisol, 17-OHP and androstenedione. This helps in deciding a true CAH child versus a sick neonate under stress with raised cortisol levels.

### **Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD)**

This is included in the core panel of screening programs of many South-East Asian countries and should also be targeted for screening in India. Data from Chandigarh suggests an incidence of 1 in 112 and from eastern India an incidence of 1 in 15. This disorder has been genotypically well mapped from different parts of the country with G6PD Mediterranean (563 C-T) being seen commonly in North India, G6PD Kerala-Kalyan (949 G-A) in Maharashtra, Kerala, Andhra Pradesh, Tamil Nadu and Punjab and G6PD Odisha (131 C-G) in tribals of Central, Eastern and Southern India.

### **Deafness**

Screening for deafness is important because provision of hearing aid early in the prelingual phase can minimize the negative impact of sensorineural hearing loss on speech and language acquisition. Techniques currently used in newborn hearing screening can discriminate peripheral (cochlear) from central (brain stem) auditory function. Two-phase screening using otoacoustic emissions (OAEs) and auditory brainstem response (ABR) allows detection of various failure patterns.

### **Expanded Panel**

The introduction of MS/MS technology for analysis has enabled us to screen for disorders of metabolism of fatty acid, amino acids and organic acids. Targeted or high risk screening may identify a higher proportion of affected neonates. MS/MS allows other disorders to be added for screening without a need for additional samples or analysis time. The initial cost of MS/MS might be quite high, but the analytical cost per sample for screening approximately 45 disorders is US \$10–20, and the addition of another disorder to the panel may be less than \$1. Most developed countries have expanded NBS programs that screen from approximately 20 to over 40 inherited metabolic diseases by MS/MS. Availability of confirmatory testing and treatment appear to be the major rate limiting factor in implementing expanded screening in India.

### **Other Disorders**

Others disorders included in many country programs are screening for cystic fibrosis, toxoplasmosis, hemoglobinopathies, biotinidase deficiency, galactosemia and, more recently, for lysosomal storage disorders. For inclusion of every new disorder in the country program, a brainstorming is required to revisit its need in the light of available evidence.

## **LOGISTIC ISSUES**

### **Optimal Timing and Method of Sampling**

The American Academy of Pediatrics has advocated the ideal time of sampling after 72 hours and within 7 days of life. However, this policy would be very difficult in Indian patients to adopt due to high birth rate, limited space in most hospitals and difficulty in keeping the mothers in the hospital for longer than 24 hours. California screening program recently evaluated the performance of screening at 12 hours and found it satisfactory. We suggest that the analytes can ideally be measured at or after 24 hours of life when enteral feeding has been established, renal function is improving and hepatic metabolism is in the process of becoming mature. At birth, the plasma levels of amino acids, organic acids and acylcarnitines are not easily distinguishable between normal infants and those born with an inborn error of metabolism. Collection of sample prior to 24 hours could compromise sensitivity of certain screening

tests. Thus, it may be ideal for our set-up to take the sample after first 24 hours of life. If a sample is collected from an infant less than 24 hours old, a repeat specimen should be taken after 24 hours.

Low birth weight or premature babies, and those in a special care nursery (SCN) or neonatal intensive care unit (NICU) should have repeated screening at 2, 6 and 10 weeks of age or until the infant reaches 1,500 g. This has been advocated primarily to evaluate neonates with a delayed rise in TSH. Newborns that require red blood cell transfusion should have a blood specimen for NBS collected prior to the transfusion. This is important for detecting galactosemia by RBC enzyme analysis and hemoglobinopathies by hemoglobin electrophoresis prior to transfusion if this is the panel being screened. A follow-up newborn screen should then be obtained 2 months after the transfusion.

### **Tool for Collection**

Newborn screening tests are most commonly done from whole blood samples collected on specially designed filter paper. This filter paper allows blood to elute out on washing without letting shreds of filter paper coelute and block the analytical machinery. The filter paper is often attached to a form containing required information about the infant and parents. This includes date and time of birth, date and time of sample collection, the infant's weight and gestational age. The form also has information about whether the baby has had a blood transfusion and any additional nutrition the baby may have received (total parenteral nutrition). A repeat specimen (if required) should be written boldly on the top.

### **Blood Sample Collection**

Dried blood spots should be collected by heel-prick on the blood sample collection cards. The heel is punctured with a firm deliberate stab with lancet on the medial or lateral aspect. The depth of the puncture should not exceed 2.4 mm which is ensured by using a lancet which will not puncture beyond the certain depth. If a second puncture is necessary, this is made a few millimeters away from the first or in other foot. At least, three (preferably five) blood spots should be collected from each neonate. Venous sample should only be collected if sampling is being done for some other test so that two pricks can be avoided. A typical sample filter paper is depicted in **Figure 1**. The divisions in the filter paper are for tests going for the fluoroimmunoassay or enzyme-linked immunosorbent assays (ELISA) system and two circles for expanded screening; this may differ from country to country. The circle marked on the card is touched gently to the hanging drop so that blood soaks through the other side. It is very important not to put drops on both sides of a circle. The card should not be pressed onto the skin. The blood spot should not be touched with a finger.

### **Drying and Transport**

The sample collected should be dried at room temperature in a horizontal position. Specially designed stands can be used for drying. Any other drying agent like a lamp, dryer or sunlight should not be used to dry the filter paper as it may degrade the analyte or the enzyme contained in the filter paper. Moisture may harm the specimen by inducing bacterial growth or altering the elution time of the specimen. In ambient temperatures, it would take 4 hours on an average before it can be sent to laboratory for testing. The sample collected can ideally be sealed in a zipped bag which should contain a desiccant, put in a paper envelope and sent for testing. Dried blood spot specimens protected in this manner can be stored at –20°C for many weeks or years.

### **Common Sample Collection Problems**

Common sampling problems include insufficient blood (not filling all circles), not enough sample to perform tests or repeat tests. Milking or squeezing the puncture site can cause hemolysis and mixing of tissue fluids with blood. Layering or applying successive

**Department of Pediatrics MAMC & LN Hospital**  
**Newborn Screening Filterpaper**

Mother's Name- Last Name, First Name

Date of First Feeding: Day Month Year Time of First Feeding

Infant's Date of Birth: Day Month Year Time of Birth Birth Weight (in Grams)

Multiple Births: Birth Order A, B, C, etc. Gestational Weeks: No. Sex: M or F

Date of Collection: Day Month Year Time of Collection

Type of Feeding: Breast TPN FORMULA- Trade Name

Special Circumstances: Second Home Birth Antibiotics Transfused

Date of Transfusion: Day Month Year

Hospital No.

Risk Factors: Sick Baby Yes No Material Pregnancy Complications: Yes No Deceased Sibling: Yes No Congenital Anomalies: Yes No (e.g. APLP, HELLP)

Father's Name - Last Name, First Name

Mother's Date of Birth: Day Month Year

Address - City, State

Contact Phone Number: City Code Number

Type of clinical Presentation

Physician Responsible for Infant Follow-up after Discharge

Physician's Phone Number: City Code Number

Physician's Fax Number: City Code Number

Gentic Lab. MAMC Bhadurshah Zafar Marg, Darya Ganj, Delhi

Use 24 Hour Clock (Noon = 1200, Midnight = 2400)  
All information must be printed firmly with ballpoint pen

ALLOW BLOOD TO SOAK THROUGH AND COMPLETELY  
FILL EACH CIRCLE APPLY BLOOD ONLY TO  
ONE SIDE OF THE FILTER PAPER

**Figure 1** Typical collection card with filter paper attached at the left end with circles to be filled and demographics to be entered

drops of blood (double collection) in the same printed circle causes caking and/or nonuniform concentrations of blood. If the blood flow diminishes, such that circles are not completely filled, then repeat the sampling technique in a new circle. Contamination of sample during collection, drying or mailing with urine samples will render the results unreliable. Humidity and moisture adversely affect the quality of sample and analyte recovery.

### COMPONENTS OF NEWBORN SCREENING: FOLLOW-UP

As the initial test in the NBS process is a screening test, there is a possibility of false positive (abnormal test, normal infant) and false negative (normal test, affected infant) results. NBS test results are mostly negative, which means that the infant does not have any IEM for which laboratory tests are performed. Screen positive results are repeated from the original dried blood spots (DBS) and when the repeated test reveals a positive result. This is called a repunch to exclude technical errors in the report. Screen positive results should be confirmed by other tests including plasma amino acid, acylcarnitine and urine organic acid profiles to avoid false abnormalities which may not be due to a metabolic disease. If the results from the confirmatory tests are positive, the sample is sent for molecular confirmation of the same.

False-positive results lead to additional testing and parental anxiety, and long-term consequences such as the vulnerable child syndrome may occur. False-negative results may lead to a delay in diagnosis, because the healthcare professional may be falsely reassured by a normal NBS result. Finally, it must be emphasized that *normal* results of newborn screenings do not rule out the presence of these disorders, because some variants of these conditions may have onset later in life, and false-negative results may occur. The clinical judgment of the pediatrician remains the most important tool in the diagnosis of all of these conditions. Proper follow-up of a *not-normal* screening result is crucial, if mortality, morbidity and disabilities are to be avoided. The primary function of the follow-up program is to locate infants with abnormal screening results and facilitate timely diagnostic testing and management. The time-frame for follow-up will vary by disorder and by the degree of abnormality of the screening result. The pediatrician is usually the provider of first contact for screen positive infants.

The determination of an abnormal newborn screen result sets into motion a cascade of notification, plan of action and documentation. In case the analyte test result is considered by the screening program to be borderline elevated, the recommendation

will be to send a repeat newborn screen to the program. A newborn discharged to home can have the repeat screen drawn in the pediatrician's clinic, healthcare facility or in the reference laboratory. Infants still hospitalized are readily retested at the hospital. This procedure is called *recall*. It is needless to stress that confirmatory biochemical and molecular tests are to be done in all screen positive cases. These tests should be performed at a medical center or in consultation with a genetic specialist or pediatric endocrinologist.

### Disease Management

Infants affected with disorders detected by NBS usually require lifelong management. For every child, care should be accessible, family-centered, continuous, comprehensive, coordinated, compassionate and culturally competent. The pediatrician plays a central role but may need consultation with experts who understand the etiology, pathophysiology, clinical heterogeneity and psychosocial issues associated with the disorder. Genetic counseling, including discussion of carrier testing of family members and prenatal diagnosis of future pregnancies, may be indicated.

### Second-tier Testing

The false positive results and relatively poor positive predictive value for some MS/MS tests have led to the development of a number of second-tier tests. Each of the secondtier tests requires a separate testing protocol and rapid turnaround of results is required. The second tier tests available and incorporated into the NBS programs are for tyrosinemia I, propionic acidemia, maple syrup urine disease (MSUD), CAH, hyperammonemia-hyperornithinemia hyperhomocitrullinemia (HHH), methylmalonic acidemia and galactosemia. The second-tier testing is usually performed on the same residual blood spots to minimize recall and undue parental anxiety.

### NEWER DEVELOPMENTS

Newer developments in the field of NBS have widened the debate on the ethics of newborn screening. One important introduction in this field is the inclusion of testing for disorders like treatable lysosomal storage disorders, which include Gaucher disease, Pompe disease, Fabry disease and mucopolysaccharidosis I to name a few. This may be vital in presymptomatic institution of enzyme replacement therapy, where it is likely to be of utmost importance. However, in resource constraint settings like ours, this may see the application at a date when resources could be allocated to them.

### IN A NUTSHELL

1. Newborn screening is probably one of the important public health programs akin to the immunization program in both predictive and presymptomatic.
2. *Core panel* indicates the basic minimum set of disorders for which screening should be advocated at a national level. These include screening for congenital hypothyroidism, congenital adrenal hypoplasia, deafness and G6PD deficiency.
3. *Expanded panel includes screening for 20–40 disorders.* The introduction of MS/MS technology for analysis has enabled us to screen for disorders of metabolism of fatty acid, amino acids and organic acids.
4. The recent program launched by the Government called RBSK program (Rashtriya Bal Swasthya Karyakram) has included screening for CH as one of the deficiencies at birth to be targeted. Probably, this initiative will initiate and integrate the process to which diseases will be added subsequently.

### MORE ON THIS TOPIC

- Colgan S, Gold L, Wirth K, et al. The cost-effectiveness of universal newborn screening for bilateral permanent congenital hearing impairment: systematic review. *Acad Pediatr*. 2012;12:171-80.
- Fernhoff PM. Newborn screening for genetic disorders. *Pediatr Clin North Am*. 2009;56:505-13.
- Hiraki S, Green NS. Newborn screening for treatable genetic conditions: past, present and future. *Obstet Gynecol Clin North Am*. 2010;37:11-21.
- Kubota M. Newborn screening. *Nihon Rinsho*. 2010;68 Suppl 8:189-95.
- Levy PA. An overview of newborn screening. *J Dev Behav Pediatr*. 2010;31:622-31.
- Orzalesi M, Danhaive O. Ethical problems with neonatal screening. *Ann Ist Super Sanita*. 2009;45:325-30.
- Wilcken B. Newborn screening: gaps in the evidence. *Science*. 2013;342:197-8.



## Section 4

# IMMUNITY, IMMUNE DISORDERS AND ALLERGY

**Section Editors** Surjit Singh, Amit Rawat

## Chapter 4.1

### Basics of Immunology

Amit Rawat, Biman Saikia

*Immunity* originates from the Latin root *immunis*, meaning *exempt* and is used to refer to a state of protection from disease, more particularly infectious disease. It was observed by our astute ancestors that individuals who recovered from particular infectious disease were subsequently protected from that disease. Thucydides, a Greek historian was perhaps the first to provide a written account of *immunity* in 430 BC. In his description of the plague of Athens, he intuitively highlights that *only those who have recovered from the plague can nurse the sick, as they could not contract the disease a second time*. There is also a reference to the concept of immunity in *Ayurveda* where it is referred to as *Vyadhiksamatva* which literally means resistance to disease.

The immune system is an intricately orchestrated and dynamic network of cells and cell-associated as well as soluble molecules which protect us from infectious agents and the development of tumors. Certain components of the immune system are phylogenetically ancient and are conserved across species in the animal kingdom. In fact, some elements of this ancient system are also found in plants. However, the immune system is also a mediator for a host of diseases including autoimmune diseases and hypersensitivity reactions. On the other hand, deficiencies of individual components of the immune system are experiments of nature which result in a group of disorders known as primary immunodeficiency diseases. The immune system also poses a formidable barrier to organ transplantation and to gene therapy using viral vectors.

The two major components of the immune system in the jawed vertebrates are the innate immune system and adaptive immune system. The innate immune system is the evolutionarily primitive and more conserved element of the immune system. Innate immunity is referred to as *Sahaja Bala* and acquired immunity as *Yuktikrita Bala* in the Ayurvedic System of Medicine.

### CELLS AND ORGANS OF THE IMMUNE SYSTEM

All mature immune cells in humans are derived from a single cell type known as the hematopoietic stem cell. Stem cells possess the property of *self renewal* and the ability to differentiate into various cell types depending on the differentiation factors acting on these cells.

**Primary lymphoid organs** The development and maturation of immune cells takes place in two major organs of the body known as the primary lymphoid organs. These include:

- **Bone Marrow** The stem cells reside in the marrow and give rise to the various progenitors; and
- **Thymus** T-cell progenitors egress the bone marrow and complete their maturation in thymus.

**Secondary lymphoid organs** The secondary lymphoid organs include the lymph nodes, spleen and specialized aggregates of lymphoid tissue in the gut and other mucosal surfaces in which the naïve immune cells encounter their cognate antigens and get activated to form effector and memory cells.

**Tertiary lymphoid organs** These are organs which are sites of infection. These include liver, lung and skin. Lymphocytes activated in the secondary lymphoid organs can return to the tertiary lymphoid organs as immune effector cells or can reside in these organs as resident memory cells.

**Cells of the immune system** Cells of the innate immune system include neutrophils, monocytes or macrophages, dendritic cells and the innate lymphoid cell whereas the predominant cells of the adaptive immune system are the T- and B-lymphocytes and their various subsets.

### INNATE IMMUNE SYSTEM

The innate immune system is essentially the first responder to microbial invasion and to damaged, injured or dead self-cells. As the first line of defense against microbes, the innate immune system institutes mechanisms to prevent, control or eliminate the invading pathogens. It also stimulates the adaptive immune system by providing the appropriate *danger signals*. The innate immune system further senses damaged and injured self-cells playing a key role in wound healing and tissue repair.

#### Components of the Innate Immune System

- **Anatomical Barriers**
  - **Physical barriers:** Epithelia of skin, mucosa of respiratory, gastrointestinal and urogenital tracts.
  - **Chemical barriers:**
    - Acidic pH (stomach)
    - Antimicrobial proteins and peptides (defensins, cathelicidins, lysozyme, lactoferrin, collectins (surfactant proteins).
- **Cellular Components of the Innate Immune System**
  - Phagocytic and antigen-presenting cells (APCs)
    - Neutrophils
    - Macrophages
    - Dendritic cells
  - Innate lymphoid cells (subset of lymphocytes with limited diversity and a restricted repertoire of antigen-recognition receptors)
    - Natural killer (NK) cells
    - Invariant NKT cells
    - B1B and marginal zone B-cells
- **Soluble Components of the Innate Immune System**
  - Plasma proteins
    - Complement components and their fragments (C1q)
    - **Collectins:** Mannose-binding lectin, surfactant proteins (SP-A, SP-D)
    - **Ficolins:** L-ficolins and H-ficolins
    - **Pentraxins:** C-reactive protein

- Cytokines and chemokines (hormones of the immune system).

Cytokines are soluble protein molecules secreted by a wide variety of immune as well as nonimmune cells that regulate the immune response by activating or inhibiting target cells on which they act. The transcription of several key cytokines is induced by the activation of pattern recognition receptors (PRRs) present on the innate immune cells.

Chemokines are a subtype of cytokines which serve as chemoattractant molecules. They mobilize immune cells by affecting the cytoskeletal proteins in the immune cells and the expression of surface-associated cell adhesion molecules.

The predominant cytokines involved in the innate immune response are as follows:

- *Proinflammatory cytokines*: Interleukin-1 (IL-1), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-6
- *Cytokines mediating antiviral action*: Type I interferons (IFN): IFN- $\alpha$  and  $\beta$
- *Chemokines*: Macrophage chemotactic protein-1 and IL-8.

### Key Features of the Innate Immune System

- Phylogenetically ancient system (evolved before the adaptive immune system).
- Does not require prior contact with the pathogen to mount an effective response.
- Activated and responds within minutes to hours after the initial encounter with a pathogen.
- Has limited diversity, constrained by a fixed repertoire of conserved receptors which respond to broad classes of pathogens.
- Has limited memory when compared to the adaptive immune system.

The features of the innate immune system have been compared with the adaptive immune system in **Table 1**.

### Recognition of Pathogens by Innate Immune System

Immune recognition by innate mechanisms is accomplished by a special class of receptors which recognize structures or moieties which are not present in host cells. These receptors are known as PRRs. Innate immune cells display an array of these PRRs on their plasma membrane as well as endosomes and lysosomes. PRRs are strategically located to recognize both extracellular and intracellular pathogens. Structures recognized by these PRRs are known as pathogen-associated molecular patterns (PAMPs).

However, these PRRs also recognize certain endogenous components released from damaged and injured self-cells. These

endogenous components recognized by the PRRs are known as damage-associated molecular patterns (DAMPs).

### Types of Pattern Recognition Receptors

There are four major types of PRRs in humans. These are located on the cell surface or inside the cell depending on the pathogens they are designed to recognize. These PRRs are:

- Toll-like receptors (TLRs)
- C-type lectin receptors
- Nucleotide oligomerization domain (NOD) or leucine rich repeat containing receptors [NOD-like receptors (NLRs)]
- Retinoic acid-inducible gene-I-like receptors.

### Toll-like Receptors (TLRs)

They constitute the best characterized and studied family of PRRs and were the earliest PRRs to be discovered. Several exciting and path-breaking discoveries have been made in the past 2 decades with regard to these receptors. Single gene mutation in TLR3 resulting in increased susceptibility to herpes simplex encephalitis has been described recently.

The association of single nucleotide polymorphisms in several of the TLRs has also been described for various infectious and noninfectious diseases.

**Human TLRs and their ligands** A total of 10 TLRs, TLRs 1–10, have thus far been identified in humans. TLRs 1–10 are conserved between mice and humans, whereas mice have additional TLRs 11–13. TLRs bind specifically to their respective PAMPs. Human TLRs with their known ligands and their location are summarized in **Table 2**.

**Signaling through TLRs** The binding of TLRs to their cognate pattern associated molecular pattern ligands results in activation of downstream signaling pathways. The signaling pathway activated is determined by the TLR and the adaptor protein that binds to the cytoplasmic domain of that TLR. This cytoplasmic domain of the TLR is known as toll or IL-1 receptor domain. Most of the TLRs bind to the adaptor protein myeloid differentiation factor 88 (MyD88). The MyD88 pathway activates the nuclear factor kappa B (NF- $\kappa$ B). The NF- $\kappa$ B is a key transcription factor which activates several genes which are important in an innate immune response. These include genes encoding for antimicrobial peptides such as defensins, proinflammatory cytokines, e.g., TNF- $\alpha$ , IL-1 $\beta$  and IL-6 and chemokines.

The other important adaptor for TLRs is TIR-domain-containing adaptor-inducing interferon- $\beta$  (TRIF). TLR3 binds exclusively to the TRIF whereas TLR4 is more promiscuous binding both MyD88 and TRIF depending on whether it is present on cell surface or the endosome respectively. The engagement of the TRIF by TLRs results in the activation of interferon regulatory factors (IRFs). These IRFs are instrumental in transcriptional upregulation of genes encoding for type I IFN. Type I IFN such as IFN- $\alpha$  and  $\beta$  have potent antiviral properties.

Mutations in adaptor proteins such as MyD88 and IL-1-receptor-associated kinase 4 involved in the signaling pathway of TLRs have also been identified.

**Nucleotide oligomerization domain (NOD) receptors/Nucleotide oligomerization domain leucine-rich repeat containing receptors (NLRs)**

The NLRs or NOD-like receptors constitute a large family of cytosolic PRRs which is activated by several intracellular PAMPs as well as DAMPs and other harmful endogenous substances. There are 23 genes in the human genome encoding for various NLRs. The NLRs are subdivided into 3 major categories based on their N-terminal domain.

**Table 1** Comparison of the key features in innate versus adaptive immunity

Key feature	Innate immunity	Adaptive immunity
Rapidity of response	Immediate within hours	Delayed with a lag phase between exposure and response
Antigenic specificity	Broad, limited repertoire and fixed	Highly specific and evolves with time during the course of an immune response
Immunologic memory	None	Exquisite memory, rapid and heightened response to previously encountered antigens
Self/nonself recognition	Present	Present, occasional lapses resulting in autoimmunity

**Table 2** Human toll-like receptors with their ligands

Toll-like receptor (TLR)	Ligands	Microbe	Location	Gene defects/polymorphisms
TLR 1	Triacyl lipopeptides	Gram-negative bacteria Mycobacteria	Plasma membrane	Susceptibility to tuberculosis
TLR 2	Peptidoglycan Zymosan Lipoproteins Phosphatidylserine glycosylphosphatidylinositol-linked proteins	Gram-positive bacteria Yeasts and fungi Mycobacteria Schistosomes Trypanosome	Plasma membrane	Susceptibility to tuberculosis, leprosy, staphylococcal infection
TLR 3	Double-stranded RNA (dsRNA)	Viruses	Endosome Lysosome	Herpes simplex encephalitis
TLR 4	Lipopolysaccharide Mannans F-protein	Gram-negative bacteria Fungi Respiratory syncytial virus	Plasma membrane Endosome Lysosome	Excessive TLR4 signaling in gram-negative septicemia
TLR 5	Flagellin	Bacteria	Plasma membrane	Associated with including risk of Legionnaires' disease
TLR 6	Zymosan Diacyl lipopeptides	Yeasts and fungi Mycobacteria	Plasma membrane	Associated with including risk of Legionnaires' disease
TLR 7	Single-stranded RNA (ssRNA)	Viruses	Endosome Lysosome	Association with hepatitis C infection
TLR 8	Single-stranded RNA (ssRNA)	Viruses	Endosome Lysosome	Association with pulmonary TB and hepatitis C infection
TLR 9	CpG dinucleotide Hemozoin	Bacterial DNA Malarial pigment	Endosome Lysosome	Polymorphisms associated with systemic lupus erythematosus
TLR 10	Unknown	Influenza virus	Endosome Lysosome	Not known

1. *NLRs*: Caspase recruitment domain (CARD)
2. *NLRBs*: Baculovirus inhibitory repeat domain
3. *NLRPs*: Pyrin domains.

Nucleotide oligomerization domain 1 and NOD2 are the best characterized members of the NLR family. They are activated by components of the cell wall peptidoglycans of intracellular and extracellular bacteria. These are produced during the synthesis or degradation of the bacterial cell walls. Both NOD1 and NOD2 form signaling complexes that activate NF- $\kappa$ B leading to upregulation of transcription of several proinflammatory cytokines.

Some NLRs do not trigger signaling cascades leading to upregulation of expression of genes which affect the innate immune response. These NLRs form complexes with other proteins that stimulate proteases that cleave inactive forms of IL-1 and IL-18 into their mature and active form. These complexes of NLRs with other proteins and proteases are collectively referred to as *inflammasomes*.

**Inflammasome** Three NLRs, namely NLRP1, NLRP4 and NLRP3 have been found to form inflammasomes. Of these the NLRP3 is the best studied and characterized. The NLRP3 is expressed on several cell types including, monocytes, macrophages, dendritic cells, neutrophils, some lymphocyte subsets and epithelial cells. The NLRP3 inflammasome comprises of multiple copies of NLRP3, the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD) and caspase 1. These components are assembled in the form of a pentameric or hexameric structure.

### Activators of NLRP3

- *Nonmicrobial or sterile activators:*
  - *Self-derived molecules and substances:* Glucose; cholesterol and urate crystals; amyloid  $\beta$ -protein; adenosine triphosphate
  - *Non-self-environmental substances:* Asbestos; silica; alloys; alum

- *Pathogen-associated activators:*
  - *Bacterial activators:* Flagellin, peptidoglycans, pore-forming toxins
  - *Virus:* Viral RNA, influenza M2 protein
  - *Fungus:* Mannan; zymosan;  $\beta$ -glucans
  - *Protozoa:* Hemozoin (malaria).

Mutations in genes encoding for various components of the inflammasome are responsible for a group of rare heritable genetic disorders known as autoinflammatory syndromes.

### ADAPTIVE IMMUNITY

Adaptive immune response can be divided broadly into two arms which function separately but not necessarily independent of each other: *humoral immunity* and *cell-mediated immunity* (CMI). This classification is based on the components of the immune system that mediate these responses viz. humoral (humor: fluid) immunity is mediated by soluble components in the plasma composed mainly of antibodies, produced by B-lymphocytes and the complement proteins whereas cell-mediated responses are mediated mainly by T-lymphocytes. These two distinct arms of the adaptive response basically execute two distinct functions. The humoral response is designed to neutralize and eliminate extracellular microbes and toxins to which antibodies are accessible. The humoral response however is ineffective against intracellular microbes and microbes which survive and replicate inside the infected cells are taken care of by the cell-mediated response, wherein the infected cell is targeted and killed by a cytotoxic T-cell response to eliminate the organism and its reservoir. Cardinal features of the adaptive immune response are:

- *Specificity for distinct antigens* This specificity exists because individual lymphocytes express membrane receptors that are capable of distinguishing subtle differences in the antigens.

- Diversity, accounted to by an extremely large number of antigenic specificities of the lymphocytes in an individual called the lymphocyte repertoire, a result of extreme degree of diversity inserted into the antigen binding regions of the T-cell and B-cell receptors (BCRs) by combinatorial gene rearrangements.
- Memory, which accounts for the enhanced response of the immune system to re-exposure to the same antigen that generated and expanded the specific clone.

### Phases of the Adaptive Immune Response

The step-wise development of the adaptive response is brought about by distinct cell populations: the nonlymphoid APCs (viz. mononuclear phagocytes, dendritic cells, epithelial cells), lymphocytes (B-cells and T-cells, the latter comprising of CD4+ (cluster of differentiation 4+) helper T-cells and CD8+ cytotoxic T-cells) and effector cells (activated T-cells and phagocytes). The adaptive response can accordingly be divided into three phases: recognition of antigen, activation of lymphocytes and the effector phase.

The initiation of the response is brought about by the APCs, which are nonspecific responses as part of the innate response, which display the antigens to the antigen-specific lymphocytes culminating in the effector response and elimination of the invading pathogen. The APCs, hence bridge the innate and adaptive responses.

### Antigen Recognition and Presentation

The fundamental interaction between the APC and the lymphocyte happens through surface receptors which in the B-cell necessarily is a membrane bound antibody molecule (BCR) and in T-cells is the T-cell receptor (TCR). This interaction is antigen specific, i.e., the BCR and/or the TCR recognize specific epitopes of the antigen and hence only specific clones from the entire repertoire of T-cells and B-cells would be engaged in the antigen recognition which will lead to a specific clonal expansion. Whereas, the BCR recognize and bind to antigenic determinants of a macromolecule directly recognizing epitopes on a tertiary folded structure, TCR can recognize only the antigenic peptides processed by the APC machinery and presented in the context of self-major histocompatibility complex (MHC) molecules. Hence, antigen recognition by T-cells is self-MHC restricted.

The MHC molecules, also called the human leukocyte antigens (HLAs) are of two classes: HLA Class I, (expressed on the surface of all nucleated cells) and HLA Class II (expressed on APCs and B-cells). An antigen presented in context to HLA Class I molecule will engage a CD8+ cytotoxic T-cell whereas its presentation through HLA Class II molecule will engage a CD4+ helper T-cell. This segregation of antigen presentation represents two basic pathways: extracellular antigens taken up by the APC via phagocytosis or endocytosis are processed in the phagolysosomes and subjected to lysosomal proteases generating antigenic peptides which are loaded onto Class II MHC molecules in the endosomes and presented to CD4+ T-cells. On the other hand, intracellular antigens, which could be ubiquitinated misfolded proteins or proteins synthesized by viruses or other intracellular pathogens are processed through the proteasome machinery to produce peptides which are then loaded onto Class I MHC molecules in the endoplasmic reticulum and presented to CD8+ T-cells. These two pathways are however not strictly segregated in the sense that cytosolic proteins can be processed through the endosomal pathway and presented through Class II MHC and vice versa (antigen cross-presentation).

### Lymphocyte Activation

The engagement of the TCR or the BCR with its cognate antigen constitutes the first signal towards activation of the responder

lymphocyte. This signal, however, in itself is not enough to drive the T-cell machinery towards activation. A second *co-stimulatory signal* is provided simultaneously through the co-stimulatory molecules.

### T-cell Activation

T-cell activation, through the self-MHC restricted peptide presentation by the APC, necessitates a physical interaction and stable adhesion between the APC and the TCR. The TCR is a clonally distributed receptor meaning that the T-cells with different antigen specificity have different TCRs. Signal transduction after peptide binding happens not only through the TCR alone but also through the noncovalently linked TCR-associated invariant protein called CD3 and  $\zeta$  proteins which together form the TCR complex. Signaling through this TCR complex constitute the first signal.

Apart from the TCR complex, the T-cells also express various other surface receptors or molecules which do not bind or recognize antigen but participate in signaling concurrent with the signal through the TCR complex for full activation of the T-cell. This constitutes the co-stimulatory second signal for T-cell activation. These molecules are collectively called the accessory molecules, which other than functioning as co-stimulatory molecules also take part in cell adhesion (for stabilizing the TCR-APC binding), regulate migration and homing to specific sites and also take part in effector functions. The co-stimulatory or accessory molecules on the T-cells have certain common characteristics:

- They bind to their ligands present on the surfaces of APCs, endothelial cells, B-cells and extracellular matrix.
- Unlike the TCR and BCR, these molecules are nonpolymorphic, i.e., they are identical on all T-cells.
- On ligand binding, they transduce signals to the T-cell leading to either T-cell activation (e.g., B7-CD28 interaction) or inhibition [e.g., B7-CTLA (cytotoxic T-lymphocyte antigen)-4 interaction].

**CD4 and CD8 coreceptors** The CD4 and CD8 molecules bind to the nonpolymorphic regions of the MHC molecules concurrent with the TCR-peptide-MHC complex binding and signal transduction, and also strengthen the T-cell APC binding. CD4 binds to MHC Class II associated peptide whereas CD8 binds to Class I-associated peptide. Since T-cells express CD4 and CD8 molecules exclusive of each other, this segregation ensures handling of extracellular microbes by the predominantly cytokine producing CD4 cells and of intracellular microbes by CD8 cytotoxic T-cells.

**CD28 and CTLA-4 coreceptors** The best defined co-stimulation of T-cells which provides the second signal are a pair of related proteins, B7-1 (CD80) and B7-2 (CD86) which are expressed on the surface of professional APCs. The corresponding ligands on T-cells are CD28 and CTLA-4 (CD152). While signaling through the former leads to T-cell activation and proliferation, binding of CTLA-4 by B7 leads to inhibition of T-cell activation and termination of T-cell responses.

**Other coreceptors** CD45, CD2, CD40L, FasL (Fas ligand), LFA-1 (lymphocyte function-associated antigen 1) [which bind to ICAM-1 (intercellular adhesion molecule 1)], VLA-4 (very late antigen-4) which bind to vascular cell adhesion molecule.

When APCs first encounter an antigen either at the portal of entry or the draining lymph node, they process the antigen and present it to the naïve T-cells (either CD4 or CD8) and leads to their activation. The consequences of this activation are as follows:

- **Cytokine production** Signaling through the TCR and the co-receptors leads to a cascade of signaling, resulting in activated transcription factors causing cytokine gene transcription and protein synthesis. One of the earliest cytokines produced by a naïve T-cell after antigen binding is IL-2 which acts as a



growth and differentiation factor not only for other T-cells but also in an autocrine manner, promote its own differentiation and growth. This autocrine effect is further enhanced by a concomitant upregulation of the IL-2 receptor on the T-cell.

- **Proliferation of the antigen specific clone** (clonal expansion) as a result of the autocrine loop involving the IL-2 and IL-2 receptor.
- **Differentiation into effector cells** which subsequently enter the circulation and again get activated on encountering the specific cognate antigen. Antigen binding to an effector cell, unlike the naïve T-cell, however, leads to effector functions. The effector CD4 cells secrete an array of cytokines whereas activation of the CD8 effector cell leads to cellular cytotoxicity and elimination of the infected target cell. Depending upon the cytokine milieu, naïve CD4 cells differentiate into either Th1 (T helper type 1) cells (under the influence of IL-12 produced mainly by activated macrophages and dendritic cells), or Th2 suppressor cells (in response to IL-4 which may be produced by the T-cells themselves). The Th1 differentiation pathway is principally in response to microbes that either infect or activate macrophages which produce large amounts of IL-12 or stimulate NK cells to produce IFN- $\gamma$  which in-turn induce IL-12 secretion by macrophages. IL-12 acts through the activation of STAT1 (signal transducer and activator of transcription 1), STAT4 and T-bet transcription factor for Th1 differentiation. Th2 differentiation on the other hand occurs in response to helminths and allergens, which cause chronic T-cell activation without much macrophage activation. It is dependent on IL-4, which functions by activating the transcription factor STAT6 and GATA3 (*guanine adenine thymine adenine* sequence-binding protein 3). Similarly,

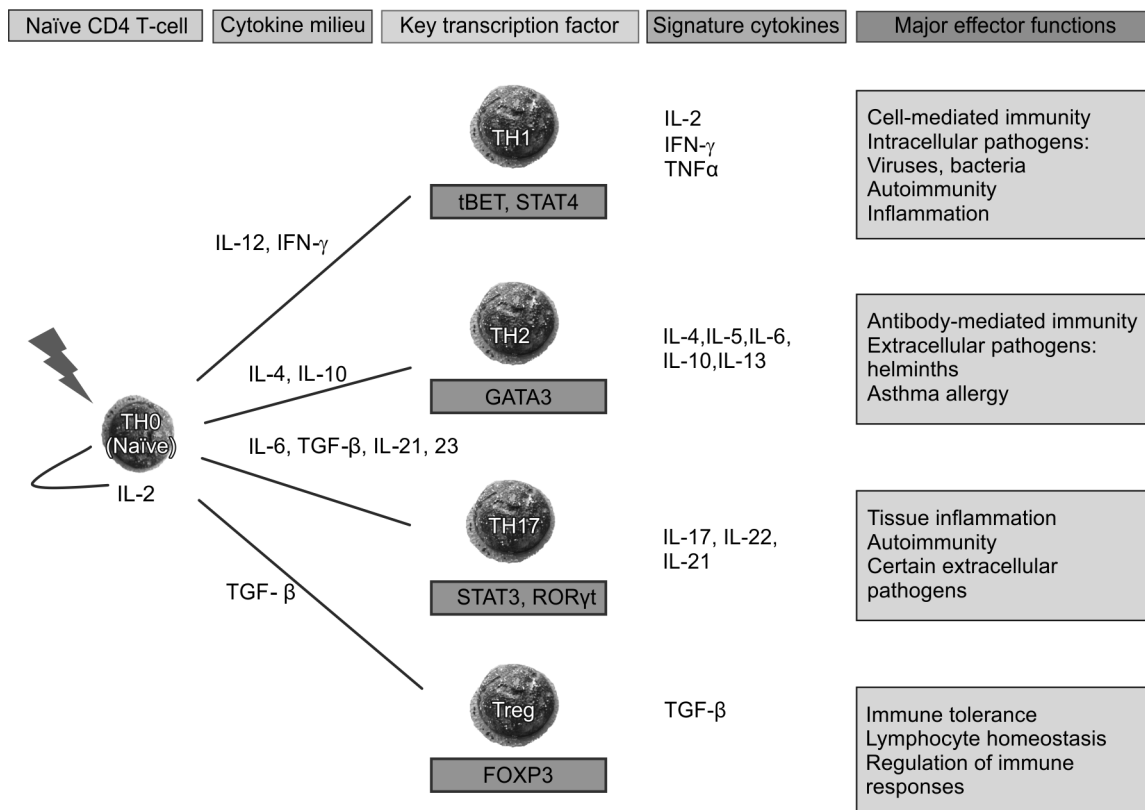
under the influence of IL-6 and TGF- $\beta$  (transforming growth factor-beta), the naïve T-cells differentiate into IL-17 producing Th17 cells through STAT3 and retinoid-related orphan receptor gamma t (ROR $\gamma$ t) transcription whereas in absence of IL-6 and presence of only TGF- $\beta$ , they differentiate into T regulatory cells through FOXP3 (forkhead box protein 3) transcription (Fig. 1).

- **Development of memory cells** This T-cell population is responsible for the accelerated secondary immune response on re-exposure to the same antigen.

### B-cell Activation

Antigen binding to the surface BCR (IgM and IgD) of the resting, mature B-cell, causes BCR cross linking which then transduces signals through the BCR associated Ig- $\alpha$  and Ig- $\beta$ . Ig- $\alpha$  and Ig- $\beta$  are disulfide linked to one another and noncovalently associated with the surface Ig and similar to the CD3- $\zeta$  in the TCR, constitute the BCR receptor complex. BCR cross-linking brings in close proximity the cytoplasmic domains of Ig- $\alpha$  and Ig- $\beta$  containing immunoreceptor tyrosine based activation motifs (ITAMs), phosphorylation of which brings about downstream signaling resulting in activation of transcription factors like Fos, Jun, NF- $\kappa$ B and Myc leading to functional activation of B-cells. The second co-stimulatory signal to the B-cells occurs through complement C3d binding to the complement receptor 2 (CR2) expressed as a membrane bound complex composed of CR2, CD19 and CD81.

Binding of the cognate antigen to the surface BCR brings about proliferation, and increased expression of HLA Class II, B7-1 and B7-2. The latter renders the B-cells capable of activating Th cells through binding to CD28 which subsequently activates the T-cell. Th cells then secrete cytokines which in-turn helps



**Figure 1** Differentiation of naïve CD4 T-cells into various effector subsets based on the cytokine milieu and key transcription factor  
 Abbreviations: IL, interleukin; IFN, interferon; TGF, transforming growth factor; STAT, signal transducer and activator of transcription; ROR $\gamma$ t, retinoid-related orphan receptor gamma t; FOXP3, forkhead box protein 3; TNF, tumor necrosis factor).

B-cell clonal expansion, isotype switching, affinity maturation and differentiation into memory B-cells. B-cell activated Th cells also express CD40 ligand (CD40L, CD154) which binds to CD40 on the B-cell and brings about B-cell maturation and isotype switching.

## Effector Phase

### Effector Mechanisms of Cell-mediated Immunity

A cell-mediated immune response is aimed at controlling two distinct situations: (a) handling microbes that reside and proliferate within the phagocyte and (b) handling microbes that infect various cell types including nonphagocytic cells and replicate in the cytosol. The former requires enhancing the phagocytic potential for microbe elimination and is brought about by Th1 cells. The latter situation requires, since the infected cell lacks phagocytic function, killing of the infected cell to eradicate the reservoir and this is brought about by CD8+ cytotoxic T-cells. The Th2 subset is required for handling large extracellular parasites like helminths (described subsequently).

**T-cell-mediated macrophage activation and the delayed type hypersensitivity** Extracellular antigen or microbes processed through the phagolysosomal machinery bring about activation of HLA Class II restricted CD4 T-cells which differentiate into Th1 and Th2 subsets. This Th1 polarization is mediated by IL-12 produced by macrophages and dendritic cells in response to: (a) microbial products such as lipopolysaccharide (LPS); (b) CD40 ligation with CD40L and (c) in response to IFN- $\gamma$  produced by NK cells. The Th1 effectors in turn produce more IFN- $\gamma$ , also contributed by the CD8 T-cells, which stimulates microbicidal function of the macrophages and increased IL-12 secretion providing an amplification loop. The activated T-cells also produce TNF- $\alpha$  and lymphotoxin which promote leukocyte recruitment and inflammation which may cause tissue injury. Activated macrophages kill phagocytosed as well as extracellular microbes by producing microbicidal reactive oxygen intermediates, nitric oxide and lysosomal enzymes.

**CD8 T-lymphocyte-mediated cytolysis** Naïve CD8 T-cells are activated by MHC Class I-associated peptides derived from intracellular microbial proteins together with a second co-stimulatory signal. The principal mechanism of cytotoxic T-lymphocyte (CTL)-mediated cytolysis is the delivery of cytotoxic granule protein to the target cell. The two granule proteins that are most important for cytolysis are perforin and granzyme.

A second mechanism of cytolysis employed by CTLs is mediated by FasL which is expressed upon CTL activation. FasL binds to Fas, which is expressed by many cell types. This interaction leads to activation of caspases and apoptosis of the target cell. Whereas perforin or granzyme pathway is the principal mechanism of cytolysis by CD8 T-cells, FasL may be more important for the cytolytic activity of some CD4 cells.

**Role of Th2 cells in cell-mediated immunity** The Th2 derived cytokines IL-4, IL-10 and IL-13 inhibit macrophage activation and the associated inflammatory response. Th2 cells thus limit the injurious consequences of CMI. Th2 cells, however, also induce inflammatory reactions that have a prominent eosinophil and mast cell component. This type of a response is required for the elimination of helminthic and ectoparasitic infestations to which macrophage-mediated responses are ineffective. IL-4 stimulates the production of helminth specific immunoglobulin E (IgE) antibodies which opsonize the parasite. IL-5 activates eosinophils which bind to the IgE coated helminths by virtue of their Fc receptors (FcRs) for IgE and release their granule content. The major eosinophil granule

proteins that are involved are major basic protein and major cationic protein, which are capable of destroying the tough integuments of helminths. The granules of mast cells which are released in a similar manner contain vasoactive amines, cytokines such as TNF and lipid mediators that induce inflammation.

### Effector Mechanisms of Humoral Immunity

Most of the effector functions of antibodies are mediated by the heavy chain constant region, with different heavy chain isotypes varying in their efficiency of carrying out the effector functions. This, however, requires binding of the antigen to the variable region of the Ig molecule thus ensuring that the effector functions are activated only on antigen encounter.

The various mechanisms by which antibodies function in host defense are:

- **Neutralization** by binding to the microbes or toxin and making them unavailable for binding to their cellular receptors either by *steric hindrance* or by *allosteric* effects.
- **Opsonization** or coating of the microbes with antibodies and promoting their phagocytosis by binding of the Fc portions of the antibody to the FcR on the phagocyte. Of the FcRs of different Ig isotypes, the ones that are most important for phagocytosis are FcRs for IgG antibodies called Fc $\gamma$  receptors (Fc $\gamma$ R). The major high affinity Fc $\gamma$ R is Fc $\gamma$ RI (CD64) which binds to human IgG1 and IgG3 strongly and weakly to IgG2 and IgG4. Binding of the Fc $\gamma$ RI (and other FcRs) also brings about activation of the phagocyte. Apart from antibodies, opsonization is also carried out by complement components C3b, iC3b and C4b through the CRs on macrophages and neutrophils.
- **Antibody-dependent cellular cytotoxicity** FcRs on NK cells, called Fc $\gamma$ RIII (CD16) binds to IgG antibodies attached to cells, resulting in NK cell-mediated lysis of the cell through release of perforin and granzyme from granules. Since Fc $\gamma$ RIII is a low affinity receptor and bind only to antibodies that are clustered on the target cell surface, free IgG in the serum does not activate the NK cells. Apart from release of perforin and granzyme, engagement of the Fc $\gamma$ RIII also induces large amount of IFN- $\gamma$  secretion by NK cells which activate macrophages.
- **Complement-mediated cytolysis** Binding of complement C3b to a target cell leads to activation of late complement components and formation of membrane attack complex which cause lysis of the target cell.

### IN A NUTSHELL

1. Immune system is an intricately coordinated and complex biological system.
2. Innate and adaptive immunity are two principal components of the immune system.
3. Innate and adaptive immune mechanisms are not mutually exclusive and there is a great deal of crosstalk between these components.
4. Immune system is a proverbial double-edged sword. An exaggerated and inappropriately regulated immune response can lead to autoimmune diseases whereas a deficient immune response can lead to immunodeficiency diseases although there are overlaps.
5. Maintenance of immune homeostasis and a stringently regulated immune response is perhaps as important as the immune system itself.

### MORE ON THIS TOPIC

Beutler B, Rietschel ET. Innate immune sensing and its roots: the story of endotoxin. *Nat Rev Immunol*. 2003;3:169-76.

- Byadgi PS. Concept of immunity in *Ayurveda*. Journal of Applied Pharmaceutical Science. 2011;1:21-24.
- Davis BK, Wen H, Ting JP. The inflammsome NLRs in immunity, inflammation, and associated diseases. Annu Rev Immunol. 2011;29:707-35.
- Hazenberg MD, Spits H. Human innate lymphoid cells. Blood. 2014;124(5):700-9.
- Heymann MC, Rösen-Wolff A. Contribution of the inflammasomes to autoinflammatory diseases and recent mouse models as research tools. Clin Immunol. 2013;147:175-84.
- Hwang YY, McKenzie AN. Innate lymphoid cells in immunity and disease. Adv Exp Med Biol. 2013;785:9-26.
- Kugelberg E. Innate lymphoid cells: breathing into allergic inflammation. Nat Rev Immunol. 2014;14:281.
- Medvedev AE. Toll-like receptor polymorphisms, inflammatory and infectious diseases, allergies, and cancer. J Interferon Cytokine Res. 2013;33:467-84.
- Netea MG, Wijmenga C, O'Neill LA. Genetic variation in Toll-like receptors and disease susceptibility. Nat Immunol. 2012;13:535-42.
- Nüsslein-Volhard C, Wieschaus E. Mutations affecting segment number and polarity in *Drosophila*. Nature. 1980;287:795-801.
- Ozkurede VU, Franchi L. Immunology in clinic review series; focus on autoinflammatory diseases: role of inflammasomes in autoinflammatory syndromes. Clin Exp Immunol. 2012;167:382-90.

## Chapter 4.2

# Laboratory Diagnosis of Immune-mediated Diseases

Biman Saikia, Deepti Suri

The clinician requiring an immunological assessment of the patient requires few basic questions to be addressed: what test to use, how to use the test, the meaning of a specific result and what action to take on receipt of a result. This requires a thorough analysis of the clinical information and an adequate and sufficient indication for evaluation. Autoimmune diseases, allergy and asthma, organ and bone marrow transplantation, lymphoid and plasma cell malignancies, and primary and secondary immune deficiencies, have all provided enough challenges and opportunities for immunologic evaluation.

Immunologically, mediated disorders, especially autoimmune diseases are diagnosed in light of clinical symptoms and not test results. Testing is complex and the following issues should always be considered:

- Very few tests provide an absolute diagnostic interpretation and needs to be correlated in terms of clinical presentation.
- Large proportions of *apparently normal* individuals may test positive for some tests, e.g., antinuclear antibodies (ANAs).
- Negative results may not exclude disease conditions (e.g., seronegative rheumatoid arthritis).
- Test results alone cannot be used to guide treatment.
- Many of these tests are carried out only in specialized laboratories and are costly.

For the ease of discussion, immunological laboratory investigations can be broadly categorized into serologic and cell/tissue-based assays and considered under different disease heads. The subsequent sections outline the common laboratory techniques employed in clinical practice under similar heads.

## AUTOIMMUNE DISEASES

Most autoimmune disorders are characterized by autoinflammation. Elevations in markers for inflammation provide initial clues to the diagnosis of these disorders. Complete blood count reveals anemia, polymorphonuclear leukocytosis, thrombocytosis and an increase in erythrocyte sedimentation rate. Quantitative C-reactive protein is an important marker of inflammation and helps in monitoring the disease. Serological assays are aimed at detecting antibodies in the serum and require a clotted peripheral blood sample without any evidence of in vitro hemolysis.

## Antinuclear Antibodies

Antinuclear antibodies (ANA) are serologic hallmarks of patients with systemic autoimmune disease. ANAs were initially discovered in 1940 using the lupus erythematosus (LE) cell test on buffy coat samples. The LE cell is a phagocyte with an ingested nucleus with disrupted chromatin because of binding of the ANAs giving it a homogeneous appearance. LE cell test is, however, cumbersome and has largely been replaced by detection of autoantibodies in serum. Detection of these autoantibodies has both diagnostic as well as prognostic implications. The ANAs help establish diagnosis of certain autoimmune diseases when suspected clinically, subclassify patients with established autoimmune disease and used to monitor disease activity. Though less specific, ANA testing has a very high negative predictive value and helps to exclude disorders with uncertain clinical findings.

## Diseases Associated with a Positive Antinuclear Antibody

A positive ANA is an essential component of the definition of some systemic autoimmune disorders, such as systemic lupus erythematosus (SLE), but can also be found in association with many autoimmune disorders not defined by these antibodies (**Table 1**). They can be encountered in a variety of infections such as mononucleosis, hepatitis C infection, *Mycoplasma* infection, subacute bacterial endocarditis, tuberculosis, human immunodeficiency virus infection, and some lymphoproliferative disorders. Their presence does not mandate the presence of illness, since they can also be found in 5–10% of otherwise normal individuals. False positive ANAs (i.e., ANAs in the absence of autoimmune disease or known antigenic stimuli) are more commonly seen in women and in elderly patients, though in low titers.

Certain drugs can induce asymptomatic ANA positivity and drug-induced lupus. Important ones are procainamide, hydralazine, minocycline, penicillamine, isoniazid, quinidine and antitumor necrosis factor agents such as infliximab. Medications identified as probable causes include anticonvulsants such as phenytoin, carbamazepine, ethosuximide, antithyroid drugs, and antimicrobials such as rifampicin, nitrofurantoin, sulfonamide,  $\beta$ -blockers, captopril, and interferon gamma. Differentiating drug-induced lupus and SLE is a clinical challenge. Serious organ involvement is rare in drug-induced lupus and in presence of hypocomplementemia and double-stranded deoxyribonucleic acid (dsDNA) antibodies. Antihistone antibodies are marker for drug-induced lupus.

## Techniques in ANA Testing

Two major techniques employed for detection of ANAs are indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA). Both techniques utilize the principle of antibody binding to antigens in a tissue substrate (IIF) or immobilized purified antigen bound to a solid support like polystyrene microtiter wells (ELISA). The most common substrate used for detection of ANAs by IIF is human epithelial type 2 (HEp-2) cells derived from a laryngeal carcinoma cell line, and offers the advantage of a large nucleus for evaluation of the different targets of ANA. Incubation of the patient's serum with the HEp-2 cells allows binding of the

**Table 1** Diseases associated with positive antinuclear antibodies

Systemic autoimmune disorders	Percentage positivity
Systemic lupus erythematosus	93
Scleroderma	85
Mixed connective tissue disease	93
Polymyositis/dermatomyositis	61
Rheumatoid arthritis	41
Pauciarticular juvenile idiopathic arthritis	71
Sjögren syndrome	48
Drug-induced lupus	100
Specific organ autoimmune disease	Percentage positivity
Hashimoto thyroiditis	46
Graves disease	50
Autoimmune hepatitis	63–91
Primary biliary cirrhosis	10–40
Primary autoimmune cholangitis	100
Idiopathic pulmonary arterial hypertension	40



ANAs to the nucleus which is then detected by using an antihuman immunoglobulin G (IgG) labeled with a fluorescent dye (most commonly fluorescein isothiocyanate) and examined under a fluorescent microscope.

### Types of ANA

The various patterns that can be discerned in HEp-2 substrates are homogeneous (or diffuse), speckled, nucleolar, and a combination of the above (mixed patterns). The recommended dilution of the serum for routinely detected ANAs is likely to vary with different reference population and it is important for each testing laboratory to determine the ideal dilution for their population by testing appropriate number of healthy individuals. Within these broad patterns are more patterns, e.g., the centromeric, and multinuclear (6–8) dot, oligonuclear (1–3) dot patterns are distinct speckled patterns. Nucleolar pattern can be further seen as diffuse nucleolar or speckled nucleolar patterns. Other rare patterns that can be seen are antibodies against mitotic spindle, midbody, and antacentriolar antibodies. The various ANA specificities associated with different ANA patterns are illustrated in **Table 2**.

Apart from ANAs, various antibodies against the cytoplasmic components, such as antimitochondrial antibodies, antigolgi antibodies, antiribosomal (ribosomal P protein) antibodies, can be easily discerned in HEp-2 cells.

Detection of ANA by IIF (**Figs 1A to F**) is based on recognition of staining patterns which are associated with certain ANAs and since ANAs of multiple specificities can give rise to the same pattern, a positive test by IIF requires further analysis either by immunoblotting techniques or specific ELISA to discern the ANA specificity. Immunoblots use either purified or recombinant antigens blotted onto nitrocellulose strips in the form of dots or line assays together with inbuilt negative and positive controls and give information on the ANA specificity on a single strip.

Commercially available ELISAs for specific ANAs, e.g., dsDNA, Smith, SSA/Ro, SSB/La, etc., can be used for ANA specificities. ELISA for generic ANA can be used for screening in lieu of IIF. Generic ELISA kits use a cocktail of antigens to coat the microtiter wells. Though the sensitivity as well as the specificities of the generic ELISAs are similar to ANA by IIF, ANA ELISA loses out on some vital information about the various patterns which help to subclassify the patients. Whereas IIF is reported as intensity of fluorescence graded as + to +++, ELISAs are reported as optical density (OD) readings above the cut off calculated on the basis of the positive control and the sample OD.

### Antineutrophil Cytoplasmic Antibodies

Antibodies directed against neutrophil cytoplasmic antigens were first described in patients with pauci-immune glomerulonephritis in 1982 and were actually believed to be associated with Ross River virus infection. By 1985, however, antineutrophil cytoplasmic antibodies (ANCA) had been linked to granulomatosis with polyangiitis (Wegener's granulomatosis), abbreviated as GPA. Within several years, a relationship among ANCA, GPA, microscopic polyangiitis, and *renal-limited* vasculitis (pauci-immune glomerulonephritis without evidence of extrarenal disease) was established. The ANCA testing currently plays a critical role in the diagnosis and classification of vasculitides, even as debate about their ultimate importance in the pathogenesis and pathophysiology of these conditions continue.

Antineutrophil cytoplasmic antibodies are directed against granule proteins of neutrophils and are found as a marker of the ANCA-associated vasculitides (**Table 3**). Detection of the ANCAs hence requires human neutrophil as the substrate for IIF studies. ANCA testing is carried out on O-positive neutrophil spots on glass slides fixed in ethanol. Ethanol fixation leads to redistribution of the positively charged granule protein myeloperoxidase (MPO) toward the negatively charged nuclear membrane leaving proteinase-3 (PR3) unaffected. This gives rise to two distinct patterns of staining in IIF: the cytoplasmic pattern (cANCA) with antibody specificity to PR3 and perinuclear pattern (pANCA) directed against MPO (**Figs 2A and B**). The former pattern is characteristically described as cytoplasmic staining with interlobular accentuation to denote the characteristic staining intensity in between the nuclear lobes, and this helps differentiate this pattern with the nonspecific atypical ANCA pattern which can arise due to antibodies directed against a variety of antigens such as lactoferrin, cathepsins, etc. Similar to ANAs, ANCA specificities can be further confirmed by specific ELISAs for MPO and PR3 or by using immunoblots.

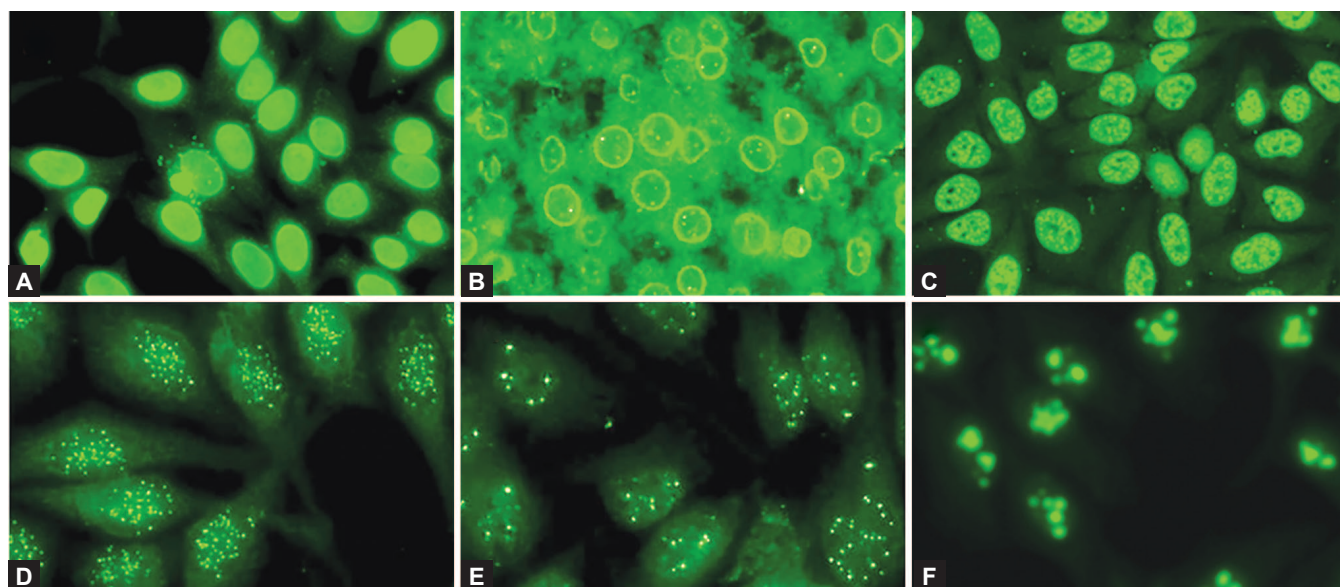
### Antimitochondrial Antibodies, Antiliver-Kidney Microsomal Antibodies, Antiparietal Cell Antibodies, Antismooth Muscle Antibodies, Antiendomysial Antibodies

Indirect immunofluorescence using frozen sections from a composite tissue block (referred to as composite testing) of rat kidney, stomach and liver is a very helpful screening test for autoimmune disorders. Degree of positivity is reported as + to +++ according to the staining intensity and the location of the positive

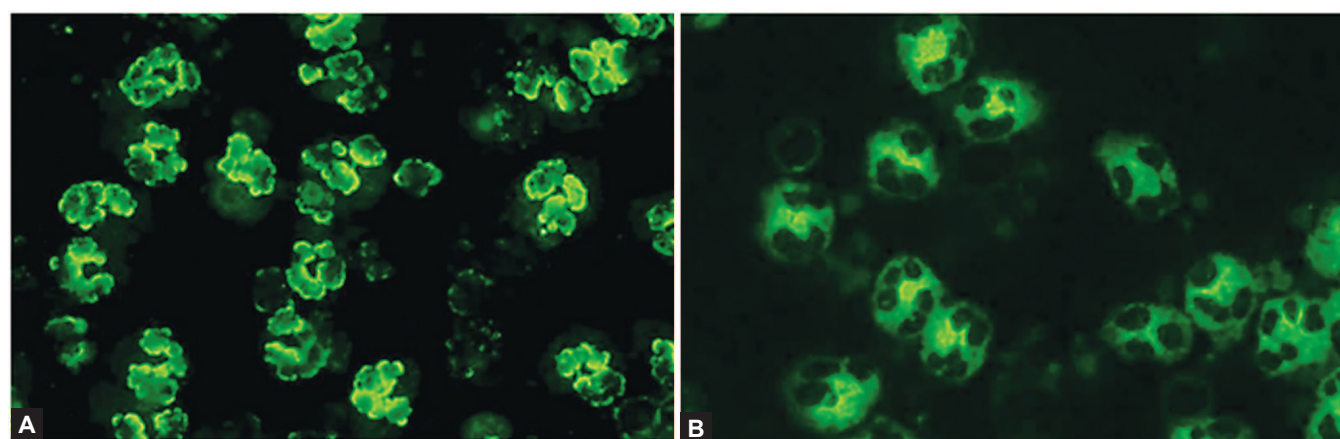
**Table 2** Association of indirect immunofluorescence antinuclear antibody patterns with disease

Pattern of ANA	Antigens specificities	Disease associations
Homogeneous (diffuse)	dsDNA	SLE (60–90%)
	Histone	Drug-induced SLE (95–100%)
Speckled	Smith	SLE (20–40%), specific
	U1RNP	MCTD (95–100%)
	SSA/Ro (Ro52 and Ro60), SSB/La	Sjögren syndrome (40–80%)
	Scl-70	PSS, diffuse form (25–75%)
Centromeric	CENP-A/B	PSS (80–90%)
Multiple nuclear (6–8) dots	SP100	PBC (34–42%)
Nucleolar-diffuse	PM Scl-100	PSS (5–10%), PM-DM (50–70%)
Nucleolar-speckled	RNA polymerase I, U3-nRNP/fibrillarin	PSS (36%)

**Abbreviations:** SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disorders; PSS, progressive systemic sclerosis; PBC, primary biliary cirrhosis; PM, polymyositis; DM, dermatomyositis; CENP-A/B, centromere protein A/B; dsDNA, double-stranded deoxyribonucleic acid; nRNA, nuclear ribonucleoprotein.



**Figures 1A to F** Indirect immunofluorescence. (A) Homogenous (diffuse) on HEp-2 cells; (B) Nuclear envelope on rat liver section; (C) Speckled pattern on HEp-2 cells; (D) Centromeric pattern on HEp-2 cells; (E) Multiple nuclear dots on HEp-2 cells; (F) Nucleolar (diffuse) on HEp-2 cells



**Figures 2A and B** Indirect immunofluorescence on O-positive neutrophils. (A) Perinuclear pattern (pANCA); (B) Cytoplasmic pattern (cANCA) with typical interlobular accentuation

**Table 3** Disease association of ANCA, percentage of occurrence and antigen specificity

Disease	IIF-ANCA	Antigenic target
Granulomatous angiitis	cANCA (75–80%)	PR3
	pANCA (10–15%)	MPO
Microscopic polyangiitis	cANCA (25–30%)	PR3
	pANCA (50–60%)	MPO
Churg-Strauss syndrome	cANCA (25–30%)	PR3
	pANCA (25–30%)	MPO
Systemic lupus erythematosus	pANCA (20–30%)	Lactoferrin
Ulcerative colitis	pANCA (40–70%)	Lactoferrin, cathepsin, MPO, BPIP

**Abbreviations:** IIF, indirect immunofluorescence; ANCA, antineutrophil cytoplasmic antibodies; cANCA, cytoplasmic ANCA; pANCA, perinuclear ANCA; PR3, proteinase-3; MPO, myeloperoxidase; BPIP, bactericidal/permeability-increasing protein.

staining gives the antigen specificity. Recommended dilutions for testing are 1:40 for adults and 1:20 for children. The pattern of positivity and their inference is shown in **Table 4**.

### Antibodies for Diagnosis of Dermatologic Disorders

Indirect immunofluorescence for dermatologic disorders is most commonly required for diagnosis of the bullous disorders, viz. pemphigus and pemphigoid. The typical tissue substrate used can be monkey esophagus or normal human skin. Incubation of the patient's sera containing antibodies against desmoglein 1 and 3 in pemphigus leads to an intracellular *basket weave* or *fish-net* staining pattern in the epithelium whereas in the pemphigoid group of disorders, antibodies against the hemidesmosomes (BP-160, BP-180) or collagen (type VII) leads to a linear pattern of staining along the basement membrane zone. The intensity of staining is graded as + to +++. The antibody specificity can then be confirmed by performing specific ELISAs for desmoglein 1 and/or 3, BP-160, BP-180, or type VII collagen, as the situation may demand.

**Table 4** Patterns of indirect immunofluorescence positivity, associated antibodies and disease

Pattern of IIF positivity in composite section	Associated antibodies	Disease association
Granular cytoplasmic positivity in proximal convoluted tubules of kidney, parietal cells and smooth muscles of stomach	Antimitochondrial antibodies	Primary biliary cirrhosis, PBC-AIH overlap
Granular cytoplasmic positivity in hepatocytes and kidney tubules. Negative staining in parietal cells	Liver, kidney microsomal antibodies	AIH type II
Granular cytoplasmic positivity in parietal cells only	Parietal cell antibodies	Autoimmune gastritis
Smooth muscles of stomach, blood vessels and glomerular mesangium	Antismooth muscle actin	AIH type I
Nuclei	ANAs	As ANAs
Basket weave staining of smooth muscles of stomach	Antiendomysial antibodies	Gluten hypersensitivity (celiac disease)

Abbreviations: PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; ANAs, antinuclear antibodies.

### Other Specific Antibodies

Antitissue transglutaminase (IgA or IgG), antigliadin antibodies (for celiac disease), anticitrullinated peptide antibodies (for rheumatoid arthritis and related disorders), anti-GAD65 (for type I diabetes), antithyroid peroxidase and antithyroglobulin (for autoimmune thyroiditis) can be performed easily using commercially available ELISA kits.

### Cell/Tissue-based Assays

Cell-based assays for diagnosis of autoimmune disorders are restricted to assessing susceptible human leukocyte antigen (HLA) type associations, e.g., HLA B27 (for ankylosing spondylitis, anterior uveitis), HLA B5 (*Behçet* disease), HLA DQ2/DQ8 for celiac disease. This can be done by using complement dependent cytotoxicity assays, flow cytometry or by DNA-based assays like sequence-specific primer (SSP) and sequence-specific oligonucleotide probes (SSOP). Rare situations may require looking at cytokine secretion assays by Enzyme-Linked ImmunoSpot, but would be mostly of academic or research significance.

Tissue-based assays, e.g., skin biopsy and kidney biopsies for direct immunofluorescence require fresh tissue in holding buffer (never in formalin) for demonstration of antigen-antibody complex deposition in tissues. Various dermatologic conditions may include pemphigus (basket-weave pattern with IgG and/or C3 deposits), bullous pemphigoid (linear IgG and/or C3 in basement membrane), IgA in linear IgA disease, IgA in dermatitis herpetiformis (deposits in papillary dermis), IgA vasculitis in Henoch-Schönlein purpura, and lupus band (IgM, IgG, IgA and C3 in a granular pattern in the upper dermis) in lupus/discoid lupus erythematosus.

## ALLERGY AND ASTHMA

Most of the symptomatic allergies involve respiratory, skin and gastrointestinal tract. A detailed clinical analysis including history and physical examination related to these systems is the key to diagnosis of allergy. A variety of tests, e.g., total serum IgE levels, skin prick test (SPT), intradermal skin test, patch test, specific IgE tests, double-blind placebo controlled oral food challenge test (OFC), examination of tissue and secretions for eosinophils and certain biochemical mediators, e.g., mast cell tryptase, eosinophil cationic protein, basophil activation, etc., are the mainstay of allergy testing. Test selection is based solely on clinical setting, e.g., oral challenge test is most suited for food allergy, patch test for contact dermatitis or any other cell-mediated allergy. The most commonly used and clinically valuable tests are SPT, patch test, OFC and allergen-specific IgE antibodies in serum. Broadly, these tests may be divided into in vitro and in vivo allergy tests (**Table 5**).

### In Vitro Tests: Serology

Total serum IgE and allergen-specific IgE by ELISA or other immunoassays are frequently ordered in suspected allergy. Total IgE levels are, however, nonspecific as raised levels may be present in parasitic, fungal, malignancy or rare disorders such as hyper-IgE syndrome. Hence, allergen-specific IgE levels are most useful in vitro test.

A number of test systems are available to measure specific IgE. Enzyme immunoassay or fluoroimmunoassays are commonly used. Hundreds of allergens such as weeds, trees, pollen, mold, food, and animal dander may be detected in a single blood sample. Sensitivity and specificity of specific IgE is good (70–80%), though testing is bit costly. Hence, though in vitro tests are more useful than in vivo tests, they may be reserved for those patients who cannot be tested by in vivo methods.

### In Vivo Tests

#### Skin Prick Test

This test is widely used in inhalant, food, drug and venom allergies for detection of allergen-specific IgE antibodies because of its high sensitivity, rapidity of results and low cost. It is performed by injecting a drop of allergenic extract into the epidermis, usually forearm or back, at an angle of 45°. For each allergen, a separate prick is made. After about 1 minute of skin prick, the extract is wiped off and after 15–20 minutes prick site is examined for development of wheal and flare response. The largest and smallest dimensions are added and divided by two. The diameter is compared to that produced by histamine which is used as a negative control. Most of the reactions positive for allergy are more than 3 mm in diameter. SPT is highly sensitive for most of the type I hypersensitivity reactions.

#### Patch Test

It is another similar test used in delayed hypersensitivity reactions, e.g., contact dermatitis, latex allergy. In this, rather than making multiple skin pricks, a patch containing tiny quantities of several allergens in individual squares or round chambers are applied either on back or forearm. The patch is kept in place for about 48 hours. Thereafter, it is removed and reading is taken in a similar manner to SPT.

#### Oral Food Challenge (OFC) Test

Though history suggesting an immediate allergic response along with positive specific IgE test is sufficient to establish food allergy without OFC, it is considered a gold standard for confirmation and monitoring of food induced hypersensitivity reactions. Nonetheless non-IgE mediated food allergies, i.e., food protein-



**Table 5** Modes of allergy testing

<i>Skin prick test</i>	<i>Patch test</i>	<i>Oral food challenge test</i>	<i>Total IgE</i>	<i>Specific IgE</i>
<i>In vivo</i>			<i>In vitro</i>	
<i>Done by physician capable to deal anaphylaxis</i>			<i>Done in laboratory</i>	
<i>Any allergy</i> Type I HS 15–20 min C/I: Eczema, patient on steroids or antihistamines, dermatographism, hypersensitive, etc. Only few allergens can be tested at a time Cheaper, faster Detailed history required ↑ Sensitive Specific Semiquantitative, Gold standard	<i>Skin allergy</i> Type IV HS 2–4 days C/I: Eczema Few allergens are tested Slow History required Sensitive, Specific Semiquantitative, excellent for cell-mediated allergy	<i>Food allergy</i> Type I HS/mixed Minutes to hours Important in mixed or non-IgE reactions Suspected allergen eliminated from diet Cheaper, slow History required Sensitive ↑↑ Specific Gold standard	<i>Any allergy</i> Type I HS Variable None Allergens cannot be tested Slightly longer History required Nonspecific Good for screening only	<i>Any allergy</i> Type I HS 2–4 hours None, safer, no interindividual variations Several allergens can be tested at a time Costly, slightly longer Detailed history and total IgE required Sensitive ↑ Specific Quantitative, excellent alternative to SPT

Abbreviations: IgE, immunoglobulin E; HS, hypersensitivity; SPT, skin prick test; C/I, contraindication(s).

induced enterocolitis and food allergy due to mixed immune responses requires OFC. Blinded OFC, in which challenge food is mixed with other food to hide its taste and texture, is given in two sessions one with active food and second with placebo by a third party (double-blind). Symptoms such as urticaria, vomiting, angioedema, wheezing, etc., are usual signs in a positive OFC.

## PRIMARY AND SECONDARY IMMUNE DEFICIENCIES

### General Principles

Always evaluate age matched-unrelated healthy control sample simultaneously for assay evaluation. Tests, especially functional assays should be performed on fresh samples. Whereas absence of protein expression (by flow cytometry) indicates disease, its presence does not rule out a disease because mutations can give rise to a nonfunctional protein which is nevertheless expressed. Functional studies are hence required. Moreover, not all mutations are pathogenic, and some may represent gene polymorphisms. Hence, population studies are important for deducing pathogenicity. Though confirmation of a primary immunodeficiency (PID) comes from genetic studies, certain entities such as combined immune deficiency (CID) warrant urgent treatment without waiting for a genetic diagnosis.

### Serology

Human immunodeficiency virus infection must be excluded in all cases of suspected immunodeficiency. Evaluation of patients with putative antibody deficiency requires measurement of total serum immunoglobulins (IgG, IgM, and IgA), IgG subclasses (IgG1, G2, G3, and G4), and assessment of antibody response to vaccination with both protein, viz. tetanus, and diphtheria toxoid and polysaccharide antigens (pneumococcal polysaccharide vaccine). Apparently, normal IgG serum levels can be detected during the first 2–3 months of life, even in the face of a severe antibody defect because at this age, most of the serum IgG is of maternal origin. For the same reason, antibody deficiency disorders do not present

during infancy and become symptomatic only after the maternal antibody levels gradually wane off. Various abnormalities in serum immunoglobulin levels and their disease associations are listed in **Table 6**.

Very low levels of serum IgG and IgA, with normal to increased serum IgM levels, may indicate a defect in class switching from IgM to IgG and IgA, the so called class switch recombination (CSR) defects. They can be caused either by activation-induced cytidine deaminase or uracil-DNA glycosylase deficiency (intrinsic B-cell defects) or CD40L or CD40 (due to impaired cross-talk between T and B lymphocytes). Though commonly referred to as hyper-IgM syndrome, majority of patients have normal serum IgM levels. The CSR defects usually present with a combined immunodeficiency like picture and presents earlier than common variable immunodeficiency.

Determination of serum IgG subclasses is of limited value on its own unless supplemented by the assessment of specific antibody titers, particularly, antibodies to tetanus and diphtheria toxoids, a measure of antibody response to protein (T-dependent) antigens. Pneumococcal polysaccharide vaccine should be used to test antibody response to polysaccharide (T-independent) antigens. Measurement of hemolytic activity of the classical (CH50) and alternative (AP50) pathways of complement activation, as well as of C3 and C4 levels, might guide in the diagnosis of complement deficiencies. Other assays may include mannan-binding lectin assay, enzymes such as adenosine deaminase, and purine nucleoside phosphorylase [severe combined immunodeficiency (SCID)].

### Cell-based Assays

The absolute neutrophil count (ANC) is markedly reduced in all forms of severe congenital neutropenias. If ANCs show periodicity, counts should be evaluated once a week for 6 consecutive weeks to identify possible decreases in the neutrophil count for documenting cyclic neutropenia. Flow cytometric assessment of surface markers of various lymphocyte subsets, intracellular signaling molecules and functional assessment of cell subsets forms the mainstay of PID diagnostics in the present era (**Tables 7 and 8**).



**Table 6** Various abnormalities in serum immunoglobulin levels and their disease associations

<i>Ig isotypes affected</i>	<i>Probable diagnosis</i>	<i>Confirmation</i>
Low IgG, IgA, IgM	Agammaglobulinemia • X-linked, common • AR, rare D/D: Transient hypogammaglobulinemia of infancy	B-cell numbers (CD19, CD20)
Low IgG with low IgM and/or IgA	CVID	B-cell numbers (CD19, CD20) B-cell subsets (CD21, CD27, sIgM, sIgD, CD38, CD138) Antibody response to pneumococcal polysaccharide vaccine
Low IgA, IgG with normal or increased IgM	Hyper-IgM syndromes	CD40, CD40L
Low IgA	Selective IgA deficiency	-
Low IgM	Selective IgM deficiency	-
Low IgG1 or G2 or G3, or G4	Subclass deficiency	Antibody response to pneumococcal polysaccharide vaccine

Abbreviations: CVID, common variable immunodeficiency; Ig, immunoglobulin; CD, cluster of differentiation; AR, autosomal recessive; sIgM, surface IgM; sIgD, surface IgD; D/D, differential diagnosis.

**Table 7** Protein-specific flow cytometric assays

<i>Disease</i>	<i>Defect</i>	<i>Flow cytometric test</i>
XLA	BTK gene defect	BTK expression on monocytes
LAD type I	$\beta$ chain of $\beta 2$ integrin	CD18, CD11c expression
IPEX	FOXP3 gene	FOXP3
Hyper-IgM syndrome	CD40-CD40L defect	CD40, CD40L
Wiskott-Aldrich syndrome	WAS gene defect	WASp
SCID X-linked	Common $\gamma$ -chain	Common $\gamma$ -chain (CD132)
Familial HLH		Perforin
ALPS	Fas-FasL defect	TCR $\alpha\beta$ +CD4-CD8- (double-negative) T-cells
Hyper-IgE syndrome (AD)	STAT3 gene defect	TH17 cells, pSTAT3 assay
CVID	Various	CD19, BAFFR, ICOS, CD81

Abbreviations: BTK, Bruton tyrosine kinase; CD, cluster of differentiation; CVID, common variable immunodeficiency; SCID, severe combined immunodeficiency; WASp, Wiskott-Aldrich syndrome protein; HLH, hemophagocytic lymphohistiocytosis; ALPS, autoimmune lymphoproliferative syndrome; AD, autosomal dominant; FOXP3, forkhead box P3; STAT3, signal transducer and activator of transcription 3; XLA, X-linked agammaglobulinemia; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; LAD, leukocyte adhesion deficiency; Ig, immunoglobulin; TH, T-helper.

Unexplained lymphopenia in early infancy, especially T-lymphopenia (CD3) is the hallmark of SCID, a medical emergency. Similar to antibody levels, comparison of lymphocyte subsets with age-matched control is very crucial for the diagnosis. Depending on the presence or the absence of T-cell (CD3), B-cells (CD19/20) and NK cells (CD16/56), SCID is classified as T-B- and T-B+ SCID with presence or absence of NK cells. Whereas a typical SCID will present very early in life with various infections, the variants of SCID resulting from hypomorphic gene mutations, which allow some degree of T-cells development, results in a graft versus host disease (GVHD) like presentation. The presence of maternal T-cell engraftment or of residual autologous T-cells in such patients

**Table 8** Functional assays used for the diagnosis of primary immunodeficiency disorders

<i>Assay</i>	<i>Disease association</i>	<i>Flow cytometric test</i>
NK cell cytotoxicity assay	Familial HLH	K562 assay by CFSE, PI staining
Phagocytosis	Various	pHrodo bioParticles phagocytosis assay
Impaired Fas-mediated apoptosis	ALPS	Annexin V, Caspase 3
Lymphocyte proliferation assays to PPD, tetanus toxoid and <i>Candida</i> antigens	Various	3H-thymidine incorporation, CFSE staining
Lymphocyte activation assays	Various	Activation markers: CD69, CD25, HLA-DR

Abbreviations: NK cell, natural killer cell; HLH, hemophagocytic lymphohistiocytosis; PPD, purified protein derivative; CD, cluster of differentiation; HLA, human leukocyte antigen; ALPS, autoimmune lymphoproliferative syndrome; CFSE, carboxyfluorescein succinimidyl ester; PI, propidium iodide.

show a relatively preserved (and even normal) T-lymphocyte count and hence requires a very high degree of clinical suspicion. CD4 lymphopenia and CD8 lymphopenia are other entities that can be picked by flow cytometry.

Antibody deficiency disorders require enumeration of B-cells (CD19, CD20). Patients with X-linked agammaglobulinemia show a virtual absence of mature B-cells and plasma cells, whereas in disorders like CVID, B-cell numbers may be normal or low. B-cell subset analysis (CD19+IgM+IgD+CD27- naive B-cells, CD19+IgM-CD27+ memory B-cells, CD19+CD21+CD38+ transitional B-cells and CD19+CD138+CD27+ plasmablasts) in such cases often reveal varying degrees of maturation arrest. Patients with CD19 deficiency related CVID will show absent B-cells, if CD19 is used alone as a B-cell marker. However, CD20 may reveal a normal number of B-cells in such patients.

Diagnosis of chronic granulomatous disease (CGD) can be easily evaluated by demonstration of reduced/absent oxidative burst due to deficiency of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity using quantitative dihydrorhodamine-123 (DHR-123) oxidation by flow cytometry. Patients with X-linked CGD (X-CGD) often demonstrate a severe

defect whereas autosomal recessive CGD (AR-CGD) often have detectable but reduced levels of NADPH activity. Female carriers of X-CGD can be easily picked up using this assay which demonstrates two populations of DHR oxidizing cells. Reduced DHR oxidation can however be seen in other conditions like glucose-6-phosphatase dehydrogenase deficiency, MPO deficiency, glutathione reductase and glutathione synthetase deficiency, and transcobalamin II deficiency; and secondary disorders including diabetes mellitus, burn, trauma, uremia, and malnutrition. Nitro-blue tetrazolium dye reduction test, though still performed at some centers can often be subjective and fails to detect carriers and patients with milder defects.

Genetic analysis of specific mutations is important not only to confirm the diagnosis but also for genetic counseling, carrier detection and prenatal diagnosis. Analysis of messenger RNA and/or protein expression together with functional assays is often required to ascertain pathogenicity of a gene mutation. PID is a rapidly expanding field with newer entities being described continuously, and patients may not fit into a well-defined known entity, and the possibility of a new syndrome or disease should always be kept in mind. Whole exome sequencing has greatly facilitated the identification of newer entities.

## LYMPHOID AND PLASMA CELL MALIGNANCIES

### Serum Protein Electrophoresis

Detection of M component in the serum can be easily done on serum electrophoresis, and densitometric quantification of the serum proteins can be assessed after knowing the total serum protein and albumin fractions biochemically. An urine sample should always be tested along with the serum sample when a plasma cell dyscrasia is suspected, because light chains are totally filtered into the urine and do not appear in the serum, unless the patient has severe renal failure with renal shutdown. Hence for diagnosing light chain disease, examination of the urine is mandatory.

In addition to detection of the M band, serum protein electrophoresis (SPE) gives various other important information useful for clinical assessment of a patient. Presence of a profound hypogammaglobulinemia in association with M component usually indicates a high plasma cell load in the bone marrow replacing the normal Ig producing plasma cells whereas in localized disease (solitary plasmacytoma) or a low plasma cell load, the SPE shows the presence of normal Ig band in the background of M component.

Urine electrophoresis often shows the presence of corresponding serum M component. In addition, light chains (Bence Jones proteins) can be seen in the  $\beta$  region in 30–40% of cases of multiple myeloma. Glomerular involvement resulting in a nephrotic syndrome like picture would reflect in a glomerular proteinuria (presence of albumin band at a stage of selective proteinuria with addition of  $\alpha_1$ ,  $\beta$  and  $\gamma$  components as the proteinuria gets more and more nonselective).  $\alpha_2$  proteins are characteristically not seen even in the face of significant nonselective proteinuria as  $\alpha_2$ -macroglobulin, the major protein component of the  $\alpha_2$  fraction, owing to its large molecular weight is not filtered into the urine. In addition, there is a concurrent increase of the  $\alpha_2$  fraction in the serum owing to its selective retention and also contributed by an increased hepatic synthesis as a part of the acute phase response. The albumin component in the serum will be reduced on the face of a prominent albumin band in the urine, and  $\beta$  fraction increased as a part of hypercholesterolemia seen in nephrotic syndrome. Presence of proteinuria (with bands in  $\alpha$  and  $\beta$  regions) in absence of albumin reflects tubular proteinuria.

## Immunofixation Electrophoresis

It can be used for characterization of the heavy and light chain components of the M-protein by using antisera against IgG, IgA, IgM, IgD, kappa and lambda overlaid onto the electrophoresed gel. Serum  $\beta_2$  microglobulin can be done by nephelometric methods. Serum free-light chain assay is a very useful adjunct to monoclonal gammopathy diagnosis and is more sensitive than SPE or immunofixation electrophoresis. Nephelometry is the method of choice for estimation of free light chains. In addition, this parameter is extremely useful for monitoring of the disease after therapy is instituted.

### Cell/Tissue-based Assays

Fluorescence in situ hybridization for demonstration of translocations, e.g., t(11;14), t(4;14) is a useful adjunct to diagnosis of plasma cell dyscrasias.

## ORGAN AND BONE MARROW TRANSPLANTATION

### Crossmatching

Pretransplant crossmatch can be done by two basic techniques: (a) serologic crossmatch using the complement dependent cytotoxicity and (b) flow cytometry-based assays (both requires freshly isolated peripheral blood mononuclear cells from the donor). While the former has the advantage of being a functional assay looking at actual complement-dependent cellular cytotoxicity (killing of the donor cell), the latter has the advantage of being more sensitive and being able to detect antidonor antibodies irrespective of complement fixation. Results are expressed as percent cell killing in complement-dependent cytotoxicity (CDC) assay and as mean fluorescence shift compared to the negative control in flow cytometric assays. Further modifications to the basic crossmatch by the CDC assay can be made by: (a) crossmatching at 4°C and 37°C; (b) enhancing sensitivity by crossmatching at 4°C and 37°C or other methods; or (c) separate T-cell and B-cell crossmatching.

### Antibody Screening and Panel Reactive Antibodies Testing

Pretransplant screening for pre-existing anti-HLA antibodies can be performed by commercially available ELISA kits, coated with Class I and Class II HLA antigens separately. By using a panel of HLA antibodies, percent panel reactive antibodies (PRA) can be calculated, a high PRA indicating a higher degree of presensitization and vice versa. PRA testing can also be done by more advanced and automated bead-based assays, viz. using the Luminex platform.

### Donor Specific Antibody Testing

Diagnosis of antibody-mediated rejection requires demonstration of donor specific antibody (DSA) as part of the diagnostic criteria. DSA can be detected by ELISA or Luminex-based methods using donor lysate and incubating with recipient's serum.

### Cell/Tissue-based Assays

Human leukocyte antigen typing by serologic technique (CDC method) requires isolation of fresh peripheral blood mononucleated cells (PBMCs) from the recipient by density gradient centrifugation. Tissue types are allocated by incubation of the PBMCs with a panel of known HLA antisera. Since antisera against Class I (HLA A, B, C) are more readily available than Class II sera, for determining Class II HLA types (HLA-DR, -DQ and -DP) DNA-based methods are preferred. DNA-based methods include SSP, SSOP, reverse SSOP and sequence-based typing.

### IN A NUTSHELL

1. Primary immunodeficiency disorders can be diagnosed with relatively simple tests such as complete blood counts, serum immunoglobulins and lymphocyte subset analysis for T, B and NK cells. Clinical suspicion forms the mainstay of diagnosis.
2. Immunologically-mediated disorders, especially autoimmune diseases are diagnosed in light of clinical symptoms and not test results.
3. Clinician should be able to answer these basic questions: what test to use, how to use the test, the meaning of a specific result and what action to take on receipt of a result.
4. A positive ANA test, especially in low titers should be interpreted with caution, and in light of the clinical features.
5. Perinuclear ANCA should not be interpreted on IIF if ANA is strongly positive. Other modalities like ELISA should be used.
6. Cytoplasmic ANCA on IIF should be reported only when the typical pattern with *interlobular accentuation* is observed.

### MORE ON THIS TOPIC

Keren DF. Antinuclear antibody testing. Clin Lab Med. 2002;22:447-74.

Notarangelo LD. Primary immunodeficiencies. J Allergy Clin Immunol. 2010;125:S182-94.

## Chapter 4.3

# Primary Immunodeficiency Disorders

Manisha Madkaikar

Primary immunodeficiency disorders (PIDs) are diverse group of inherited conditions, mostly monogenic, resulting in susceptibility to infections, allergy, autoimmunity and cancer. As more than 200 immunodeficiencies have been described till date affecting various components of immune system, they pose a formidable challenge for both clinicians and scientists. Diagnostic procedures and algorithms are continuously updated as new and new PIDs are added to the existing list every year. While early phenotypic diagnosis helps in initiation of lifesaving treatment, genetic diagnosis becomes important for prognosis, genetic counseling and exploring novel targeted therapeutic interventions.

Though in several developed and developing countries approximate incidence and prevalence of PID is known, the incidence of PID in India is unknown. Based upon the incidence of PID in other countries of 1 in 10,000, it is estimated that the number of PID patients in India is at least 100,000. The diagnosis of PIDs in India is often delayed either because of lack of awareness about PID or unavailability of diagnostic facilities. In addition, endemic nature of multitude of infections, and nutritional deficiencies complicate the suspicion and therefore, diagnosis of PID.

### CLASSIFICATION

The International Union of Immunological Societies has proposed a classification of PIDs which provides a framework to help in the diagnostic approach to patients. In the recent classification, PIDs are classified into 9 major categories according to the component of the immune system primarily involved:

1. Combined T-cell and B-cell immunodeficiencies (CIDs)
2. Other well-defined immunodeficiency syndromes
3. Predominantly antibody deficiencies
4. Diseases of immune dysregulation
5. Congenital defects of phagocyte number and function
6. Defects in innate immunity
7. Autoinflammatory disorders (AIDs)
8. Complement deficiencies
9. Phenocopies of PID.

Under each broad category, there are multiple subcategories with different genetic defects and every year newer diseases are added to the list. However, there are certain common PIDs (< 20% of the listed) which account for more than 90% of the total PIDs diagnosed. This chapter will focus on the important clinical manifestations of common PID and the diagnostic approach for these disorders.

### CLINICAL MANIFESTATIONS

Recurrent infection is the predominant clinical manifestation in these patients. However, even in normal infants and children, the immune system is not fully developed. With exposure to different pathogens, recurrent infections are common in young children. While most children with recurrent infections have a normal immune system, it is important to recognize a child with an

underlying PID from a normal child so that further investigations can be ordered selectively. To help clinicians, the European Society of Immunodeficiencies has suggested 10 warning signs for suspicion of PID. They are listed in **Box 1**.

#### BOX 1 The 10 warning signs for suspicion of primary immunodeficiency disorders

1. Four or more new ear infections within 1 year
2. Two or more serious sinus infections within 1 year
3. Two or more months on antibiotics with little effect
4. Two or more pneumonias within 1 year
5. Failure of an infant to gain weight or grow normally
6. Recurrent, deep skin or organ abscesses
7. Persistent thrush in mouth or fungal infection on skin
8. Need for intravenous antibiotics to clear infections
9. Two or more deep-seated infections including septicemia
10. A family history of primary immunodeficiency disorders.

While evaluating patients for PID, that rather than emphasizing exact numbers of different infections or special definitions of severity; it is more important to consider the infection type, the circumstances under which infections occur, and which organs and tissues they affect. A single episode of infection with any pathogen of low pathogenicity, such as atypical mycobacteria or *Pneumocystis jirovecii* must be investigated for underlying PID after ruling out the possibility of infection with human immunodeficiency virus while most children with respiratory tract infection with common organisms can be observed safely. Many PIDs have unique susceptibilities to some pathogens and/or sites of infections that are listed in **Table 1**. However, this list is far from being complete and there is significant overlap between the infections seen in different categories of PID.

Apart from infections, other clinical manifestations especially age at presentation, pattern of infections, noninfectious manifestations, such as autoimmunity, skin manifestation, skeletal manifestations, malignancies, etc., and family history give an important clue to the underlying immune defect and are crucial for further laboratory evaluation and diagnosis. The important clinical manifestations of common PIDs in each category are summarized here.

### COMBINED T-CELL AND B-CELL DEFICIENCIES

There are 22 different genetic defects listed under this category most common being *X-linked severe combined immunodeficiency* (SCID) or Common gamma chain SCID followed by autosomal recessive (AR) adenosine deaminase (ADA) deficiency and IL7R deficiency. In the most severe form, i.e., SCID, there is a virtual lack of functional T-cells and immune function. Patients with *classical SCID* present within the first year of life usually within first 6 months. Affected infants generally appear well at birth, but within the first few months, demonstrate failure to clear infections and present with persistent respiratory tract or gastrointestinal infections, failure to thrive and, sometimes, apparent food intolerance. Persistent respiratory tract infections either viral and/or due to *Pneumocystis jirovecii*, with bronchiolitis-like signs are common. Persistent viral diarrhea with failure to thrive is an important sign. Extensive persistent superficial candidiasis is more common. However, severe invasive fungal infections are rare. Disseminated *Bacillus Calmette-Guérin* (BCG) infection is another common presentation in Indian patients due to early immunization. Skin lesions (often a mild reticular skin rash, which may be thickened and lichenoid) showing presence of acid-fast



**Table 1** Clues to the presence of primary immunodeficiency

PID	Antibody deficiency	Combined immunodeficiency	Phagocytic defects	Complement deficiencies
Infectious complications	Upper and lower respiratory tract (otitis, sinusitis, pneumonia) GI tract, skin infections sepsis, meningitis	Systemic viral infections gastroenteritis	Respiratory tract Liver of lung abscesses Lymphadenitis GI diseases Urinary tract problems	Meningitis Systemic bacterial infections
<b>Organisms</b>				
Bacteria	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Neisseria meningitidis</i> , <i>Mycoplasma pneumoniae</i>	As for antibody deficiencies, also: <i>Salmonella typhi</i> , <i>Listeria monocytogenes</i> , enteric flora	<i>S. aureus</i> , <i>P. aeruginosa</i> , <i>Nocardia asteroides</i> , <i>S. typhi</i>	As for antibody deficiencies: Especially <i>N. meningitidis</i> in deficiency of later components
Viruses	Enteroviruses	All, especially: CMV, respiratory syncytial virus, EBV, parainfluenza type 3	No	No
Fungi		<i>Candida</i> species, <i>Aspergillus</i> species, <i>Cryptococcus neoformans</i> , <i>Histoplasmosis capsulatum</i>	<i>Candida</i> species, <i>Aspergillus</i> species	
Mycobacteria	No	Nontuberculous, including BCG	Nontuberculous including BCG	No
Protozoa	<i>Giardia lamblia</i>	<i>Pneumocystis jirovecii</i> , <i>Toxoplasma gondii</i> , <i>Cryptosporidium parvum</i>	No	No

Abbreviations: PID, primary immunodeficiency disorders; GI, gastrointestinal; BCG, Bacillus Calmette-Guérin; EBV, Epstein-Barr virus; CMV, cytomegalo-virus.

bacilli on histological analysis with or without slightly deranged liver function are the common manifestations in disseminated BCG disease.

Some SCID patients may present with an eczematous rash, hepatosplenomegaly and lymphadenopathy (features quite different from *classical* SCID) along with recurrent infections. These symptoms are due to residual abnormally active T-cells which either arise in the patient because the genetic defect preventing lymphocyte maturation is not complete (Omenn syndrome) or from maternal lymphocytes that have crossed the placenta and engrafted in the child (SCID with maternal fetal engraftment). There is considerable similarity between the clinical features in these conditions, though they are usually more severe in Omenn syndrome.

Hair, including eyebrows and eyelashes, is usually lost as the rash evolves. Along with other clinical features of classical SCID, staphylococcal or *Pseudomonas* skin infections are particularly common and are often associated with elevated serum immunoglobulin (Ig) E levels with a marked eosinophilia.

Abnormalities in purine metabolism, due to ADA deficiency or purine nucleoside phosphorylase (PNP) deficiency result in the accumulation of toxic metabolites that damage lymphocytes. In ADA deficiency, the lymphocyte numbers may be normal at birth but fall rapidly. They also have bony changes like flaring of the anterior rib ends, blunting of the inferior angle of the scapula and pelvic dysplasia which are pathognomonic. PNP deficiency in addition presents with neurological features including a characteristic dysarthria and spastic diplegia.

Some patients may present with atypical form of SCID also called as *leaky SCID*. These patients have residual low number of T-cells ( $>300/\text{mm}^3$ ) and usually survive beyond 12 months of age. They present with severe infections which resolve only after

prolonged therapy. They may also present with autoimmune manifestations. They often result from hypomorphic mutations in genes normally associated with classical SCID retaining some protein function.

## WELL-DEFINED SYNDROMES WITH IMMUNODEFICIENCIES

Primary immunodeficiency disorders listed under this category have syndromic clinical manifestations along with the immunodeficiency. These syndromes are generally associated with variable degree of T-cell immunodeficiency. The common diseases listed under this category include Wiskott-Aldrich syndrome (WAS), DNA repair defects including ataxia-telangiectasia, DiGeorge anomaly (chromosome 22q11.2 deletion syndrome) and hyper-IgE syndromes (HIES).

### Wiskott-Aldrich Syndrome

This is a rare X-linked immunodeficiency disorder caused by mutation in Wiskott-Aldrich syndrome protein (WASp) gene. Classic WAS is characterized by thrombocytopenia with small platelets, eczema, recurrent infections, and increased risk for autoimmunity and malignancy. Hypomorphic mutations in WASp gene result in milder clinical form called X-linked thrombocytopenia.

Ataxia-telangiectasia is an AR disorder characterized by progressive neurologic impairment, variable immunodeficiency, impaired organ maturation, X-ray hypersensitivity, oculocutaneous telangiectasia, and a predisposition to malignancy.

### DiGeorge Syndrome

DiGeorge syndrome (DGS) is caused by deletions of the long arm of chromosome 22 at position q.11 and is very heterogeneous

with variable expression of the different features including the immunodeficiency ranging from normal T-cell numbers and function to complete DGS with a T-negative SCID-like picture. Classically it comprises of T-cell deficiency (due to thymic hypoplasia), hypoparathyroidism, cardiac malformations and facial abnormalities.

### Job Syndrome

These are HIES characterized by eczema in infancy, recurrent staphylococcal skin abscesses, recurrent pneumonia and serum IgE-levels. Both autosomal dominant (AD) and AR inheritance have been described. AD-HIES caused by heterozygous, dominant-negative mutations in *signal transducer and activator of transcription 3* (*STAT3*) is more common. In this form of HIES extra-immune manifestations occur, including skeletal abnormalities including a typical facial appearance, scoliosis, hyperextensibility, pathologic fractures, retained primary dentition, craniosynostosis, and retained primary teeth are common. The AR-HIES is characterized by recurrent viral and bacterial infections, extreme eosinophilia and elevated IgE without skeletal or dental abnormalities. The AR-HIES is caused by mutations in *dedicator of cytokinesis 8* (*DOCK8*) gene and rarely by a monogenetic defect in the cytoplasmic tyrosine kinase (*TYK2*) gene.

### PREDOMINANTLY ANTIBODY DEFICIENCIES

These are the most common type of immunodeficiencies, accounting for approximately 50% of all PIDs. More than 20 antibody-deficiency disorders are defined to date, the common ones include X-linked agammaglobulinemia (XLA; also known as Bruton agammaglobulinemia), common variable immunodeficiency (CVID), and selective IgA deficiency. They are characterized by an increased susceptibility to sinopulmonary infections with bacteria, particularly *Streptococcus pneumoniae* and *Haemophilus influenzae*. They are also prone to develop severe enteroviral infections. Other clinical manifestations such as diarrhea, fatigue and autoimmune manifestations (particularly autoimmune cytopenia and arthritis), are also seen in these patients.

Patients with CVID present commonly between 20 years and 40 years with similar symptoms. Other complications commonly seen in patients with CVID are chronic lung disease, systemic granulomatous disease, autoimmunity, lymphoid hyperplasia and infiltrative disease, gastrointestinal disease, and the development of hematolymphoid malignancies.

Milder antibody deficiencies especially *IgA deficiency* is a common immunological variant seen in 1:400–1:500 healthy individuals and more than 90% of the cases are asymptomatic. A subgroup of IgA-deficient patients develops recurrent sinopulmonary and gastrointestinal infections typical of antibody deficiency, yet invasive infections such as meningitis or sepsis generally do not occur. These patients must be investigated for associated antibody deficiency such as IgG2 subclass deficiency. IgA-deficient individuals are at an increased risk of developing autoimmune disease, particularly systemic lupus erythematosus and rheumatoid arthritis, and gastrointestinal disease such as inflammatory bowel disease and celiac disease. A higher prevalence of asthma and allergies has also been reported.

Other category under antibody deficiency is *hyper-IgM syndromes* (HIGM). These are a heterogeneous group of genetic disorders resulting from mutations in the genes directly or indirectly involved in B-cell signaling via CD40 and required for class switch recombination and somatic hypermutation. At least five distinct molecular defects, including mutations of the genes coding for the CD40 ligand (*CD40L*) and inhibitor of nuclear factor kappa-B kinase subunit gamma [IKK-gamma, NF-kappa-B essential

modulator (*NEMO*)] genes, both X-linked; and mutations of *CD40*, activation-induced cytidine deaminase (*AICDA*), and uracil-DNA glycosylase (*UNG*), associated with AR-HIGM syndromes. The common clinical manifestations include severe recurrent sinopulmonary infections intermittent or persistent neutropenia, autoimmune manifestations and malignancies. Since patients with CD40 and CD40L deficiency also have associated T-cell function defects, they are prone to infections with opportunistic organisms, such as *Pneumocystis carinii* pneumonia, chronic diarrhea due to *Cryptosporidium* infection leading to sclerosing cholangitis and are also categorized under CID.

### DISEASES OF IMMUNE DYSREGULATION

#### Hemophagocytic Lymphohistiocytosis

This is a rare life-threatening disease of immune regulation clinically characterized by prolonged fever, cytopenia and hepatosplenomegaly. Low or absent natural killer (NK) cell and CD8+ cytotoxic T-lymphocyte (CTL) cytotoxicity is one of the hallmarks of HLH and leads to prolonged and excessive activation of antigen presenting cells (macrophages, histiocytes) and CTLs resulting in multisystem inflammation. HLH may occur as a primary (genetic) condition due to mutations in genes important in the pathway of granule-mediated cytotoxicity or as a secondary condition where identical clinical findings may arise secondary to infectious, rheumatologic, malignant, or metabolic conditions. Several genetic causes predispose patients to HLH and these include familial hemophagocytic syndrome (FHL; in whom HLH is often the only presenting manifestation), immunodeficiencies with albinism and various primary immunodeficiencies which in particular diseases associated with impaired response to infection with Epstein Barr virus where HLH may occur though frequently along with other clinical manifestations. Defects in *PRF1* (FHL2), *UNC13D* (FHL3), *STX11* (FHL4) and *STXBP2* (FHL5) are known causes of FHL whereas the underlying molecular basis for FHL1. All these genes encode for proteins important for granule-mediated cytotoxicity. Central nervous system manifestations, like from seizures, altered mental status, cranial nerve palsies, blindness, unconsciousness, ataxia, etc., are also seen in patients with FHL especially FHL2.

#### Autoimmune Lymphoproliferative Syndrome

It is a disorder of lymphocyte homeostasis characterized by non-malignant lymphadenopathy, splenomegaly, autoimmunity mostly directed toward blood cells and increased risk of lymphoma. The median age of first presentation is 24 months of age, but with increasing awareness of the condition, adults with autoimmune complications are now being diagnosed more frequently. The most common mutation found in patients with autoimmune lymphoproliferative syndrome (ALPS), seen in around 70% of the patients, is the germ line heterozygous FAS mutation. Patients with somatic FAS mutations are now the second largest group of known genetic mutations in ALPS, followed by patients with caspase 10 (*CASP10*) and Fas-ligand (*FASLG*) mutations, respectively. All these mutations are inherited in an AD manner. However, cases with homozygous or compound heterozygous mutations have also been reported.

### PHAGOCYTE DEFECTS

Phagocytic leukocytes are an essential component of the innate immune system that has evolved to respond rapidly to the presence of invading bacteria, fungi, and parasites. Patients with defects in phagocytic function are predisposed to intracellular microorganisms and typically have an early dissemination of the infection.

## Chronic Granulomatous Disease

It is characterized by recurrent infections involving the skin and respiratory system. The majority of infections in chronic granulomatous disease (CGD), such as cellulitis, liver abscess, otitis media, pneumonias, pyoderma and periodontal disease, are caused by *Staphylococcus aureus*. Infection due to *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia* species, and *Aspergillus* species are strongly of CGD.

## Myeloperoxidase Deficiency

It is necessary for intracellular killing of certain organisms by neutrophils and monocytes. A complete or partial deficiency of myeloperoxidase deficiency leads to mildly prolonged respiratory burst. Patients are often asymptomatic but susceptibility to *Candida* and *Staphylococcus* infections may be seen.

## Leukocyte Adhesion Deficiency

These syndromes result from failure of leukocyte to defend the host because of missing or dysfunctional surface adhesion molecules. Leukocyte adhesion deficiency (LAD) type I results from mutations in the *ITGB2* gene encoding for the  $\beta 2$  subunit (CD18) of  $\beta 2$ -integrin. It is the most common of the LAD syndromes presenting soon after birth with omphalitis and delayed separation of the cord (often beyond 21 days). High resting neutrophil count, recurrent bacterial infections of skin and mucosal surfaces which are necrotic rather than pustular with frequent dissemination and sepsis, poor wound healing and periodontal disease are common clinical manifestations. LAD type II syndrome results from a general defect in fucose metabolism, causing the absence of Sialyl-Lewis X and other fucosylated ligands for the selectins.

Affected patients present early in life, have recurrent bacterial infections with persistent leukocytosis, but do not have delayed separation of the umbilical cord. The infections are generally not life-threatening. These patients also have severe mental retardation, short stature, a distinctive facial appearance and the rare Bombay (hh) blood phenotype.

Leukocyte adhesion deficiency type III syndrome results from defects in *Kindlin-3* and *CalDAG-GEF1* genes. These patients have severe bleeding tendencies along with recurrent severe bacterial infections and leukocytosis. CD18 molecule is structurally intact in these patients and they show significant abnormalities in leukocyte and platelet integrin activation.

## Severe Congenital Neutropenia

The child has persistently low absolute neutrophil count (ANC) with elevated monocytes and eosinophils counts. Cyclic neutropenia patients present with drop in ANC every 3–4 weeks with fever, infections and mouth ulcers.

## Interferon- $\gamma$ /Interleukin-12 Pathway Defects

Patients with defects in interferon gamma receptor 1 (IFN- $\gamma$ R1), INF- $\gamma$ R2, interleukin 12 receptor beta 1 (IL-12R $\beta$ 1), IL-12 p40, and STAT1 have been identified through their extreme susceptibility to nontuberculous mycobacteria and BCG. These defects, all of which have been identified because of mycobacterial infection, have been grouped as Mendelian susceptibility to mycobacterial disease. They present early in life with disseminated severe infections, especially if they have received BCG vaccination, and have poor to absent granuloma formation. *Salmonella* and certain viral infections (herpes simplex virus, cytomegalovirus, parainfluenza, and respiratory syncytial virus) are also seen. Mortality in these children is high, and infections are severe and recurrent.

## DEFECTS OF INNATE IMMUNITY

Over the last few years, several defects in innate immunity have been discovered representing a new group of PIDs characterized by defects in pathogen recognition receptor signaling. The important four defects listed under this category include genes involved in nuclear factor kappa-light-chain-enhancer of activated B-cells (NF- $\kappa$ B) activation important in toll-like receptor (TLR) signaling: *NEMO*, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (*I $\kappa$ B $\alpha$* ), interleukin-1 receptor-associated kinase 4 (*IRAK4*) and myeloid differentiation primary response gene 88 (*MyD88*). Patients with anhidrotic ectodermal dysplasia and immunodeficiency, which is caused by mutations in *NEMO* and *I $\kappa$ B $\alpha$* , have sparse hair, dry skin, and conical teeth and are at increased risk of severe infections caused by pyogenic bacteria and atypical mycobacteria.

Patients with *IRAK4* deficiency and *MyD88* deficiency are at increased risk of invasive bacterial infections, like meningitis, sepsis, arthritis, osteomyelitis and abscesses, due to *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* often in the absence of fever. These PIDs improve with age and patients often have no further invasive bacterial infections beyond their teenage years. These patients should receive conjugated and nonconjugated bacterial vaccines, antibiotic prophylaxis, and IgG replacement during the first decade of life.

## AUTOINFLAMMATORY DISORDERS

The disorders included under this category of PID are monogenic inherited disorders caused by dysregulation of innate immune system leading to aberrant inflammasome activation. To date, 12 monogenic AIDs have been identified; the common ones being: familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), tumor necrosis factor receptor-associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndrome (CAPS). Clinical manifestations include recurrent inflammatory episodes with fever, and frequent involvement of the skin, serous membranes, eyes, joints, lymph nodes, gastrointestinal tract, and nervous system. Each of these syndromes varies in severity, duration, frequency and site of inflammatory signs and symptoms and their response to therapy with different anti-inflammatory and immunomodulatory therapy.

## Familial Mediterranean Fever

It is caused by loss-of-function mutations within the *MEFV* gene and is the most common AID. The classic phenotype is characterized by recurrent acute febrile episodes lasting 12–72 hours, sometimes triggered by stress, physical exercise. They may be associated with polyserositis especially peritonitis, arthritis, and erysipelas-like erythema usually localized on the surface of the legs between the hip and knee and/or on the top of the foot. In second phenotype of FMF, patients present as systemic amyloidosis as the sole manifestation of the disease.

## Mevalonate Kinase Deficiency

It is due to mutations in the *MVK* gene, encoding the second enzyme of mevalonate pathway. MKD usually starts in childhood within first 5 years of life with abrupt febrile flares that occur every 4–6 weeks and last about 3–7 days on average, with headache, mouth ulcers, abdominal pain, vomiting, and/or diarrhea with joint involvement in the form of arthralgia and/or arthritis, especially affecting large joints, a nonspecific maculopapular rash. The episodes are sometimes induced by vaccinations or viral infections. Attacks are generally more frequent during childhood and adolescence, but the disease may persist into adulthood in more than half of patients.



## Tumor Necrosis Factor Receptor-associated Periodic Syndrome

It is caused by mutation in *TNFRSF1A* gene. This is the most common dominant form of AID in Europe, historically known as *familial Hibernian fever*. Patients complain of inflammatory attacks of extremely variable duration and intensity (from 1–2 days to 3–4 weeks), accompanied often by sterile peritonitis with abdominal pain, diarrhea/constipation, nausea, and vomiting. Mono or bilateral periorbital edema is a characteristic feature of the disease, often associated with conjunctivitis and periorbital pain. Secondary amyloidosis is seen in 25% of the patients.

## Cryopyrin-associated Periodic Syndromes

These are a group of AID transmitted by AD inheritance caused by mutations in the *NLRP3* gene encoding for cryopyrin, a crucial inflammasome protein that directly activates IL-1 $\beta$ . There are three known forms of CAPS. The least severe is *familial cold autoinflammatory syndrome* which usually appears in early childhood and is characterized by brief recurrent inflammatory episodes triggered by exposure to cold or sudden change in temperature. *Muckle-Wells syndrome* is the clinical phenotype of medium severity with recurrent or chronic inflammatory symptoms often associated with episcleritis, neurosensorial deafness, and secondary amyloidosis (in up to 25% of cases). Finally, *chronic infantile neurological cutaneous articular syndrome* also known as neonatal-onset multisystem inflammatory disease, the most severe form presents with additional clinical manifestations like hypertrophic arthropathy involving both epiphyses of long bones and kneecaps, uveitis, papilledema, optic nerve atrophy leading to blindness, elevated intracranial pressure, deafness, and growth retardation.

## COMPLEMENT DEFICIENCIES

The complement system is a key component of innate immunity. More than 45 genes encoding the proteins of complement components or their isotypes and subunits, receptors, and regulators have been discovered. Deficiencies of all the soluble components and many membrane receptors and regulatory proteins have been described. Most of them are AR, although deficiency of C1q esterase is AD and that of properdin is X-linked. Genetic deficiency of any early component of the classical pathway (C1q, C1r/s, C2, C4, and C3) is associated with autoimmune diseases due to the failure of clearance of immune complexes and apoptotic materials. They also have impairment of humoral response and varying degree of susceptibility to bacterial infections especially encapsulated bacteria like *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *H. influenzae*. Deficiencies of mannan-binding lectin and the early components of the alternative (factor D, properdin) and terminal pathways (from C3 onward components: C5, C6, C7, C8, C9) predominantly present with increase susceptibility to bacterial infections especially *Neisseria meningitidis*. Although blood-borne systemic infections, such as bacteremia and meningitis, are the most common manifestations, localized infections, like sinusitis, otitis and pneumonia, may also be seen in the complement deficient individuals. Also the prevalence of complement deficiencies is significantly higher in individuals with systemic meningococcal infections especially patients with recurrent disease (40%) and with positive family history (10%) or an unusual serotype of the meningococcus (20–50%).

## PHENOCOPIES OF PID

In the new updated PID classification of 2013, a new category, *phenocopies of primary immunodeficiencies*, has been added to the existing classification. This includes disorders which manifest

as inherited deficiencies of the immune system, but are not due to germ line mutations. Acquired mechanisms, such as somatic mutations and autoantibodies to cytokines or other immunologic factors, are implicated in their pathogenesis. The disorders included in this broad category include:

- Disorders with somatic mutations in the Kirsten rat sarcoma viral oncogene homolog (*KRAS*) and neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*) genes mimicking a ALPS like phenotype
- Disorders with autoantibodies to cytokines and other immunological factors such as IL-17, IL-22, IFN- $\gamma$ , IL-6, granulocyte-macrophage colony-stimulating factor and C1 inhibitor.

## LABORATORY APPROACH

The investigations are largely guided by the clinical presentation of the patient, the suspected immune defect and the results of initial laboratory evaluation. The laboratory approach toward diagnosis of patients with PID can be broadly divided into two: approach for patients with recurrent infections and diagnosis of other PID either with syndromic manifestation, AIDs and disorders of immune dysregulation. Patients in the second category require totally different set of investigations and many of the diseases in this category have their individual diagnostic criteria. Discussing them individually is beyond the scope of this chapter and hence we will focus on evaluation of patients with recurrent infections.

For evaluation of patients with recurrent infections, the first and the most important step is to look at the complete blood count carefully. Look for ANC, absolute lymphocyte count (ALC), eosinophil counts, monocytes and platelet count carefully. Low ALC suggests combined immunodeficiency (CID) while low ANC suggests severe congenital neutropenia (SCN) or autoimmune neutropenia. Low platelet counts with low mean platelet volume suggest WAS. Persistently elevated ANC suggests LAD type I while high ALC is seen in patients with ALPS. Eosinophilia is often associated with HIES and Omenn syndrome. The most useful first-line immunological investigations include lymphocyte subset analysis, serum Ig levels and nitroblue tetrazolium test (NBT).

The panel of antibodies used lymphocyte subset analysis should include CD3, CD4, CD8, CD56/16, CD19 and human leukocyte antigen-DR (HLA-DR). It is aimed at measuring the absolute and relative number of:

1. B-cells (CD19+)
2. T-cells (CD3+)
3. T-helper cells (Th, CD3+/CD4+)
4. T-cytotoxic cells (Tc, CD3+/CD8+)
5. Natural killer cells (CD3-/CD56+/CD16+)
6. Activated T-cells (CD3+/HLA-DR+).

The total lymphocyte numbers and T-lymphocyte subsets are age dependent, being markedly increased in newborns and young infants and decreasing with age. In infants below 4 months of age, a CD4 count of less than 1000/mm<sup>3</sup> is generally associated with impaired cellular immunity, whereas the corresponding value is less than 500/mm<sup>3</sup> in children over 2 years of age and in adults. Immunosuppressive therapies like steroids also significantly alter the values of T- and B-cell subsets and should be interpreted carefully.

The results of these initial tests usually give an important clue to the underlying immune defect. Patients with low T-cell counts are likely to have CID. Patients with low or absent B-cell, low Ig levels and normal T-cell come under the category of predominantly antibody deficiency. Patients with abnormal neutrophil count or abnormal neutrophil function suggest defects in the phagocytic system. Large number of flow cytometry-based assays which measure cell number, cell function or expression of particular antigen/molecule on the cells help in diagnosis of individual disorders.



## Evaluation of Suspected CID

Lymphocyte subset analysis is abnormal in most cases of SCID and in many cases of CID. SCID is categorized broadly as T+ SCID and T- SCID depending on presence or absence of the T-cells. There are many genetic defects which can lead to T- SCID phenotype. The B-cells and NK cells count in these patients give an important clue to the underlying molecular defects (**Flow chart 1**). However, there is significant overlap between these categories and hence specialized tests, like CD132 and CD127 expression, functional studies, like pSTAT5 activation in lymphocytes after IL-2 stimulation, estimation of enzymes, like ADA and PNP in red blood cells, radiation sensitivity test, etc., are required for specific diagnosis.

Patients with normal T-cell numbers can still have CID. This is usually seen with patients with Omenn syndrome, major histocompatibility complex (MHC) class I or MHC class II deficiency, zeta-chain-associated protein kinase 70 (ZAP-70) deficiency, etc. These patients can be evaluated by doing T-cell proliferation assays (for evaluation of T-cell function), expression of HLA-DR on T and B-cells (for MHC class II expression) and T-cell receptor V $\beta$  repertoire analysis (for assessment of diversity of immune response).

## Evaluation of Patients with B-cell Defect

Patients with suspected B-cell defects require estimation of B-cell numbers (CD19, CD20 and CD79a), serum Ig levels (IgG, IgA, IgM, IgE and IgG subclasses). Patients with absent B-cells and markedly reduced Ig are suggestive of agammaglobulinemia which can be XLA or AR agammaglobulinemia. Patients with XLA will have absent or reduced expression of protein Bruton tyrosine

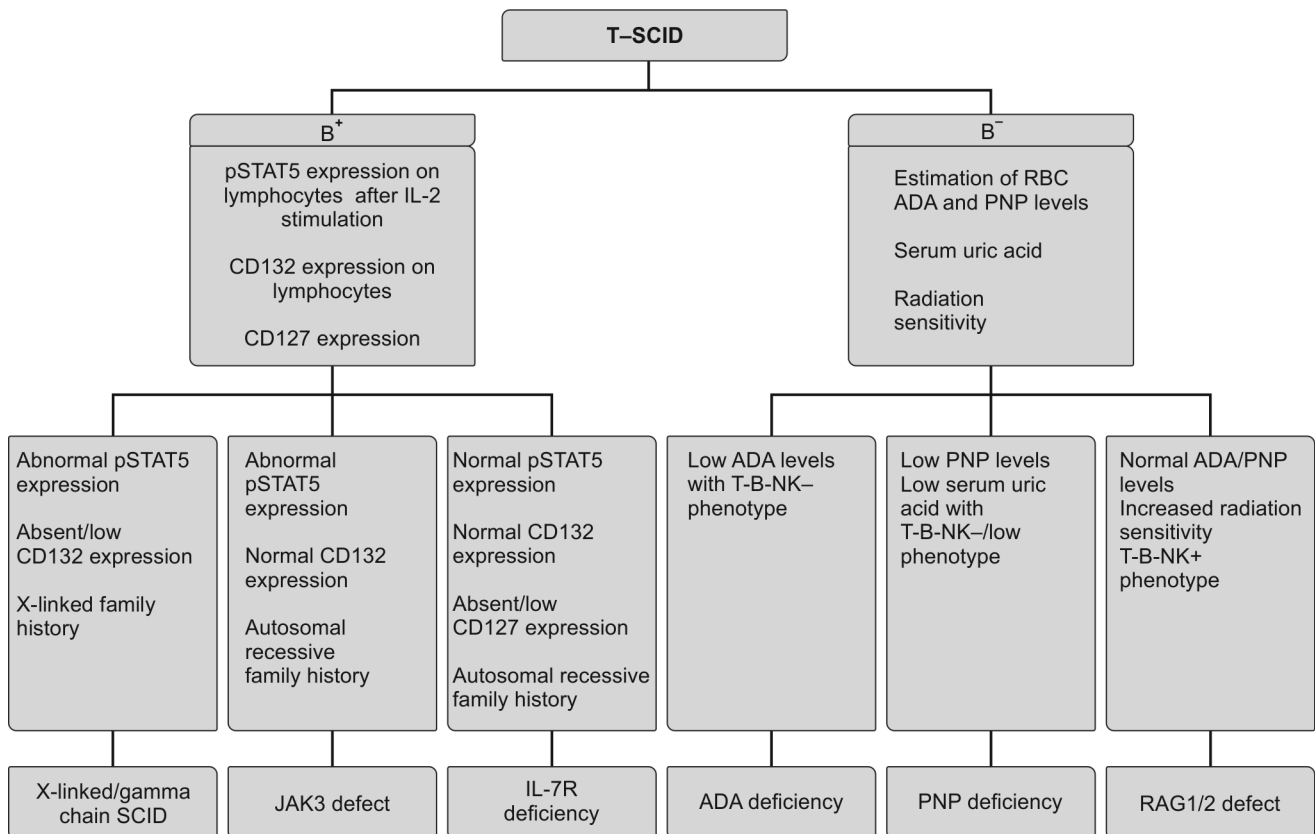
kinase with carrier mothers showing mosaic pattern. Patients with reduced Ig with normal to low B-cells with abnormal specific antibody responses suggest CVID. Patients with HIGM have markedly low IgG and IgA with normal to elevated IgM levels. They can be further evaluated by studying expression of CD40 and CD40L (CD154) expression on B-cells and T-cells, respectively. Patients with X-linked HIGM will have abnormal CD154 expression on T-cells after stimulation and carrier mothers will show mosaic pattern.

Patients with strong clinical suspicion of antibody deficiency with normal or only modestly reduced Ig levels should be evaluated for specific antibody titers (usually IgG) in response to vaccine antigens and IgG subclass levels. This approach involves immunizing a patient with protein antigens (e.g., tetanus toxoid) and polysaccharide antigens (e.g., pneumococcus) and assessing pre- and postimmunization antibody levels. In many PIDs, antibody responses to these antigens are diminished or even absent.

## Evaluation of Patients with Phagocytic Defects

In a patient with suspected phagocytic defect one must look at the ANC. A patient with low ANC with early neonatal presentation is suggestive of SCN. Characteristically, there is marked monocytosis with levels often 2–4 times that of normal. There may be associated anemia and mild thrombocytosis attributable to chronic inflammation. Bone marrow examination shows the presence of early precursor cells but very few mature cells beyond the promyelocyte stage or *promyelocyte arrest*. Patients with cyclic neutropenia have oscillations of neutrophil count with a periodicity of around 21 days. At the nadir, neutrophil counts are

**Flow chart 1** Evaluation of patients with common T-SCID



**Abbreviations:** SCID, severe combined immunodeficiency; pSTAT5, phosphorylated *signal transducer and activator of transcription 5*; IL, interleukin; JAK3, Janus kinase 3; ADA, adenosine deaminase; PNP, purine nucleoside phosphorylase; RAG, recombination activating gene; CD, cluster of differentiation; RBC, red blood cell; T-B-NK-, T-cell negative, B-cell negative and natural killer cell negative; T-B-NK+, T-cell negative, B-cell negative and natural killer cell positive.

generally less than  $0.2 \times 10^9/L$  for 3–5 days, after which they rise rapidly to levels near the lower limit of normal, about  $2 \times 10^9/L$ . Both SCN and cyclic neutropenia commonly result from mutations in neutrophil elastase gene (*ELA-2*).

Patients with suspected CGD have normal or elevated ANC and can be diagnosed by NBT and dihydrorhodamine test. These tests can also detect carrier mothers in X-linked CGD. Final confirmation of underlying defect can be done by studying the intracellular expression of gp91 for X-CGD and p22, p67 or p47 for AR-CGD followed by molecular analysis of the affected gene. Patients with LAD type I can be easily diagnosed by flow cytometric analysis of CD18, CD11a, CD11b and CD11c expression on peripheral blood leukocytes.

### Evaluation of Patients with Disorders of Innate Immunity

Standard immunological laboratory tests, such as blood cell and differential cell counts (platelet counts, ALC, neutrophil and eosinophil counts), lymphocyte subsets and CH50 (total complement activity) determinations will be normal in most patients suffering from a defect of the TLR/NF- $\kappa$ B pathway, whereas Ig levels are variable in MyD88, IRAK4 and NEMO deficiencies. The diagnosis of defects of the TLR/NF- $\kappa$ B pathway is, therefore, challenging and requires specific laboratory evaluations of TLR function. Enzyme-linked immunosorbent assays (ELISAs) or related assays are used to measure the ex vivo production of a number of cytokines [tumor necrosis factor alpha (TNF $\alpha$ ), IL-6, IL-10, IL-12/IFN- $\gamma$  and type I IFNs] by whole blood or peripheral blood mononuclear cells after stimulation with different TLR ligands. Rapid flow cytometry methods for detecting intracellular TNF $\alpha$  production or shedding of CD62L after stimulation with TLR ligands are useful screening tools for functional evaluation of TLR/NF- $\kappa$ B pathway. Depending on the results of these assays further genetic evaluation can be performed.

### Evaluation of Patients with Complement Deficiency

Initial evaluation is done with the CH50 (which tests the classical and final lytic components except C9) and AH50 (which tests alternative and final lytic pathways) assays. It is advisable that the assays be performed when the patient has completely

recovered from immune complex disease or infection. Both the tests require (X the) blood to be taken atraumatically and serum be separated within 1 hour and stored at  $-70^\circ\text{C}$ . If either of these screening tests identifies failure of a complement pathway on two occasions, the specific component defect should be determined.

### IN A NUTSHELL

1. Diagnosis of specific PID from a large spectrum of disorders requires expertise in clinical and laboratory evaluation.
2. Suspecting PID based on various clinical manifestations is the most important step in diagnosis of PID.
3. Wide array of assays are available for evaluation of immune system which help immensely in the diagnosis of PIDs.
4. Knowledge of clinical presentation of these disorders, correct interpretation of initial results of immunophenotyping of lymphocytes is essential for choosing the appropriate test for specific diagnosis.
5. There is very little data available from India on PID. Being a country with the second largest population in the world, we are likely to have large number of patients with PIDs.
6. Recognizing a suspicious case of PID at a regional hospital level is important to ensure timely referral to a specialized center for diagnosis and treatment for these patients.

### MORE ON THIS TOPIC

- Abramovits W, Oquendo M. Introduction to autoinflammatory syndromes and diseases. *Dermatol Clin*. 2013;31:363-85.
- Bousfiha AA, Jeddane L, Ailal F, et al. A phenotypic approach for IUIS PID classification and diagnosis: guidelines for clinicians at the bedside. *J Clin Immunol*. 2013;33:1078-87.
- International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies. Primary immunodeficiencies: 2009 update. *J Allergy Clin Immunol*. 2009;124:1161-78.
- Maggina P, Gennery AR. Classification of primary immunodeficiencies: need for new molecular insights, and practical approach to diagnosis and treatment. *Ann Allergy Asthma Immunol*. 2014;112:489-95.
- Ochs HD, Hagin D. Primary immunodeficiency disorders: general classification, a revised approach? *J Allergy Clin Immunol*. 2013;131:292-4.

## Chapter 4.4

# Therapy for Primary Immunodeficiency Disorders

Revathi Raj, Surjit Singh

The field of primary immunodeficiency disorders (PIDs) is still at its infancy in India. Each year, a significant number of infant and early childhood deaths could be due to an unrecognized immunodeficiency disorder. Exciting therapeutic developments have occurred in the care of these children including availability of intravenous immunoglobulins, optimal supportive care with antibiotics, hematopoietic stem cell transplantation and gene therapy. Early diagnosis and prompt referral to a center of excellence goes a long way in ensuring a high rate of cure for these children who pose fresh and interesting challenge at every stage of management.

## MANAGEMENT OF ANTIBODY DEFICIENCIES

Intravenous immunoglobulins (IVIG) were first introduced in 1952 to treat children with immunodeficiency. IVIG contains pooled immunoglobulin G (IgG) from over a thousand plasma donors and it is a sorbitol based formulation to minimize reactions during administration. IVIG given at a dose of 400 mg/kg every 28 days intravenously has made long-term survival a reality in patients with X-linked agammaglobulinemia. Other indications include children with severe combined immunodeficiency as a bridge to hematopoietic stem cell transplantation, common variable immunodeficiency, hyper IgM syndrome and Wiskott-Aldrich syndrome. Details of IVIG therapy are provided in a separate chapter in this *Section*.

## SUPPORTIVE THERAPY

### Prophylactic Antibiotics

Antibiotic prophylaxis is the standard of care in several PID. Pneumocystis pneumonia (PCP) is the hallmark infection in T-cell deficiency. This can be prevented by using co-trimoxazole at 5 mg/kg/day of trimethoprim 3 days a week. Fungal infections, particularly *Candida* causing oral thrush can be prevented by the use of fluconazole at 6 mg/kg/day. Children with neutrophil dysfunction like chronic granulomatous disease and hyper IgE syndrome can be managed with prophylactic co-trimoxazole to prevent staphylococcal infections and itraconazole at 5 mg/kg/day on a daily basis to prevent *Aspergillus* infection. Children with complement deficiency who are at risk of infection from diplococci can be managed with penicillin prophylaxis at Penicillin G at 400 mg or 400,000 units for above 5-year-old children twice a day and 200 mg or 200,000 units twice a day for children below 5 years of age.

### Diet in Primary Immunodeficiency Disorders

Children with PID need to be taken care of in a safe and clean environment. A low bacterial diet helps prevent diarrhea and sepsis. The use of tap water for mouth care must be avoided to prevent the risk of acquiring chronic *Cryptosporidium* diarrhea. Exposure to woodwork or building construction can result in *Aspergillus pneumoniae*. Breastmilk is the optimal diet for infants. Hypoallergenic formulae like rice or soya based diet will help prevent loose stools and failure to thrive. Children with neutrophil dysfunction are asked to consume freshly prepared home cooked foods and to avoid salads and fresh fruits, other than those in

which the skin can be peeled and consumed in a fresh manner. Soft cheese can result in listeriosis and is to be avoided. Pasteurized milk and yogurt are safe for consumption. Canned foods are best to be avoided.

## Treatment of Infections

Children with PID are present with infections and need to be treated in an aggressive manner with specialists input from the *Infectious Diseases* department. Bacterial infections are most common and the source of infection is usually the child's own body. Streptococci from the throat, staphylococci from the nostrils and skin, gram-negative bacteria from the gastrointestinal tract are all commonly seen and need to be treated with appropriate antibiotics based on local antibiotic policy. Complement deficiency children are prone to infections with opsonization defect and can be treated with penicillin or cephalosporins after appropriate cultures when they present with a fever. Atypical bacterial infections like *Burkholderia* or *Stenotrophomonas* are seen in children with chronic granulomatous disease. If the child does not respond to upfront broad spectrum antibiotics, early imaging with CT chest and bronchoscopy and culture will help guide further therapy. A baby with severe combined immune deficiency presenting with respiratory distress could be harboring cytomegalovirus, pneumocystis or disseminated BCG infection. Early intervention with ganciclovir, high dose cotrimoxazole or antituberculous drugs will help stabilize the child for transplantation.

## DEFINITIVE THERAPY

Hematopoietic stem cell transplantation is the only curative option for children with immune deficiency. In 1968, hematopoietic stem cell transplantation (HSCT) was first performed for a child with severe combined immunodeficiency (SCID). At the same time, another child with Wiskott-Aldrich syndrome (WAS) transplanted from a matched sibling. Since then, HSCT techniques have advanced due to high resolution human leukocyte antigen (HLA) typing, the availability of alternative donors like umbilical cord blood, less toxic chemotherapeutic conditioning and graft-versus host disease (GVHD) prophylaxis. Supportive care has improved with newer antifungal agents, rapid detection of viral infections using PCR-based assays enabling pre-emptive antiviral treatment before the onset of organ damage. Increased awareness of primary immunodeficiency (PID) amongst general pediatricians has led to earlier diagnosis and referral to specialist centers and better outcomes.

### Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) aims to give stable donor stem cell engraftment to help regain full immune system. The overall survival has increased to 80% for babies with a genotypical donor and nearly 70% for those given matched unrelated donor (URD) HSCT. It is important to have precise molecular diagnosis as the prognosis can then be accurately assessed. For instance, the outcome following HSCT for patients with B negative forms of SCID such as RAG deficiency is less good than for those with B positive forms and those with Artemis deficiency have a worse prognosis than those with RAG deficiency because of the associated cellular radiosensitivity.

**Donor choice** The first step involved in HSCT is to identify a HLA matched donor for donating stem cells. The best HLA matched donor is a sibling and so any siblings of the patient should be tissue typed along with parents and if possible the extended family. If there are no matched family donors, search in the National and International unrelated donor registries is done as a high priority to obtain a donor at the earliest. There are currently 19 million adult

and over 500,000 cord blood donors that can be accessed through the Bone Marrow Donors Worldwide registry.

**Stem cell source** Bone marrow is the choice for source of stem cells and is harvested under general anesthesia from the posterior iliac crests. The option of donating peripheral blood stem cells (PBSC) rather than bone marrow is more appealing for adult donors as this avoids a general anesthesia. Umbilical cord blood stem cell transplantation (UCSCT) is a readily available stem cell source when a matched sibling donor is unavailable. The advantages of UCSCT include quick access to the cord blood unit and ease of arranging date of transplant, absence of risk to donor, lower risk of latent viral transmission and graft versus host disease (GvHD) and finally a higher chance of matching rare HLA haplotypes. Half matched parent or sibling transplantation is called haploidentical HSCT and is offered if there are no matched donors in unrelated or cord blood registries. This is used as a last choice as immune reconstitution is delayed for over 6 months to a year exposing the children to infections over prolonged periods of time.

**Assessment of donor and recipient** The donor and recipient need to go through mandatory tests including those for HIV, HBsAg, anti-hepatitis C antibody, VDRL, cytomegalovirus, herpes simplex virus and blood group.

### Preparation of Patient

Once the decision to transplant has been made and a donor selected each organ system should be assessed so that any infection is treated prior to transplant. Many children with PID fail to thrive and are malnourished and it is important to improve their nutritional status prior to transplant. This may be by high calorie enteral feeding via nasogastric tube or parenteral nutrition through a central venous catheter.

**Conditioning** Conditioning aims to create space in the recipient marrow niche to enable donor stem cells to engraft more easily. Newer drug combinations like treosulfan and fludarabine are superior when compared to busulfan and cyclophosphamide and have helped to reduce transplant related toxicity and ensure excellent survival. Infants with T negative, B positive, NK negative SCID can have stem cell infusion with no conditioning as they rarely reject a new graft.

**Stem cell infusion** The stem cells harvested from the donor are transfused into the recipient into a central vein. In haploidentical transplantation, T-lymphocytes are depleted from the stem cells to remove of alloreactive lymphocytes enabling transplantation across HLA barriers. The most commonly used method, the Miltenyi CliniMACS system, uses an organic iron bead attached to an anti-CD34 antibody to isolate purified CD34+ HSCs from the other cells by passing the HSC source through a magnetic column and the purified CD34+ HSC fraction is infused into the patient.

**Supportive care** Infections, veno-occlusive disease, mucositis, graft versus host disease and graft rejection are the main complications seen after infusion of stem cells.

**Post-transplantation immune-reconstitution** Full immune-reconstitution can take up to 2 years post-transplant. The children need to remain on immunoglobulin replacement for around 6 months post-transplant or until evidence of immunoglobulin production as evidenced by an increase in IgM production. Vaccines are then introduced and antibiotic prophylaxis can be discontinued. Children should be monitored for endocrine dysfunction— particularly thyroid dysfunction, growth and late side effects.

## GENE THERAPY

Children with SCID were the first to be treated with novel methods like gene therapy where the missing gene is introduced into the cells by a viral vector system. Gene therapy is now used for SCID, Wiskott-Aldrich syndrome and chronic granulomatous disease.

## ENZYME REPLACEMENT

Children with SCID due to deficiency of the enzyme adenosine deaminase have benefitted from replacement of the enzyme. Long-term results for drug safety over a decade are now available. The disadvantage is the huge costs involved and commitment to lifelong infusions.

### IN A NUTSHELL

1. Matched sibling donor transplantation for primary immunodeficiency disorders offers over 80% chance of cure.
2. Early referral for hematopoietic stem cell transplantation (HSCT) before the onset of organ damage ensures optimal outcome.
3. Novel stem cell sources such as T-cell depleted haploidentical stem cells and cord blood stem cells have ensured that every child is offered a chance of cure.
4. Enzyme therapy and gene therapy help alleviate symptoms in some forms of PID.
5. Intravenous immunoglobulin use is the backbone of care in children with primary immunodeficiency.

## MORE ON THIS TOPIC

- Amrolia P, Gaspar B, Hassan A, et al. Non-myeloablative stem cell transplantation for congenital immunodeficiencies. *Blood*. 2000;96:1239-46.
- Anderson D1, Ali K, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. *Transfus Med Rev*. 2007;21(2 Suppl 1):S9-56.
- Kohn DB. Gene therapy for childhood immunological diseases. *Bone Marrow Transplant*. 2008;41:199-205.
- Slatter MA, Rao K, Amrolia P, et al. Treosulfan-based conditioning regimens for hematopoietic stem cell transplantation in children with primary immunodeficiency: United Kingdom experience. *Blood*. 2011;117:4367-75.



## Chapter 4.5

# Intravenous Immunoglobulin

Sujoy Khan, Surjit Singh

Intravenous immunoglobulin (IVIG) is prepared from pooled human plasma of between 3,000 and 15,000 healthy donors and contains predominantly of polyvalent immunoglobulin G (IgG). The large number of donors in the pool allows a broad range of anti-infective and immunomodulatory activities and is therefore the treatment of choice for primary immunodeficiency diseases like antibody deficiency and several autoimmune conditions. IVIG was first demonstrated to be useful in immune (idiopathic) thrombocytopenic purpura in childhood in the early 1980s and since then, use of Ig has been found to be beneficial in several different areas in pediatric practice (Table 1).

Immunoglobulins are comprised within the gamma portion of plasma proteins (Fig. 1) generated by an individual's immune system and are composed of five different isotypes (IgG, IgA, IgM, IgD and IgE), of which IgG is the most abundant. Polyvalent human immunoglobulins are produced along with several other therapeutic plasma proteins (such as coagulation factors, albumin) from the pooled plasma through a process called fractionation. The plasma can be collected either through the quicker process of blood donation (average 30 minutes, 5–6 donations per year) or through plasmapheresis (donation takes 1–1.5 hours, 20 donations possible per year). Only specialized plasma collection centers can deal with the latter as they require large equipment and freezer capacity and need to fulfill specific criteria including a small compensation amount to the donor for time spent in donations. Individual donor units are screened for hepatitis B and C viruses and HIV. After the cryoprecipitate is removed, cold ethanol (Cohn) fractionation of the resultant precipitate is used in several steps, a process developed in the 1940s by Professor Edwin J Cohn. The product is then treated by solvent-detergent (SD) or other chemicals, by pasteurization or nanofiltration for viral inactivation or virus removal, with some manufacturers adding a prion filter to further reduce the chances of transmission of prion disease. The final sterile product has a wide spectrum of antibacterial and antiviral including possibly antiparasitic antibodies.

Human Ig contains more than 95% IgG with minimal quantities of IgA and IgM but the latter globulin fractions do not have a therapeutic significance because of their short half-life (<7 days). The IgG portion in all preparations has half-life between 18 days and 25 days, with physiologically similar IgG subclasses, have minimal anticomplementary activity, diverse antibacterial and antiviral activity, and negative for hepatitis B surface antigen, hepatitis C virus, and HIV.

## MECHANISMS OF ACTION

The human body uses a distinct mechanism of the physiological role of IgG that is dependent on both the Ig dose (such as replacement 400–600 mg/kg or high-dose 1–2 g/kg body weight) and the pathological process under consideration.

## Effects due to the Antibody Binding Portion of Immunoglobulin G

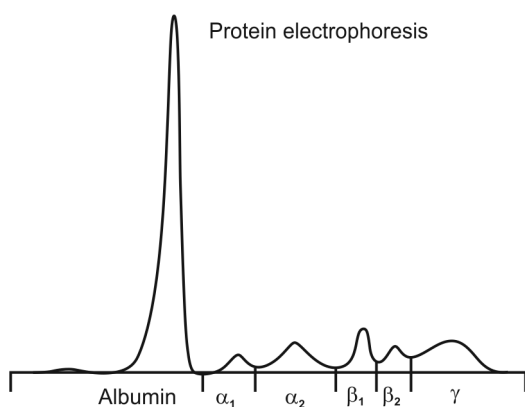
Even though commercially available IVIG preparations are known to have significant batch-to-batch variations of pathogen-specific antibodies, the large donor pool allows the neutralization of a wide range of pathogens including superantigens. In vitro studies have shown that IVIG has significant inhibitory effects on mitogen induced T-cell proliferation, but more when the IgG is intact with both complement binding Fc and F(ab')<sub>2</sub> portions. Laboratory studies have shown that IVIG has the ability to suppress the proliferation of antigen-specific T-cells without inducing apoptosis, a mechanism thought to be important in ameliorating antigen-dependent and antigen-independent inflammatory processes in autoimmune conditions. IVIG contains Fas-blocking antibodies reducing keratinocyte death in toxic epidermal necrolysis.

As the IgG in IVIG is derived from a donor pool, it was thought to be an *end product*, but study into the in vitro differentiation of dendritic cells with IVIG from patients with X-linked agammaglobulinemia (XLA) who lack B-cells and antibodies proved that it contains germ line encoded natural IgG antibodies (i.e., can be generated in the absence of infection or vaccination). Dendritic cell differentiation is impaired in XLA, and the defect was reversed by natural antibodies (in the IVIG) reactive with CD40. Furthermore, anti-idiotypic antibodies in IVIG possibly play a role in the treatment of immune thrombocytopenic purpura (ITP).

**Table 1** Uses of intravenous immunoglobulin in pediatric practice

Immunology	Hematology	Dermatology	Neurology	Rheumatology and others
Primary antibody deficiency (XLA, CVID, HIGM, WAS and others)	Immune thrombocytopenic purpura	Kawasaki disease	Guillain-Barré syndrome	Systemic lupus erythematosus
Severe combined immunodeficiency	Neonatal allo (iso) immune thrombocytopenia	Blistering disorders	Childhood myasthenia gravis (myasthenic crisis, or before thymectomy)	Systemic onset JRA
Post-HSCT	Postbone marrow transplant	DRESS syndrome		Pediatric HIV infection
	Autoimmune neutropenia			Premature neonates
	Autoimmune hemolytic anemia			Autoimmune uveitis
	Parvovirus-B19 associated aplasia			Burn patients
	Hemophagocytic lymphohistiocytosis			

Abbreviations: XLA, X-linked agammaglobulinemia; CVID, common variable immunodeficiency; HIGM, hyper-IgM syndrome; HSCT, hematopoietic stem cell transplantation; JRA, juvenile rheumatoid arthritis; HIV, human immunodeficiency virus; WAS, Wiskott-Aldrich syndrome.



**Figure 1** Electropherogram showing peaks of different plasma proteins including immunoglobulins (gamma portion, extreme right)

### Effects of Intravenous Immunoglobulin due to Binding to Fc Receptor

The binding of IgG Fc to the only inhibitory Fc receptor (FcγRIIb) and the activating (FcγRI and FcγRIII) Fc receptors exerts several effects. IVIG competitively binds to FcR on macrophages in the liver and spleen and this is the postulated mechanism behind clearance of cells in autoimmune cytopenia. Binding of IVIG to the inhibitory receptor FcγRIIb prevents phagocytosis. Ig therapy induces the proinflammatory cytokines interferon gamma (IFN-γ), interleukin-6 (IL-6) and IL-1Rα (may be up to 1,000 fold), while IL-1 and IL-2 are downregulated by IVIG. However, this is always not the case as evident in children with ITP who go into remission; IVIG therapy induces the anti-inflammatory T helper cell (Th2) cytokines. This may be due to: (1) differential control of FcR expression, such as cross-linking of FcRI on macrophages, that leads to (2) downregulation of IL-12 production and hence of Th1 cytokines.

### Effects of Intravenous Immunoglobulin due to Complement-Fc Binding

Intravenous immunoglobulin modulates complement activity, as seen in the clinical response to IVIG in patients with dermatomyositis, a complement-mediated microangiopathy. IVIG also activates the classical and alternate pathway, as antibodies do; however, high-dose IVIG is able to *breakdown* immune complexes thus preventing further complement-mediated amplification.

### Antibodies against Soluble and Membrane Molecules

Intravenous immunoglobulin preparations contain cytokines, cytokine inhibitors, soluble CD4 including major histocompatibility complex class II molecules. The various stabilizing agents used such as the sugars maltose and sucrose can also exert an effect that can inhibit in vitro mitogen responses [such as phytohemagglutinin (PHA)—and to a lesser extent, phorbol myristate acetate (PMA)-induced proliferative responses] but the clinical effect appears minimal.

### Intravenous Immunoglobulin Expands Regulatory T-cells Population

A special subpopulation of T-cells that suppress activation of the immune system and maintain tolerance to self-antigens has been extensively characterized. The thymus produces these *self-check* T-cells that can be CD8+ or CD4+CD25+Foxp3+ regulatory

T-cells (also referred to as the *naturally occurring* Tregs). Treg cells produce the immunosuppressive cytokines transforming growth factor beta (TGF-β) and IL-10, which provides an explanation of their function in preventing autoimmunity. Studies have shown that IVIG modulates various myeloid and lymphoid cell populations. High-dose IVIG in autoimmune disease induces a down-modulation of monocyte-derived dendritic cells and expression of co-stimulatory molecules, which in turn prevents autoreactive T-cell proliferation. Experiments have shown that prophylactic infusion of IVIG prevented the development of experimental autoimmune encephalomyelitis, an accepted animal model for multiple sclerosis (MS). The protection was associated with peripheral increase in Tregs' number and function. Other investigators have also shown that IVIG inhibited expression of adhesion molecules on dendritic cells that prevented relapses of MS.

### Differential Effects of Intravenous Immunoglobulin due to IgG Glycosylation Status

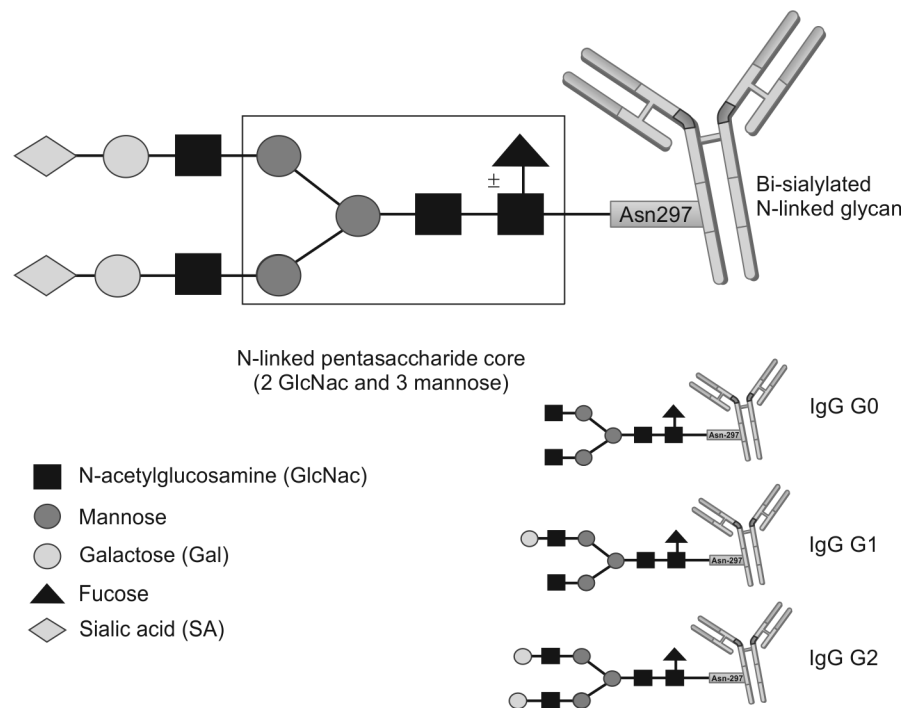
G Bock and S Harnett in their book "*Carbohydrate recognition in cellular function*" (John Wiley and Sons, 1989) had commented that "...while the functions of DNA and proteins are generally known... it is much less clear what carbohydrates do". This holds true in most aspects of medicine even today. The major serum Ig, IgG, is a glycoprotein and the constant domains of the heavy chain (Fc portion) undergo modification at a single site (Asn297) by covalent bonds with carbohydrates (N-linked glycosylation). Over 30 different glycans (fucose, galactose, sialic acid) have been detected at this site (**Fig. 2**). Glycosylation of the Fc portion of IgG is considered to be essential in the maintenance of an open conformation of the heavy chains to engage specific FcγR. Disruption of glycosylation of Fc region disrupts several effector functions and results in increased agalactosylated IgG levels (G0 glycoform), which enhance immune complex formation in rheumatoid arthritis and are associated with various autoimmune diseases. The sialylation status of IgG in IVIG remains unknown in commercial Ig preparations, and is theoretically plausible that a low fraction is fully glycosylated that can engage inhibitory FcR, given the requirement of high doses to treat autoimmune diseases like cytopenia (ITP, autoimmune neutropenia).

## MAJOR CLINICAL INDICATIONS OF INTRAVENOUS IMMUNOGLOBULIN

### Primary Immunodeficiency Disorders

The advent of IVIG (intravenous) in the 1970s paved the way to the first major randomized trials of Ig replacement therapy and showed that IVIG was not only as good but perhaps superior to intramuscular immunoglobulin (IMIG) in reducing infection frequency in primary antibody disorders. The pros were quite obvious: use of relatively small doses of IVIG at 0.15 g/kg were effective; significantly less painful than IMIG. Clinical studies by various groups established the concept of *trough IgG* and that maintenance of a trough serum IgG level in excess of 5 g/L using doses of 0.6 g/kg (600 mg/kg) resulted in (1) greater reduction in infections; (2) significant improvement in spirometric indices compared to those patients who received 0.2 g/kg and (3) significantly better quality of life indices.

It is now universally accepted amongst clinical immunologists that trough IgG levels should definitely be maintained within the age matched normal reference range for patients with antibody deficiency with individual patients benefiting from higher through levels (sometimes > 8 g/L). Most centers use 0.4–0.6 g/kg (400–600 mg/kg) of IVIG every 21–28 days and aim for a trough



**Figure 2** The different sugar moieties on the IgG molecule

IgG level more than 5 g/L. Several studies have documented decrease in incidence of pneumonias in children with XLA and common variable immunodeficiency once IVIG is commenced. IVIG therapy, however, does not lead to reversal of lung pathology such as bronchiectasis despite persistent trough IgG more than 5 g/L, suggesting that disturbance of the immune system needs to be checked in certain primary or acquired antibody disorders than simply replacing the *missing* IgG.

### Immune Thrombocytopenic Purpura

Immune thrombocytopenia is characterized by thrombocytopenia, increased bone marrow megakaryocytes and reduced platelet survival. The first-line of treatment for children with ITP is a short course of corticosteroids failing which a single dose of IVIG (0.8–1.0 g/kg) should be used. In some patients, IVIG can be used instead of corticosteroids (Grade IV evidence). There is no evidence to support using corticosteroids for longer courses given the multiple complications associated with them. Anti-D may be considered for first-line therapy in Rh+ nonsplenectomized children with recognition of the risks such as active bleeding or in those with evidence of autoimmune hemolysis, where anti-D is contraindicated.

### Kawasaki Disease

Intravenous immunoglobulin together with high-dose aspirin is an established first-line therapy for acute Kawasaki disease (KD). The most important therapeutic benefit of high-dose IVIG (2 g/kg) lies in the prevention of development of coronary artery aneurysms, from 20% to 25% in untreated KD to less than 5% after IVIG therapy. **Table 2** provides a scoring system to judge efficacy of IVIG given during the acute phase.

### Bone Marrow Transplantation

Intravenous immunoglobulin has been shown to be effective in young bone marrow transplant patients (age > 20 years) in the first 100 days post-transplant for the prevention of systemic and local infections, interstitial pneumonia of infectious and

**Table 2** Harada Scoring system to predict response to IVIG in Kawasaki disease (given during first 9 days of onset of disease)

Predictor	Value
White cell count	$\geq 12 \times 10^9/\text{L}$
Platelet count	$\leq 3.5 \times 10^9/\text{L}$
C-reactive protein	$\geq 40 \text{ mg/L}$
Hematocrit	$< 35\%$
Albumin	$< 35 \text{ g/L}$
Age	$\leq 12 \text{ months}$
Sex	Male

Score 1 for each category; IVIG indicated if Score  $\geq 4$  in the acute phase; IVIG not indicated if Score  $< 3$ .

idiopathic etiologies [product insert for some brands of IVIG also recommends checking acid-base balance while use of product due to possibly presence of sugars (maltose) as stabilizer in critical bone marrow transplant patients].

### Human Immunodeficiency Virus Infection

Monthly courses of IVIG treatment was shown to significantly (1) decrease the frequency of serious and minor bacterial infections (laboratory-proven and clinically diagnosed); (2) frequency of hospitalizations; (3) increased the time patients were free of serious bacterial infection and (4) preventing primary bacteremia (including *Streptococcus pneumoniae* bacteremia) including acute pneumonias.

### SIDE EFFECTS OF INTRAVENOUS IMMUNOGLOBULIN

The side effects can be broadly classified into infusion-related side effects, transfusion transmitted infections and physiological effects of increasing serum IgG levels (usually related to high-dose IVIG therapy, **Table 3**). Close monitoring is required especially for

**Table 3** Side effects of immunoglobulin therapy

Immediate reactions—usually infusion related	Mild to moderate reactions: Headache, chill, nausea, backache, muscle pain (up to 1% of reactions); majority of cases this is related to the rate or speed of infusion <i>Severe:</i> Anaphylaxis with IVIG products; the premise with most of these are due to anti-IgA antibodies in IgA-deficient patients and IgA levels in IVIG products
Intravenous immunoglobulin transfusion-related infections	<i>Hepatitis C:</i> Several outbreaks to date in medical literature; this led to the additional antiviral steps in the manufacturing process (last known outbreak in 2001) <i>Prions:</i> No documented case of clear cut transmission; prion filtration step also introduced by some manufacturers
Effects of rise in serum IgG levels (usually related to high-dose IVIG)	<i>Renal:</i> Renal impairment (reversible in most cases, some related to maltose in products) <i>Hematological:</i> Thromboses, hemolysis, cytopenia (neutropenia) <i>Neurological:</i> Acute aseptic meningitis <i>NB:</i> Assure that patients are not volume depleted prior to the initiation of the infusion of IVIG <i>Dermatological:</i> Eczema, urticaria, erythema multiforme, vasculitis
Undesirable effects	Antibodies in IVIG preparations may interfere with the response to live viral vaccines such as measles, mumps and rubella. Therefore, use of such vaccines should be deferred until approximately 6 months after IVIG administration Response to BCG vaccine is not affected by IVIG therapy

Abbreviations: IVIG, intravenous immunoglobulin; BCG, Bacillus Calmette-Guérin.

the first few doses when patients develop chills and rigor, which becomes less common as they progress through several infusions. Intercurrent infections must always be treated with antibiotics and patients examined before commencing infusions to avoid wastage of product. A checklist of training needs must be met before patients can be considered safe for administering their infusions at home.

### Infusion-related Side Effects

Common reactions associated with infusions are immediate and typically include headaches, flushing, chills, myalgia, arthralgia, nausea/vomiting and abdominal pain. Moderate to severe reactions are uncommon and usually seen with initial infusions that include chest tightness, hives, including (rarely) anaphylactic reactions in some patients. Immediate reactions need to be recognized as minor ones can be avoided or diminished by lowering the infusion rate or stopping the infusion for some time. Patients should be treated with oral paracetamol, antihistamine and the infusion restarted or continued at a slow rate. Severe reactions will require immediate cessation of infusion, and treatment with hydrocortisone, adrenaline, bronchodilators and antihistamines. After a severe reaction, switching to a different brand of IVIG should be considered.

### Side Effects of High-dose Intravenous Immunoglobulin Therapy

A serious and late reaction that is almost always seen with high-dose IVIG is the aseptic meningitis syndrome. This usually begins within several hours to 2 days following IVIG and is characterized by severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid studies are recommended and frequently positive with pleocytosis up to several thousand cells per mm<sup>3</sup> (granulocytes), and elevated protein levels up to several hundred mg/dL.

### Intravenous Immunoglobulin-induced Cytopenia including Neutropenia

Intravenous immunoglobulin products from various manufacturers when used in high doses (2 g/kg) have been reported to induce

neutropenia, and reports including a retrospective comparative cohort study on children with ITP that showed IVIG therapy resulted in significantly more neutropenic episodes (18 of 64 IVIG courses, 28%) than anti-D therapy (0 of 64, 0%). The reassuring fact is that IVIG-induced neutropenia is transient (counts return to normal within 2 weeks) and apart from oral ulcers, no severe infectious complications have been reported to occur during the episode.

The autoantibodies in IVIG preparations that potentially lead to neutropenia are: (1) antineutrophil antibodies, atypical antineutrophil cytoplasmic antibodies (ANCA) and antiSiglec-9 (sialic acid-binding Ig-like lectin, Siglec) antibodies. Others have suggested that increase in leukocyte aggregation by IVIG leads to neutropenia. It is possible that IVIG preparations bind to neutrophils in an FcγR-dependent manner leading to neutropenia, but findings of significant titers of atypical ANCAs in various IVIG batches that were capable of inducing peroxide generation in TNFα-primed human neutrophils in FcγR-independent manner also merit consideration of whether this can lead to neutropenia.

### Intrinsic Differences Exist between Commercial IVIG Preparations

Commercially available IVIG preparations do not provide information on the glycosylation status of the IgG in the product. Even when concentration of soluble molecules, such as CD4 or IgA levels, are concerned, there are differences within products (**Table 4**), although why side effects are observed in IgA-deficient patients with a low level IgA in an IVIG product, versus no clinically significant effects in a very low versus low level IgA product are not known, suggests other mechanisms may be at play. It would be interesting to note that perhaps contain only a small fraction of the IgG in IVIG products is sialylated IgG (**Fig. 2**), and thus high doses are required to have a clinically significant immunomodulatory effect when used in autoimmune diseases like ITP, *Guillain-Barré syndrome* and myasthenic crisis. Significant differences observed in Fc sialylation between commercial IVIG preparations may result during the purification process and antiviral steps employed (pH 4/pepsin treatment, caprylate or chromatography, SD treatment) which differ between manufacturers (**Table 4**).



**Table 4** Comparison of various commercial immunoglobulin products

Product	Manufacturer	Stabilizers and pH	Viral inactivation steps
Gamma IV (5% lyophilized)	Bharat Serum and Vaccines Limited, India	9–11% maltose pH 4–5	Pasteurization, solvent/detergent, PEG precipitation, pH 4
Octagam (IV, 5%)	Octapharma, UK	100 mg/mL maltose, Triton X-100, TNBP (pH 5.1–6.0)	Solvent/detergent, pH 4 incubation, ultrafiltration, chromatography
Gamimune N (IV, 10%)	Talecris Biotherapeutics Inc., Research Triangle Park, NC 27709 USA	0.16–0.24 M glycine Buffer capacity 35 mEq/L; osmolality is 274 mOsmol/kg solvent (pH 4.25)	Solvent/detergent, pH 4 incubation, ultrafiltration, chromatography
Flebogamma (IV, 5%)	Grifols, Spain	5% D-sorbitol, PEG (pH 5.0–6.0)	Pasteurization, solvent/detergent, double sequential nanofiltration, fraction precipitation, PEG precipitation, pH 4
Sandoglobulin® NF Liquid (IV, 12%)	CSL Behring, Switzerland	L-proline, L-isoleucine, nicotinamide	Depth filtration, pH 4/pepsin, nanofiltration
Subcuvia (SC, 16%)	Baxter AG, Industriestrasse 67, A-1221 Vienna	Glycine, sodium chloride	Ultrafiltration, chromatography, solvent/detergent
Subgam® (SC, 14–18%)	BPL Bio Products Laboratory, Elstree, Hertfordshire, UK	Sodium acetate trihydrate, sodium chloride, glycine, sodium hydroxide, polysorbate 80, HCl for pH adjustment	Ion exchange chromatography, solvent/detergent (6 hr at 37°C), low pH incubation
Vivaglobin (SC, 16%)	CSL Behring, Switzerland	Glycine, sodium chloride, HCl, NaOH for pH adjustment (pH 6.4–7.2)	Depth filtration, pH 4/pepsin, nanofiltration

**Abbreviations:** IV, intravenous; SC, subcutaneous; PEG, polyethylene glycol; TNBP, tri-n-butyl phosphate [part of solvent/detergent (S/D) treatment process that is a mixture of TNBP and Triton X-100, highly effective against enveloped viruses]; treatment with pepsin at pH 4 rapidly inactivates lipid-enveloped viruses; cold ethanol fractionation (ethanol at low pH) is first step for all products and is virucidal (HIV).

### IN A NUTSHELL

1. Intravenous immunoglobulin is a blood product, and all precautions for safe use must be taken as per any blood product.
2. Intravenous immunoglobulin therapy has unequivocal role in the management of primary immunodeficiency disorders.
3. For some autoimmune diseases, especially KD, IVIG plays a crucial role and recommended as the first choice of treatment.
4. Serious reactions with IVIG can occur especially in high doses, but does not necessarily mean alternative products cannot be used.
5. All IVIG products are different, and it is recommended that named products are prescribed to patients to help in tracking transfusion transmitted diseases should they occur.

### MORE ON THIS TOPIC

- Aghamohammadi A, Moin M, Farhodi A, et al. Efficacy of intravenous immunoglobulin on the prevention of pneumonia in patients with agammaglobulinemia. *FEMS Immunol Med Microbiol*. 2004;40:113-8.
- Ballow M. Optimizing immunoglobulin treatment for patients with primary immunodeficiency disease to prevent pneumonia and infection incidence: review of the current data. *Ann Allergy Asthma Immunol*. 2013;111:S2-5.

- Bayry J, Lacroix-Desmazes S, Donkova-Petrini V, et al. Natural antibodies sustain differentiation and maturation of human dendritic cells. *Proc Natl Acad Sci USA*. 2004;101:14210-5.
- Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J Allergy Clin Immunol*. 2002;109:1001-4.
- Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. *N Engl J Med*. 2012;367:2015-25.
- Imbach P, Barandun S, d'Apuzzo V, et al. High-dose intravenous gamma-globulin for idiopathic thrombocytopenic purpura in childhood. *Lancet*. 1981;1:1228-31.
- Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. *Clin Exp Immunol*. 2005;142:1-11.
- Khan S, Doré PC, Sewell WA. Intravenous immunoglobulin-induced neutropenia. *Pediatr Allergy Immunol*. 2010;21:892-3.
- Lassiter HA, Bibb KW, Bertolone SJ, et al. Neonatal immune neutropenia following the administration of intravenous immune globulin. *Am J Pediatr Hematol Oncol*. 1993;15:120-3.
- Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117:4190-207.
- Oates-Whitehead RM, Baumer JH, Haines L, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev*. 2003;CD004000.
- Provan D, Chapel HM, Sewell WA, et al. Prescribing intravenous immunoglobulin: summary of Department of Health guidelines. *BMJ*. 2008;337:a1831.

## Chapter 4.6

# Approach to a Child with Allergic Disorder

H Paramesh

In the year 1819, John Bostock presented his paper on allergic rhinitis which took him 9 years to collect 28 cases. He was the first one to state that in mid-June patients feel itching of eyes (conjunctivitis) followed by sneezing, runny nose (allergic rhinitis) later leads to chest tightness (asthma). Now we are recognizing it as united airway disease.

The development of allergic inflammatory responses starting with intrauterine environment extends through the early years of life. Although one has allergic traits, the final expression of an individual's atopic background is highly influenced by various environmental exposures. The important environmental influences are the timing, dose of exposures, early infections, home environment and exposure to environmental pollution. Understanding the natural history of allergic diseases and the interventions that may modify the development of allergy is essential in determining prognosis and providing advice for children at risk for allergic sensitization and disease. This chapter will focus on clinical and laboratory evaluation and basic principles of management of children with common allergic disorders.

## PATHOPHYSIOLOGY

There are many types of cells, which play different roles in induction of allergy.

- **Epithelial cells** They form the major barrier to the outside world.
- **Goblet and mucus glands** Secrete mucus, which forms a layer above the epithelium so that the allergen or germs will slide away.
- **Dendritic cells** Act like immigration officers and make sure the protein, bacteria or parasites cannot pass through undetected. They break the foreign protein into small fragments called epitopes and present the same to T-lymphocytes to decide what action to be taken.
- **T-lymphocytes** Are the brains of the immune system and they decode the further course of action on allergen protein.

- **B-lymphocytes** Produce antibodies and arm the mast cells for activation.
- **Mast cells** Muscle man of immune system, produce histamine and other aggressive chemicals. In addition, they signal other cells for help, the eosinophils. Usually mast cells are beneath the epithelium but when an allergic attack begins they start migrating up between the epithelial cells.
- **Eosinophils** These cells produce potent proteins like major basic protein, cationic protein, eosinophil derived neurotoxin and eosinophil peroxidase. These proteins are toxic to parasites and also attack the epithelium and sensory nerves causing hyper-response to nonallergic stimuli.
- **Neutrophils** It is a primary emergency cell of the immune system for any infection.

When sensitized mast cell is re-exposed to allergen there is an early phase reaction in few minutes where degranulation occurs, releasing preformed histamine and proteases. Mediators like cysteinyl leukotrienes prostaglandins, platelet activating factor, bradykinin, interleukins, tumor necrosis factor, granulocyte-monocyte colony-stimulating factor (GM-CSF) are produced causing effects on blood vessels and nerve. In the late phase response which occurs in 2–8 hours postallergen exposure, the chemokines released by mast cells attract eosinophil, basophil, monocyte, lymphocytes causing infiltration and inflammation. The cascade of allergic reaction is shown in **Figure 1**.

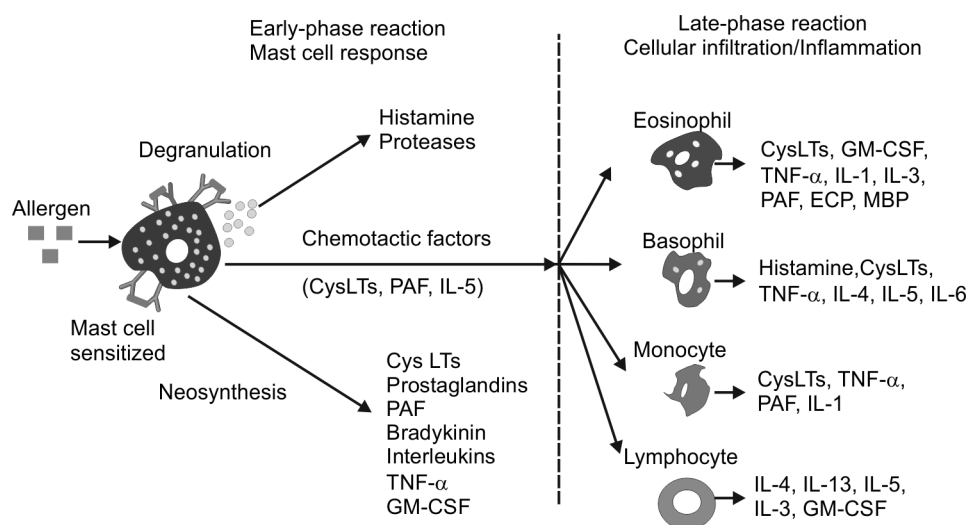
## CLINICAL EVALUATION

### Atopic Dermatitis

The clinician has to suspect atopic dermatitis with six basic criteria: History of flexural dermatitis; onset under 2 years of age; presence of itching rashes on facial, extensor surface involvement in infancy, flexural area in childhood and adolescents; personal and family history of atopy; history of dry skin; and visible flexural dermatitis with lichenification. The diagnosis of atopic dermatitis cannot be made without the history of itching. The itching intensifies in the evening and disrupts the sleep.

### Allergic Rhinitis

Allergic rhinitis is a chronic inflammatory disease of the upper airway. Due to the poor perception of symptoms and severity



**Figure 1** The allergic cascade

**Abbreviations:** CysLTs, cysteinyl leukotrienes; PAF, platelet activating factor; IL, interleukin; TNF, tumor necrosis factor; GM-CSF, granulocyte-monocyte colony-stimulating factor; ECP, eosinophil cationic protein; MBP, major basic protein.

by the doctor and patients, it is often treated as recurrent upper respiratory infection. In allergic rhinitis, the four major symptoms are sneezing, itching, rhinorrhea and nasal congestion. Any two or more of these symptoms for more than 1 hour for most of the days is diagnostic of allergic rhinitis. In addition, ask for nasal sniffing, lacrimation, headache, palatal pruritus, snoring, mouth breathing, bruxism and sleep difficulty.

### Asthma

Diagnosis of asthma in under 5-year-old is a challenge, since there is no objective supporting evidence. Usual symptoms consist of recurrent or persistent wheeze, cough, dyspnea with chest tightness, worsening at night and early morning, exacerbation with viral infection and on exposure to allergens, weather changes and with physical and emotional stress along with personal and family history of atopy. In a child in whom lung function shows more than 12% improvement after administration of nebulized bronchodilators, is an objective supportive evidence for diagnosis of asthma.

A few pointers of allergic airway diseases are listed in **Box 1**.

#### BOX 1 When to suspect allergic airway disease?

- Family history of atopy
- History of other atopic features in the child
- Afebrile episodes of respiratory distress
- Recurrence with complete clearance in between
- Sneezing with no purulent discharges (unless with secondary infection)
- Do not respond to antibiotics
- Responds to antihistamines and bronchodilators
- Usually same site involved, like middle lobe atelectasis, in asthmatics under the age of 5 years due to lack of lung collaterals
- These children have lymph nodes unlike in immune deficiency diseases.
- They have seasonal pattern.

### LABORATORY EVALUATION

Laboratory evaluation is aimed to confirm atopy, measure and assess the degree of airway obstruction variability and reversibility, and to look for features of inflammation and hypersensitivity.

### Tests to Confirm Allergic Background

Eosinophilia ( $> 4\%$ ) is suggestive; however worm infestations so common in our country can also cause eosinophilia. Absolute eosinophilia more than 1,500/cu mm or eosinophilia of 20% is suggestive of a systemic problem other than allergy. Nasal smear eosinophilia more than 5% is suggestive of allergic rhinitis. The nasal mucosal pH is alkaline in allergy but it is acidic with infective rhinitis.

### Tests to Measure Airway Obstruction and Reversibility

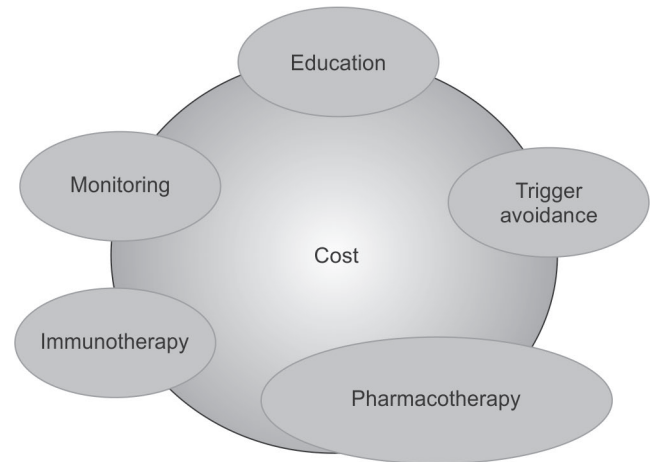
In allergic rhinitis, one can measure respiratory airflow and assess nasal airway resistance and their response to treatment. Spirometry can help diagnose airway obstruction in large, medium and small airways and can assess the severity. Asthmatics have low forced expiratory volume in 1 second ( $FEV_1$ ) and low forced vital capacity (FVC) and  $FEV_1$  ratio and low forced expiratory flow (FEF). Peak expiratory flow rate measurement is simple, quick and less expensive. It helps in finding response to bronchodilators and is beneficial for follow-up cases and it is a must instruments in the clinic. It measures large and medium airway dysfunction and is effort dependent. Impulse oscillometry is noneffort dependent measure of central and peripheral airway disease in all age group. Fractional exhaled nitric oxide (FeNO) measuring is a promising test but needs standardization. Other tests for bronchial hypersensitivity include *challenge tests* with histamine, methacholine and exercise.

### Tests to Confirm Atopy

These have been described in Chapter 2 of this Section and include measurement of serum immunoglobulin E (IgE), skin prick test, patch test, and radioallergosorbent test.

### MANAGEMENT OF ALLERGIC DISEASE

Management involves education, avoiding allergens and irritants, pharmacotherapy, immunotherapy and regular follow-up (**Fig. 2**). Specific drug management of individual disorders is detailed in respective chapters.



**Figure 2** Management issues in allergic disorders

### Immunotherapy

Immunotherapy is an effective mode of therapy in allergic rhinitis and asthma in reducing the sensitization to new allergens and preventing the allergic march from allergic rhinitis to asthma. The effect persists even after discontinuation of therapy for 5 years and may help in preventing airway remodeling. Sublingual route is the most preferred route as it is painless, child friendly and carried out at home with allergists monitoring.

### Anti-IgE Therapy

Omalizumab is a treatment option in patients with elevated specific IgE level. It down regulates the number of IgE receptors and tissue eosinophils and mast cells. It is recommended in children above 5 years. Only drawback is its cost and its potential risk to increase helminthic infections.

### Parental Education

It should be stressed that allergy is a noncontagious disease, does not spread to others; the main pathology is a chronic inflammation of skin or airways. Controller medicines should be used for a long time. Parents need to identify the triggers and remove them from the immediate environment of the child. The home environment should be made smoke free. Pets are not a major concern but they should not share the bedroom with children. For better control of the disease better compliance of medicines with proper technique is essential. Always involve grandparents in our culture along with parents for better compliance.

### Follow-up

Monitoring the asthma and allergic rhinitis children is very important in terms of developing a teamwork and gaining confidence and trust in disease control is assessed at regular intervals of 3 months in a stable patient and always assess the technique of inhalation, dosage, quality of life, sleep and activity. The dose has to be reduced by 25–50% every 3 months and the last drug used should be the first one to

go. Always infuse confidence, trust and positive approach to life, and plan according to social economic determinants of family.

### IN A NUTSHELL

1. Allergic diseases are increasing globally more so in developing countries.
2. Rapid urbanization is one of the major contributing factors.
3. Urban children suffer more from allergic manifestations than rural children.
4. Allergy is a chronic inflammation affecting skin and respiratory system.
5. Allergy is an interaction of genetics and the environment.
6. Immunotherapy in pediatric age group does help in preventing *allergic march*.
7. Encourage traditional food habits, good cross ventilated houses to build to our needs and yoga exercise.

### MORE ON THIS TOPIC

Paramesh H. Allergic diseases in children. In: Parathasarathy A. Case scenarios: Pediatric and Adolescent Practice. New Delhi: Jaypee; 2014. pp. 598-611.

Paramesh H, Cherian E. Pediatric allergies—epidemiology and management. In: Shaikh WA. Principles and Practice of Tropical Allergy and Asthma. Mumbai: Vikas Medical Publishers; 2006. pp. 603-14.

Paramesh H. Outdoor and indoor air pollution on respiratory health. In: Shankar PS. Advances in Respiratory Medicine. Mumbai: Vishwas Printers; 2013. pp. 1-10.

Wallenberg A, Schnopp C. Evolution of conventional therapy in atopic dermatitis. Immunol Allergy Clin North Am. 2010;30:351-68.



# Section 5 FLUID AND ELECTROLYTES

Section Editor Rakesh Lodha

## Chapter 5.1 Body Fluids

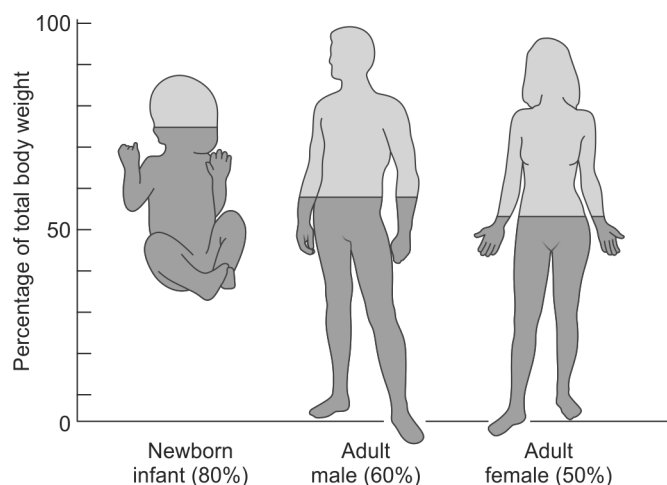
Raghuvamsi Chaitra, Suchitra Ranjit

The homeostasis of fluid in the human body remains remarkably constant in a wide variety of conditions. The regulation is complex and is essential for optimal functioning of every organ system in the body. In health, water homeostasis is determined by the intake and output of water and its distribution in the body. However, during illnesses this balance is lost leading to deterioration and numerous complications.

### FLUID DISTRIBUTION

In health, water comprises approximately 60% of the total body weight (BW) in young adult males and about 50% in a young adult female. Since adipose tissue has less water, an obese person will have proportionately lower body water content in comparison to a lean individual. Neonates have water comprising up to 80% of BW and this gradually decreases with age (**Fig. 1**). Of the total body water, two-third (40% of BW) is intracellular fluid (ICF) and one-third (20% of BW) is extracellular fluid (ECF) (**Fig. 2**).

The ECF compartment is divided into the interstitial fluid (fluid in between tissue cells), the blood (plasma) and another small compartment of fluid known as transcellular fluid. This compartment includes fluid in the synovial, peritoneal, pericardial, and intraocular spaces, as well as the cerebrospinal fluid; it is usually considered to be a specialized type of ECF.



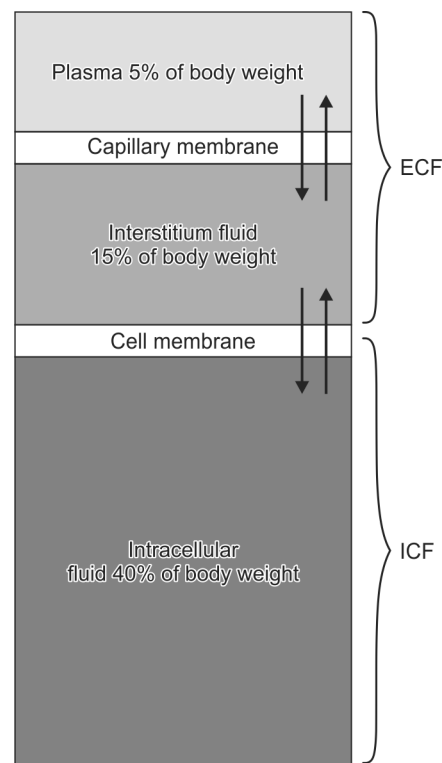
**Figure 1** Distribution of body water. Shaded area represents amount of body water

### Constituents of Extracellular and Intracellular Fluids

Both the ECF and ICF contain differing concentrations of electrically charged ions. The major cation (positively charged) in the ECF is sodium and potassium is the major cation in the ICF. The major negatively charged anion in the ECF is chloride, while phosphate and proteins comprise the anions in the ICF (**Table 1**).

A *solvent* is a liquid, solid, or gas into which another solid, liquid, or gaseous substance can dissolve (the *solute*). The result is a *solution*, which is in the same physical state as the solvent, for example, sugar in water. To form a solution, the solvent and solute undergo a reaction with breaking and forming of physical bonds. This is contrasted with a mixture where no physical or chemical reaction occurs when one substance is added to another, and the two remain separate.

Within the human body, fluid has a dual role as it is simultaneously a solution and a mixture at the same time. The solvent is water; the solutes are many including sodium, potassium, and chloride ions, other solute molecules, e.g., sugar and urea, and also gases including oxygen and carbon dioxide. Intracellular and ECF contains proteins, while the intravascular fluid contains



**Figure 2** Body fluid compartments  
Abbreviations: ECF, extracellular fluid; ICF, intracellular fluid.

**Table 1** Osmolar substances in extracellular and intracellular fluids

	Plasma (mOsm/L H <sub>2</sub> O)	Interstitial fluid (mOsm/L H <sub>2</sub> O)	Intracellular fluid (mOsm/L H <sub>2</sub> O)
Sodium	142	139	14
Potassium	4.2	4.0	140
Calcium	1.3	1.2	0
Magnesium	0.8	0.7	20
Bicarbonate	108	108	4
Amino acids	2	2	8
Lactate	1.2	1.2	1.5
Glucose	5.6	5.6	
Urea	4	4	4

Source: Data from Guyton and Hall, Text book of Medical Physiology, 11th edition. Philadelphia, PA, USA: Elsevier Saunders; 2006.

proteins, fats, and blood cells making these fluids mixtures as well as solutions.

### Principles of Regulation of Fluid Exchange and Osmotic Equilibrium between ICF and ECF

**Osmolarity and osmolality** Osmoles are units used to express the osmotic activity of solutes in body fluids such that one mole ( $6.02 \times 10^{23}$  molecules) of solute particles has osmotic activity equal to 1 Osmole/L of solution. One mole of glucose per liter of a solution has an osmolarity of 1 Osm/L while a molecule like NaCl, which dissociates into two ions, sodium and chloride, will have an osmolarity of 2 Osm/L in a solution containing 1 mol/L of NaCl. Since logistically, an osmole is too large a unit for expressing osmotic activity of solutes in the body fluids, the unit milliosmole (mOsm) (equals 1/1,000 osmole) is used.

**Osmolarity** is the number of osmoles of solute per unit volume of solution and is expressed as osmoles/L. Osmolality is the number of osmoles of solute per unit weight of solvent and is expressed as osmoles/kg. These terms are used to quantify how much of a solute is dissolved in a solution; the main difference is that when temperature changes, volumes (osmolarity) will change, but mass (osmolality) remains the same.

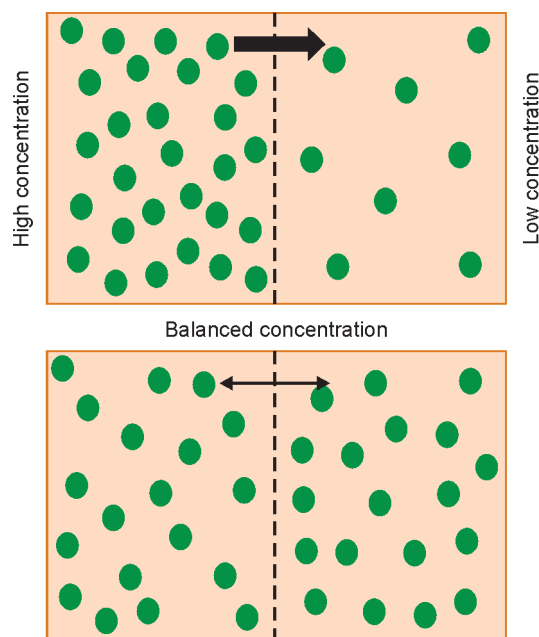
The osmolality of plasma may be estimated by summing the major solute particles in plasma, i.e., sodium, potassium and chloride ions, glucose, and urea. As sodium chloride and potassium chloride dissociate in a solution to form two ions each, the serum sodium and potassium ion concentrations are doubled when calculating serum osmolality.

$$\text{Plasma osmolality} = 2 * [(\text{Na} + \text{K})] + [\text{glucose}(\text{mg/dL})]/18 + [\text{BUN}(\text{mg/dL})]/2.8$$

Note: If blood urea nitrogen (BUN) is not available, use urea/6

**Tonicity** Tonicity differs from osmolality in that it is influenced only by the solutes which are unable to cross a semipermeable membrane separating two solutions. The tonicity of two solutions separated by a membrane can be described in relative terms depending on the concentration of solution, so that a solution may be as hypertonic, isotonic or hypotonic (higher, same or lower concentration respectively, of solute on one side compared to solute on the other side of the membrane).

**Diffusion** Rather than the movement of fluid, diffusion results in the movement of solutes and substances from an area of high concentration to one of low concentration (Fig. 3).



**Figure 3** Diffusion: Diffusion of molecules across a semipermeable membrane from an area of high concentration to an area of low concentration

Source: <https://www.moodle.kent.ac.uk/external/mod/book/tool/print/index.php?id=2396&chapterid=81>.

**Facilitated diffusion** The carrier molecules transport substances from high to low concentrations. This form of transport does not require energy (Fig. 4).

**Active transport** Here, substances move against concentration gradients, and the energy for this active transport is supplied by membrane ATP pumps (Fig. 5).

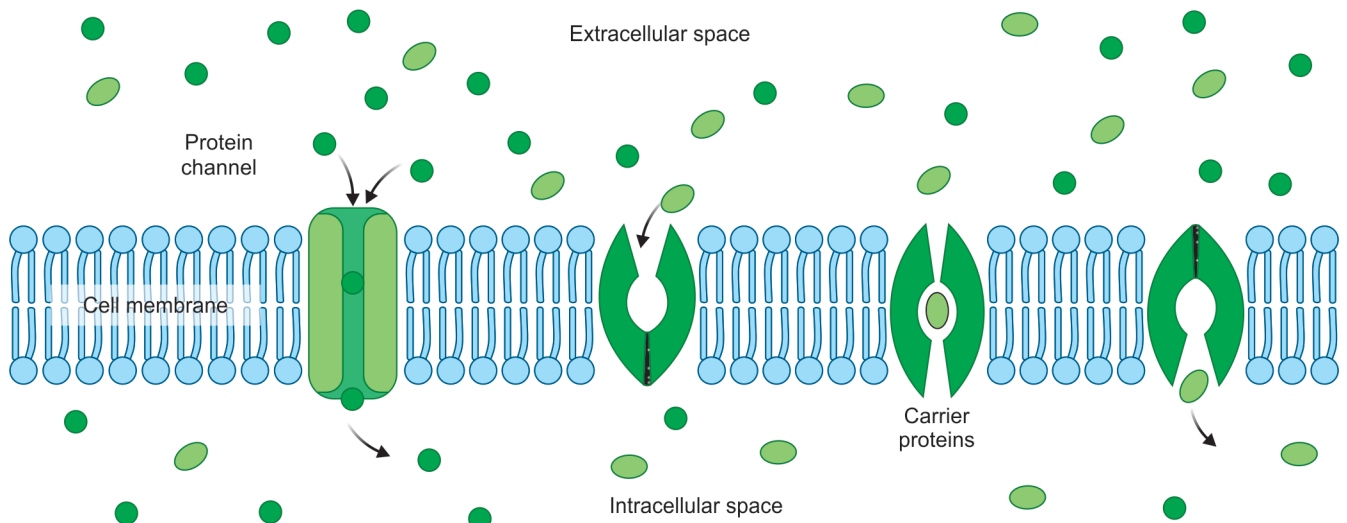
**Osmosis** This is the passive movement of water from a dilute solution (i.e., relatively hypotonic) to a more concentrated solution (i.e., relatively hypertonic) across a selectively permeable membrane. The permeability of the membrane is said to be selective as it permits free movement of water molecules from one side to the other but does not allow any solute particles to cross. For example, when NaCl is added to the ECF, water moves from ICF to ECF; this principle governs hypertonic saline treatment of patients with cerebral edema (Fig. 6).

**Oncotic pressure** Oncotic pressure is the osmotic pressure generated by large molecules (especially proteins) in solution.

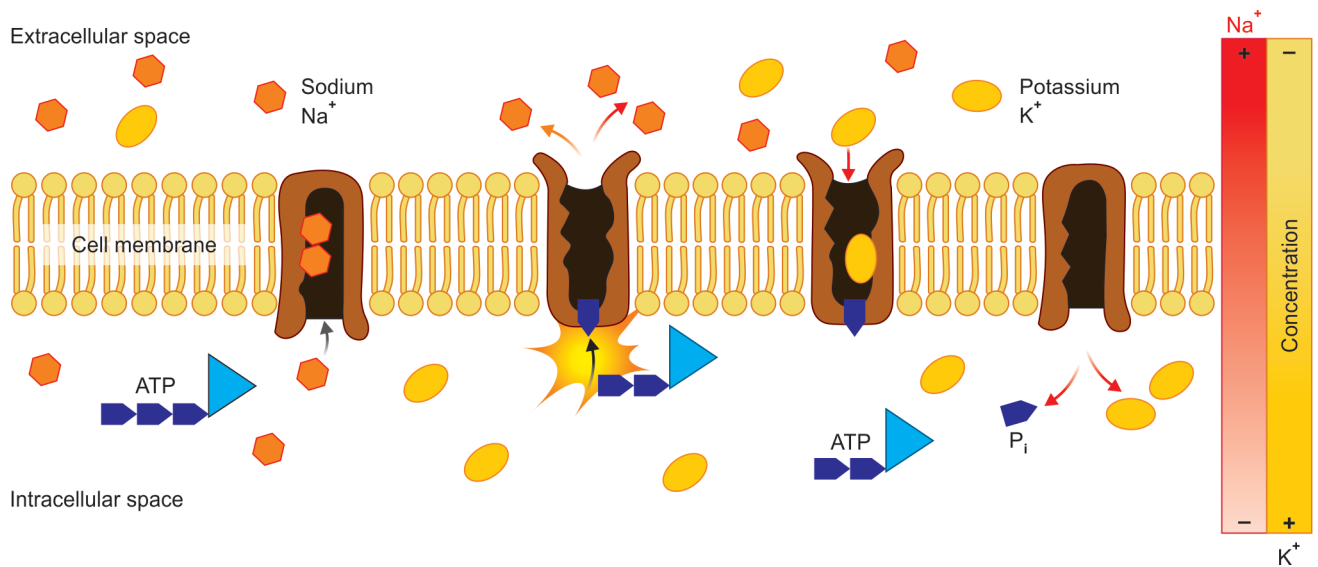
### What Regulates the Movement of Water Between Fluid Compartments?

Selectively permeable membranes separate the intravascular, interstitial, and ICF compartments from each other. The capillary wall separates the intravascular and interstitial compartments, while the ICF and ECF compartments are separated by the cell membrane. The two membranes have different properties (Fig. 2).

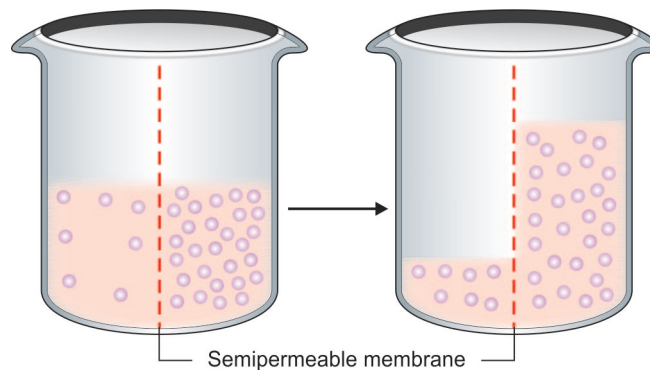
**Capillary wall** The movement of fluid across a capillary wall is passive and determined by filtration and passive diffusion. Filtration is determined by hydrostatic (blood pressure) and oncotic pressures, the well-known Starling forces. These Starling forces act to drive water out of the capillary into the interstitium and, in the process, passively drag dissolved solutes with it. Diffusion refers to the movement of solutes from an area of high concentration to an area of lower concentration. The water crosses the capillary wall via the gaps between cells or directly through the cell membrane.



**Figure 4** Facilitated diffusion: Transport substances from high to low concentrations by carrier proteins  
 Source: [http://www.en.wikipedia.org/wiki/File:Scheme\\_facilitated\\_diffusion\\_in\\_cell\\_membrane-en.svg](http://www.en.wikipedia.org/wiki/File:Scheme_facilitated_diffusion_in_cell_membrane-en.svg). Accessed October 21, 2014.



**Figure 5** Active transport of solute across the cell membrane against the concentration gradient using energy  
 Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate.  
 Source: [http://www.en.wikipedia.org/wiki/File:Scheme\\_sodium-potassium\\_pump-en.svg](http://www.en.wikipedia.org/wiki/File:Scheme_sodium-potassium_pump-en.svg)



**Figure 6** Osmosis: movement of water across a semipermeable membrane

**Cell membrane** The movement of most solute and water across this membrane occurs via transmembrane proteins or ion channels which provide different permeability to different solutes. In a steady state, the ICF and ECF are in osmotic equilibrium and hence, no water movement occurs.

In order for water to move between ECF and ICF, a difference in tonicity must exist between the two sides of the cell membrane. Any difference in extracellular or intracellular tonicity is due a change in the solute concentration in either fluid compartment. Water then moves by osmosis up a concentration gradient from a hypotonic to hypertonic compartment. The cell membrane is essentially impermeable to  $\text{Na}^+$  ions, and so the  $\text{Na}^+$  concentration in the ECF principally governs the distribution of water between ECF and ICF. The ECF  $\text{Na}^+$  concentration is controlled by various neuroendocrine controls via the kidneys. The net movement of fluid between the two compartments can occur in either direction and depends on the balance of various forces acting across the membrane.

## NORMAL DAILY INTAKE AND OUTPUT OF FLUID

To assure optimal functioning of the body systems, it is essential that the overall amount of body water remains constant. Appropriate distribution across all of the fluid compartments at all times is just as vital. This process whereby the body tries to ensure the correct fluid balance is maintained is called *homeostasis*. In health, as part of the body's normal function, water and electrolytes are continually being lost. These need to be replaced to maintain equilibrium. In certain situations, losses are increased, e.g., diarrhea, burns. Abnormal losses may also occur when fluid is abnormally distributed, resulting in too much in some or too little in the other body's fluid compartments, e.g., postoperatively or in sepsis. These fluid losses may be termed *sensible* meaning that it is easily seen and measured, e.g., urine output and losses from the gastrointestinal tract, while other fluid losses are often referred to as *insensible* meaning they are harder to see and measure, e.g., evaporative fluid loss from the skin and respiratory tract. Normal insensible fluid loss is 400 mL/m<sup>2</sup> of body surface area.

## Sweat

Sweating is centrally controlled by thermosensitive neurons located in the preoptic and anterior regions of the hypothalamus; this can be an important source of fluid loss as the rate of sweating can vary between 100 mL/day and 8,000 mL/day. Sweat is not pure water; it always contains a small amount (0.2–1%) of solute. At any given time, the actual electrolyte content of sweat varies depending on emotional state, diet, exercise, acclimatization, and some hereditary factors, e.g., cystic fibrosis. Sodium is the major electrolyte lost in sweat and losses can range from 5 mmol/day to 50 mmol/day (**Table 2**). Sweating is different from insensible loss from the skin; the latter is lost by evaporation which is pure water.

## Urine

The formation of urine is a complex process and occurs due to highly sophisticated mechanisms including glomerular filtration, tubular secretion and reabsorption. The volume and composition of urine can vary widely and depends principally on the intravascular fluid volume and composition as the state of kidney function. For a patient with normal hydration and kidney function, there is an obligatory volume of urine produced and electrolyte loss in a 24-hour-period. The obligatory loss is a result of the daily solute intake and metabolic waste products, e.g., urea, creatinine and drug metabolites, all of which increase ECF tonicity, and need to be excreted. For healthy patients with normal renal function urine osmolality can range from 50 mOsm/kg to 100 mOsm/kg H<sub>2</sub>O up to around 1,200 mOsm/kg H<sub>2</sub>O.

**Table 2** Electrolyte composition of various body fluids

Fluid	$\text{Na}^+$ (mEq/L)	$\text{K}^+$ (mEq/L)	$\text{Cl}^-$ (mEq/L)
Gastric	20–80	5–20	100–150
Pancreatic	120–140	5–15	90–120
Small bowel	100–140	5–15	90–130
Bile	120–140	5–15	80–120
Ileostomy	45–135	3–15	20–115
Diarrhea	10–90	10–80	10–110
Burns	140	5	110
Sweat			
Normal	10–30	3–10	10–35
Cystic fibrosis	50–130	5–25	50–110

Source: Data from Behrman RE, Kliegman RM, Jenson HB. Nelson Textbook of Pediatrics. 17th ed. Philadelphia: WB Saunders; 2003.

Alterations in the intravascular fluid volume and osmolality affect the kidney's glomerular filtration rate and tubular resorption resulting in a variable amount of sodium chloride in the filtrate reaching the distal tubule of the kidney. This is detected by a region called the *juxtaglomerular apparatus* (JGA) which is responsible for producing and secreting the hormone renin which controls the renin-angiotensin-aldosterone system (RAAS).

When a patient is hypovolemic (low circulating intravascular volume) or has high osmolality (dehydration), a higher concentration of sodium chloride in the filtrate is presented to the JGA, stimulating an increase in renin production thereby activating the RAAS. One of the actions of the RAAS is to increase sodium and water reabsorption in the proximal tubule (by the action of angiotensin II) and in the collecting ducts [by the action of aldosterone and antidiuretic hormone (ADH)]. The increased water resorbed will tend to return intravascular fluid volume and osmolality toward normal.

## Gastrointestinal Tract

In a normal person, over a day, large volumes of electrolyte-rich fluid are secreted into and reabsorbed from the gut in a continuous manner. The source of the gut fluid is oral fluid consumed by the individual, and also secretions of saliva, gastric juices, and small intestine secretions. Virtually all ( $\approx 98\%$ ) of this fluid is reabsorbed resulting in only 200 mL/day of fecal water loss. This highly efficient continuous recycling of fluid results in a very small fraction of fluid remaining in the gut lumen at any one time; this is considered the transcellular fluid. If the continuous recycling mechanism is disturbed on account of persistent diarrhea or vomiting, then the large volumes of electrolyte-rich fluid secreted proximally will be lost and not be reabsorbed distally. This results in fluid and electrolyte losses culminating in dehydration of the individual.

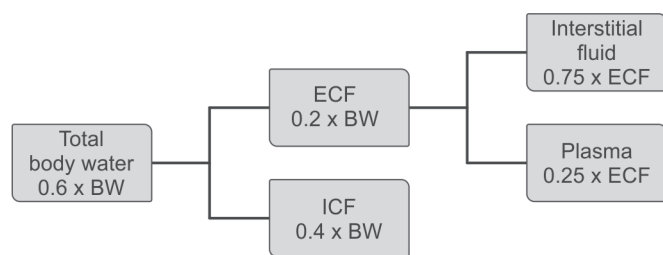
## Respiratory Tract

Exhaled gases from the respiratory tract are fully saturated with water vapor but contain no solutes. The respiratory fluid loss is usually in consequential, but may be considerable in a tachypneic patient with high minute ventilation, especially if the patient is administered dry gases, e.g., nonhumidified oxygen.

## HORMONAL MECHANISMS

Vasopressin (antidiuretic hormone, ADH) is an important hormone which is responsible for maintaining intravascular volume and osmolality. Vasopressin is stored in the posterior pituitary and its secretion is increased in various conditions, such as hypovolemia,





**Figure 7** Body fluid distribution  
Abbreviations: BW, body weight; ECF, extracellular fluid;  
ICF, intracellular fluid.

hyperosmolality, emotional upsets, pain and stress. Vasopressin act on V2 receptors on the basolateral membrane of the renal collecting ducts, leading to water reabsorption via newly inserted aquaporin water channels. Angiotensin II and aldosterone, along with ADH pay a key role in the control of ECF osmolality and sodium concentration.

### Applied Physiology

Example to calculate fluid distribution in different compartments in a child weighing 20 kg using the flow diagram in **Figure 7**.

Total body water	: $0.6 \times 20 \text{ kg}$	= 12 liters
ECF volume	: $0.2 \times 20 \text{ kg}$	= 4 liters
ICF volume	: $0.4 \times 20 \text{ kg}$	= 8 liters
Interstitial fluid	: $0.75 \times 4 \text{ liters}$	= 3 liters
Plasma	: $0.25 \times 4 \text{ liters}$	= 1 liter

*What happens to ECF volume when fluids of various tonicity are infused?*

- If an isotonic saline solution (0.9% NaCl or Ringer's lactate) is infused into the ECF compartment, the osmolality of the ECF does not change; therefore, no osmosis occurs through the cell membranes.
- If a hypotonic solution (isolyte P, 0.45% NaCl) infused into the ECF, the osmolality of the ECF decreases and some of the extracellular water diffuses into the cells until the intracellular and extracellular compartments have the same osmolality.
- If a hypertonic solution (3% NaCl, mannitol) is infused into the ECF compartment, the ECF osmolality increases and

causes osmosis of water out of the cells into the extracellular compartment. This causes increase in extracellular volume and decrease in intracellular volume.

### IN A NUTSHELL

1. Water is a major constituent of the human body, accounting for 60% of the BW. Body water is divided between two major compartments ICF and ECF. Two-thirds of the water is in the ICF, and one-third is in the ECF.
2. Osmotic pressure gradients between ICF and ECF are responsible for water movement between these compartments.
3. The ECF is divided into a vascular compartment (plasma) and an interstitial fluid compartment. Starling forces across capillaries determine the exchange of fluid between these compartments.
4. Sodium is the major cation of ECF and potassium is the major cation of the ICF.
5. Tonicity is a way of describing the relative solute concentrations of two solutions which are separated by a selectively-permeable membrane.
6. Daily water intake should balance daily water loss (sensible plus insensible loss) to maintain tight fluid balance which is required for optimal functions of tissue.

### MORE ON THIS TOPIC

- Aune GJ. Fluids and Electrolytes. In: Custer JW, Rau RE. The Harriet Lane Handbook. 18<sup>th</sup> ed. Philadelphia, PA, USA: Elsevier; 2009. pp. 301-25.
- Barret K, Brooks H, Boitano S, Barman S. Ganong's Review of Medical Physiology. 23<sup>rd</sup> ed. USA: McGraw-Hill; 2010.
- Guyton AC, Hall JE. The Body Fluid Compartments, Extracellular and Intracellular Fluids, Interstitial Fluid and Edema. In: Guyton AC, Hall JE. Textbook of Medical Physiology. 11<sup>th</sup> ed. Philadelphia, PA, USA: Elsevier Saunders; 2006. pp. 291-306.
- Lynch RE, Wood EG. Fluid and Electrolyte Issues in Pediatric Critical Illness. In: Fuhrman BP, Zimmerman JJ, Carcillo JA, Relvas M, et al. Pediatric Critical Care. 4<sup>th</sup> ed. Philadelphia, PA, USA: Elsevier; 2011. pp. 944-5.

## Chapter 5.2

# Maintenance Fluid Therapy

Banani Poddar, Kirti M Naranje

Intravenous (IV) fluid therapy is the most common medical intervention in hospitalized children. It is one of the essential supportive care treatments for a variety of diseases. Traditionally, IV fluids are intended to provide free water and electrolytes in a fasting patient. However, with rapid advances in medical care, IV fluid therapy has become more challenging and complex. Five common reasons to infuse IV fluid in a hospitalized child are listed in **Box 1**. This chapter will focus on maintenance fluid therapy in children and does not pertain to neonates who have their own distinctive fluid and electrolyte requirement.

### BOX 1 Indications for IV fluids

- Maintaining hemodynamics
- Normalizing intracellular fluid volume
- Replacing ongoing renal and nonrenal losses
- Providing glucose to brain, and
- Providing maintenance fluids to match the daily insensible water losses.

## MAINTENANCE FLUIDS

Maintenance fluid therapy, in general, implies that a precise volume and electrolyte content is prescribed to a child who cannot be fed orally or via feeding tube, assuming that fluid and electrolyte balance is normal to begin with. It intends to maintain homeostasis till the time the child is able to take orally and control his own fluid balance. Maintenance fluids are solutions containing water, dextrose and electrolytes. The major objectives of any maintenance fluid therapy are to: (1) prevent dehydration; (2) prevent electrolyte disturbances; (3) prevent ketoacidosis, and (4) prevent protein degradation.

Maintenance therapy is most frequently used in preoperative and postoperative surgical children, though a large proportion of acutely ill children do require fluids as maintenance requirement. It is important to identify when to administer maintenance fluids in a child. A healthy adolescent can easily tolerate 12–18 hours of fasting as compared to an infant who needs maintenance fluids within 8 hours of being kept nil per orally. This is because infants tend to get dehydrated more rapidly than older children. Similarly, it is essential to make sure that a child is not receiving maintenance fluids for an indefinite period in hospital. These fluids are typically devoid of sufficient calories, proteins, fats, vitamins and minerals and can cause 0.5–1% body weight loss daily. Maintenance fluids are meant to be used for shorter time periods. Those children in whom enteral feeds cannot be started beyond a few days should be shifted on to total parenteral nutrition in order to meet adequate nutritional requirements. This is especially true in undernourished children.

## Estimation of Electrolyte Free Water

One of the fundamental constituents of maintenance fluid therapy is water because body loses water daily through various routes. These can be via urine or stool (measurable) or evaporative losses such as through skin, lungs (nonmeasurable). Similarly, there is obligatory loss of electrolytes through body daily. **Table 1** depicts the average daily water and electrolyte losses through various organ systems. One of the purposes of any maintenance fluid is to replace these insensible water and electrolyte losses. Almost 60% water loss is through urine. The kidneys play an important role in regulation of water balance and have the capacity to concentrate

or dilute urine in response to wide variations in fluid intake. This is advantageous since the majority of traditional formulas for estimating maintenance water need lack absolute precision. Provision of electrolyte-free water (EFW) via maintenance fluid gives adequate margin of safety for the body homeostatic mechanisms to adjust urinary water losses with the aim to prevent disturbances in hydration status of a child.

Conventionally, maintenance fluid volumes are calculated by formulas based upon body weight (**Table 2**). Other methods include those based on body surface area (Crawford) and age (Wallace). The body weight method was first published in 1957 in a landmark study by Holliday and Segar. Since then, it has been most popular, convenient and universally accepted for estimation of water requirements. This method assumes that fluid losses occur normally (insensible or obligatory losses) and approximately 1 mL equals 1 kcal energy generated. In addition, alterations in maintenance volume are required in conditions whenever there are increased losses through skin, lungs or urine (**Table 3**). Thus, maintenance fluid volume needs to be increased in situations of excessive transcutaneous losses like fever, burns, undue sweating, and use of radiant warmer or phototherapy. It also needs to be augmented in a tachypneic or tracheostomized child who is not receiving humidified oxygen and in those who have excessive gastrointestinal (diarrhea, nasogastric suction, vomiting) as well as urinary losses (polyuria). The causes for decreased water requirement include oliguria/anuria, use of humidifier for oxygen therapy, hypothyroidism and use of incubator.

Recently, there has been a lot of criticism of the traditional weight-based formulas, mainly for overestimating EFW volumes in maintenance therapy. Firstly, these calculations are derived from findings in healthy children and cannot be extrapolated to critically sick children due to differing physiology. Secondly, this method of estimating EFW requirements is based on caloric

**Table 1** The daily fluid and electrolyte losses (expressed as per 100 calories of metabolism per day)

Route	Water (mL/kg)	Na(mEq/kg)	K(mEq/kg)
Evaporative			
Lung	15	0	0
Skin	40	0.1	0.2
Stool	5	0.1	0.2
Urine	65	3.0	2.0
<b>Total</b>	<b>125</b>	<b>3.2</b>	<b>2.4</b>
Metabolic water produced	-10	-	-
<b>Net balance</b>	<b>115</b>	<b>3.2</b>	<b>2.4</b>

**Table 2** Holliday and Segar calculation of maintenance water volumes based on body weight. Also shown are the hourly maintenance fluid rates

Body weight*	Maintenance water #	Hourly maintenance fluid rate†
Till 10 kg	100 mL/kg	4 mL/kg/h
10–20 kg	1,000 mL + 50 mL for every kg >10 kg	40 mL/h + 2 mL/kg/h for each kg >10 kg
20 kg and above	1,500 mL + 20 mL for every kg above 20 kg	60 mL/h + 1 mL/kg/h for each kg above 20 kg

\* Body weight (BW) should preferably be child's lean body weight estimated by using 50th percentile of BW for the child's height

# Upper limit for maintenance water is 2.4 liters for an adult size patient

† Maximum fluid rate should be restricted to 100 mL/h

**Table 3** Required alterations in maintenance fluid volume in diverse clinical states

Clinical state	Route	Adjustments in maintenance fluid volume
Fever (persistent)	Skin	Increase volume by 10–15% for every 1°C above 38°C
Tachypnea Tracheostomy	Lungs	Increase volume by 20–50% (note: do not increase if child is receiving humidified oxygen therapy either noninvasively or via ventilator)
Polyuria	Urinary	Measure actual urinary output every 1–2 hourly and add to maintenance volume for next 1–2 hours
Anuria		Exclude urinary loss from maintenance volume
Oliguria		Measure actual urinary output every 6–12 hourly and add to maintenance volume for next 6–12 hours

expenditure and energy production. The calculation of energy expenditure based on body weight has been found to be unreliable in acute diseased states. Also, the insensible losses in a sick child is varied due to diminished muscle activity, decreased dietary intake, altered cutaneous blood flow and environmental factors such as temperature, humidity and air circulation. The net energy expenditure in critically ill children may be as low as 50–60 kcal/kg/day. A low metabolic state because of physical immobility, use of sedation, muscle relaxants and mechanical ventilation contributes to low caloric requirements in acute illness. Further, in critically sick children there are various osmotic (hypovolemia, hypotension, serum osmolality) and nonosmotic (pain, drugs, anesthetic agents, nausea, stress) stimuli for the release of vasopressin from posterior pituitary which leads to accumulation of EFW. Lastly, EFW may be generated by kidneys due to *desalination* phenomenon; it has a poorly understood mechanism and is presumed to occur as a result of excretion of hypertonic urine in children who receive isotonic or near-isotonic fluids.

### Composition of Maintenance Intravenous Fluids

As stated earlier, the maintenance fluid normally contains glucose, water and electrolytes. The commonest IV fluids used in day to day practice are 0.2% NaCl and 0.45% NaCl in 5% dextrose. Sodium and

potassium are the chief electrolytes required in a typical maintenance fluid regime. Sodium and potassium can be added at 3.0 mEq/kg/day and 2.0 mEq/kg/day to the fluid. This is based on estimates derived from dietary requirement and sodium intake to urinary excretion ratio in healthy breast-fed infants. IV solutions are also commercially available with or without added potassium chloride at concentration of 10 mEq/L and 20 mEq/L. Other commonly available IV fluids are listed in **Table 4**. Other electrolytes like calcium, magnesium, phosphate, bicarbonate and vitamins and minerals can be added to maintenance fluid in desired concentration. It may be a good idea to start with 0.45% normal saline along with 5% dextrose and 20 mEq/L of potassium chloride (provided child is passing adequate urine) as maintenance therapy in an unwell child. However, type of fluid should be modified according to clinical state. The advantages of commercially available IV fluids are that they are ready to use, requires no preparation time and are less costly. Conversely, IV solution can be customized and prepared in hospital pharmacy; the disadvantage being more cost and time of preparation and risk of contamination if strict aseptic precautions are not followed. Mixing various IV fluids to obtain the desired content of glucose and electrolytes at the bedside is a frequent practice but can be a source of infection if attention is not paid to asepsis.

### Glucose and Maintenance Fluids

In general, dextrose forms one of the vital components of maintenance fluid in children in order to avoid the risk of hypoglycemia. However, hyperglycemia has been found to be associated with negative prognosis in critically ill children, especially in traumatic brain injury and burns. Further, hyperglycemia has been found to reduce immune function and increase mortality risk in sick children. Therefore it may be judicious to avoid glucose in maintenance fluid in older children, particularly in vulnerable group of patients, such as traumatic brain injury and burns, with a caution to monitor blood sugar levels vigilantly in order to avoid hypoglycemia. For smaller infants it is desirable to keep a minimum glucose infusion rate of 4 mg/kg/min and monitor blood sugar levels in order to prevent hypoglycemic effects on developing brain. The energy generated from the commonly used IV fluids containing 5% dextrose is 17 calories/100 mL. This accounts for around 20% of daily caloric needs. The aim is to prevent generation of ketones and minimize protein degradation in the body. However, it is not sufficient enough to prevent weight loss; hence the rationale for starting total parental nutrition if oral feeds cannot be started beyond a few days in a sick child.

**Table 4** Composition of commonly used intravenous solutions

Intravenous fluid	Glucose content (g/dL)	Na <sup>+</sup> K <sup>+</sup>		Concentration in mEq/L				Lactate/Acetate	Osmolality (mOsm/L)	Electrolyte*-free water (%)
		Na <sup>+</sup>	K <sup>+</sup>	Cl <sup>-</sup>	Ca <sup>++</sup>	Mg <sup>++</sup>	PO <sub>4</sub>			
5% dextrose in water (D5)	5	-	-	-	-	-	-	-	252	100
10% dextrose in water (D10)	10	-	-	-	-	-	-	-	505	100
0.2% NaCl in 5% dextrose in water (N/4 saline in 5D)	5	34	-	34	-	-	-	-	321	78
IsoLyte P in 5% dextrose in water (Iso P)	5	25	20	29	-	3	3	23 (acetate)	340	84
0.45% NaCl in 5% dextrose in water (N/2 saline in 5D)	5	77	-	77	-	-	-	-	406	50
0.9% NaCl in 5% dextrose in water (DNS)	5	154	-	154	-	-	-	-	560	0
Lactated Ringer's solution (RL)	-	130	4	109	3	-	-	28	273	16
Lactated Ringer's solution in 5% dextrose in water (RL in 5D)	5	130	4	109	3	-	-	28	525	16

\*From Choong K, Bohn D. Maintenance parenteral fluids in the critically ill child. *J Pediatr* (Rio J). 2007;83:53-10.

## HYPOTONIC VERSUS ISOTONIC FLUIDS

One of the important considerations in selecting appropriate maintenance fluids is osmolality of the infused fluid. The normal serum osmolality in human body ranges from 285 mOsm/kg to 295 mOsm/kg. Infusing an IV fluid with low osmolality can cause movement of free water from plasma to red blood cells and may cause hemolysis. Hence, IV fluids which have osmolality equal to or slightly greater than normal plasma osmolality are safer than hypotonic fluids. Thus, infusing plain 5% dextrose in water or 0.2% or 0.45% NaCl (without dextrose) can create trouble and should be avoided. Further, recent literature suggests that hypotonic fluids are responsible for occurrence of hyponatremia with serious neurological consequences in children. To prevent the occurrence of hyponatremia as a result of IV fluid therapy, the two practices would include reducing the fluid rate and/or use of isotonic fluids as maintenance therapy, thus decreasing the accumulation of excess water and thereby its harmful effects. However, there is no consensus as to which practice is superior.

In spite of vast literature on the dangers of hypotonic maintenance fluids, a recent survey of pediatric residents found that nearly 78% continued to use hypotonic maintenance fluids in four diverse clinical circumstances classically associated with excess antidiuretic hormone (ADH) secretion. The role of isotonic fluids has been largely restricted to restore intravascular volume as a resuscitation fluid. The main concerns with the use of isotonic fluids as maintenance therapy are risk of hyperchloremic metabolic acidosis, circulatory overload in at risk patients, excess renal solute loading and hypernatremia. But these side effects have not been well-substantiated in literature. On the contrary, use of isotonic fluids may also be associated with occurrence of hyponatremia as a result of *desalination* phenomenon especially in postoperative period.

### Maintenance IV Fluids and Hyponatremia

The incidence of hyponatremia in hospitalized children has been found to vary from 9.2% to 31% as reported in different studies. It is also the commonest electrolyte abnormality found in hospitalized children. There are many factors including use of hypotonic fluids, excess solute diuresis, less caloric expenditure and overestimation of fluid requirement with traditional formulas. In addition, there are a variety of stimuli for the release of ADH in a critically sick child (as discussed earlier), which further contributes to retention of excess free water in the body leading to hyponatremia. Nonetheless, accumulation of EFW alone may not be the only mechanism for causation of hyponatremia in critically sick children; contribution of other mechanisms also needs to be explored. The signs and symptoms of hyponatremia may be subtle such as nausea and vomiting which are often attributed to other reasons. Therefore, hyponatremia is often unanticipated and under-recognized until overt signs of raised intracranial pressure or seizures develop. Since sodium is the principal cation in ECF which maintains ECF volume and regulates movement of water across cell membrane, it explicates the development of intracellular fluid retention and consequent edema in presence of significant hyponatremia. This is particularly important in smaller children who have greater intracellular fluid volume per total skull volume in their brains. Hence, even a small increase in intracellular fluid volume may cause significant cerebral edema which in turn can lead to serious neurological sequelae in children. In a recently conducted systematic review of maintenance IV fluids in hospitalized children, hypotonic fluids have been found to increase the development of hyponatremia by odds of 17 as compared to isotonic fluids. Thus, isotonic fluids may be more physiological to use as they maintain the plasma osmolality and may decrease the incidence of unfavorable effects of hyponatremia. Further, isotonic fluids may cause the ADH levels to return to normal more rapidly when compared to hypotonic fluids as reported in a study by Powell et al.

## Restricted Volume of Maintenance Fluids

What constitutes an ideal volume for maintenance fluid is still debated worldwide. Conventional calculation often leads to overestimation of required fluid volume and consequent side effects of excess free water retention including hyponatremia. Provided that the intravascular volume is maintained, maintenance fluid volume and rate can be limited up to a range of 40–66% of the standard. This view is being increasingly favored in many studies. Use of isotonic saline in such cases may not be completely helpful. Hence, restriction of maintenance fluid volumes may be a more appropriate strategy; though presently there is not much evidence in literature showing clear advantage of using restricted fluid volumes and reduction in incidence of hyponatremia. Also it is prudent to restrict fluid volumes in patients with problem of antidiuresis due to various reasons particularly renal dysfunction. Conservative fluid strategy targeting a negative or even fluid balance has also been found to be beneficial in patients with acute respiratory distress syndrome after correction of shock.

## PRESCRIBING MAINTENANCE FLUID THERAPY

Prescribing maintenance fluid therapy appears to be routine in pediatrics. However, one should not ignore the potential morbidity and mortality linked with this simple daily intervention. Hence, it is imperative that maintenance fluid in a child should be prescribed with extreme vigilance and the same care and precaution should be taken as with any drug prescription. It is important to remember that fluid administration should be tailored according to individual needs and no single fluid is ideal for all situations. There is no evidence that a single fluid is better than other and the notion that *one size fits all* does not have scientific substantiation.

While choosing appropriate maintenance fluid, one should always determine the goal and indication in each clinical scenario. Selection of fluid for maintenance therapy in acute disease states and postoperative period should not only satisfy the daily electrolyte and water requirements but should also be aimed at maintaining the tonicity balance while they are at heightened risk of developing electrolyte imbalance, particularly hyponatremia. Physiologic parameters, body weight, fluid balances and laboratory investigations like blood glucose levels and serum electrolytes should be monitored at regular intervals in order to prevent complications from maintenance fluid therapy. Holliday-Segar's formula continues to guide IV fluid prescription; however, it should be modified according to the clinical condition. Syringe infusion pumps or pediatric drip set to administer IV maintenance fluid is desirable, especially in smaller children to avoid inadvertent fluid overload.

Isotonic fluids may be more physiological to use in settings where higher osmolality needs to be maintained such as acute gastroenteritis with dehydration, severe sepsis with hypovolemia, salt losing nephropathy (Bartter syndrome, adrenal insufficiency), hypothyroidism, etc. Isotonic fluids are also indicated in conditions where there is ADH excess with or without hypovolemia such as postoperative state, central nervous system infections, pulmonary diseases (pneumonia, asthma, and bronchiolitis) and glucocorticoid insufficiency.

Conservative fluid strategy should be employed in situations of edema like congestive cardiac failure, nephrosis, cirrhosis and hypoalbuminemia. Fluid should also be limited to around 400–600 mL/square meter of body surface area in oliguric conditions such as renal failure due to acute glomerulonephritis, acute tubular necrosis and end-stage renal diseases. Recent literature also supports restricted fluid strategy in certain disease settings like acute respiratory distress syndrome and traumatic brain injury, once the intravascular volume is restored to normal.

The indications for hypotonic fluids include conditions of free water deficit (e.g., hypernatremia); renal concentrating defects



such as nephrogenic diabetes insipidus, recovery phase of acute tubular necrosis, reflux nephropathy, obstructive uropathy, tubulointerstitial nephritis, etc. The other reasons to administer hypotonic fluid are the problems of extrarenal free water loss like burns, fever, gastrointestinal losses and in premature neonates.

There are still many unanswered questions regarding IV fluid therapy in children such as ideal concentration of dextrose, ideal concentration of chloride and efficacy of half normal saline versus isotonic saline. Further research is required to clarify these concerns about maintenance IV fluid therapy in children.

### IN A NUTSHELL

1. Intravenous fluid therapy composition and rate should be tailored to the clinical situation.
2. Maintaining tonicity balance may be more important in acute disease states than just meeting the insensible water losses and daily electrolyte requirement.
3. Traditional formulas to calculate fluid requirement often overestimate the fluid needs in critically ill children.
4. Hyponatremia is the single most common electrolyte abnormality observed in hospitalized children and it has significant neurological morbidity if undiagnosed and untreated.
5. Isotonic fluid may be more physiological as maintenance therapy than hypotonic fluids.
6. Adequate monitoring of physiological and biochemical parameters including blood glucose and serum electrolytes should be done when a child is on IV fluid therapy.

### MORE ON THIS TOPIC

- Choong K, Bohn D. Maintenance parenteral fluids in the critically ill child. *J Pediatr (Rio J)*. 2007;83:S3-10.
- Choong K, Kho ME, Menon K, Bohn D. Hypotonic versus isotonic saline in hospitalised children: a systematic review. *Arch Dis Child*. 2006;91:828-35.
- Finberg L, Kravath R, Hellerstein S. Water and Electrolytes in Pediatrics: Physiology, Pathophysiology and Treatment. 2<sup>nd</sup> ed. Philadelphia: WB Saunders; 1993.
- Freeman MA, Ayus JC, Moritz ML. Maintenance intravenous fluid prescribing practices among paediatric residents. *Acta Paediatr*. 2012;101:e465-8.
- Greenbaum L. Maintenance and Replacement Therapy. In: Kliegman RM, Stanton BF, St.Geme JW, Schor NF, Behrman RE. *Nelson Textbook of Pediatrics*. 18<sup>th</sup> ed. Philadelphia: Saunders Elsevier; 2007. pp. 309-16.
- Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics*. 1957;19:823-32.
- Moritz ML, Ayus JC. Intravenous fluid management for the acutely ill child. *Curr Opin Pediatr*. 2011;23:186-93.
- Powell KR, Sugarman LI, Eskenazi AE, et al. Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy. *J Pediatr*. 1990;117:515-22.
- Shafiee MA, Bohn D, Hoorn EJ, Halperin ML. How to select optimal maintenance intravenous fluid therapy. *QJM*. 2003;96:601-10.
- Srinivasan V, Spinella PC, Drott HR, et al. Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. *Pediatr Crit Care Med*. 2004;5:329-36.

## Chapter 5.3

# Acid-Base Equilibrium

Dinesh Raj, Rakesh Lodha

The acid-base equilibrium of the body is tightly regulated to maintain the systemic arterial pH between 7.35 and 7.45. This tight regulation is necessary as various enzymatic and metabolic processes function optimally in this range. Compensatory mechanisms are activated when pH crosses these limits, which attempt to restore the pH toward normal. The initial attempt to normalize the pH is made by extracellular and intracellular chemical buffering which is followed by respiratory or renal compensation. Disturbances of acid-base balance are commonly encountered in the emergency and critical care setting. A thorough understanding of the underlying pathophysiology leading to the acid-base disorders is needed to correctly diagnose and effectively manage the patient. This chapter reviews the physiology of acid-base equilibrium.

Hydrogen ion ( $H^+$ ) concentration is very closely regulated in the extracellular fluid (ECF) to maintain its concentration around 40 nmol/L (corresponding to a pH of 7.4). Despite acids and bases being added to the ECF, the compensatory mechanisms attempt to maintain the  $H^+$  concentration in a narrow range to ensure physiologic body functions. The physiological processes leading to decrease or increase in pH are referred as *acidosis* and *alkalosis*, respectively, whereas, *acidemia* and *alkalemia* indicate the state of an abnormal pH.

### NET ACID PRODUCTION

The metabolism of carbohydrates and lipids results in production of  $CO_2$ . The daily production of  $CO_2$  is in the range of 10,000–15,000 mmol/L. Apart from these volatile acids, there is generation of nonvolatile or fixed acids from the metabolism of proteins containing acidic amino acids. Byproducts of cellular metabolism (acetic acid, lactic acid, and pyruvic acid) are added to the ECF, adding to the acid load. Organic anions from diet and metabolism of basic amino acids add to the alkali load of the ECF. Apart from the volatile acids, around 1–2 mEq/kg of fixed or nonvolatile acids are generated. Lungs are responsible for the disposal of volatile acids, whereas kidneys eliminate the nonvolatile acids from the body.

### CARBON DIOXIDE TRANSPORT

An understanding of  $CO_2$  transport is important as enormous quantities of  $CO_2$  is produced in the body and exhaled by the lungs.  $CO_2$  is transported in the blood in three forms: dissolved  $CO_2$ , as carbonic acid, and bound to proteins predominantly hemoglobin. The red blood cell is responsible for the transport of around 75% of  $CO_2$ ; rest is transported in plasma.

**Dissolved  $CO_2$**  Carbon dioxide is 20 times more soluble than oxygen in blood. As a result, large quantities of  $CO_2$  can be transported dissolved in blood with little increase in partial pressure. Because of the high solubility and diffusing capacity, its partial pressure in alveoli and pulmonary end-capillaries is essentially the same.

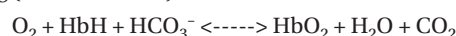
**Carbonic acid ( $H_2CO_3$ )** The combination of  $CO_2$  and water leads to the formation of carbonic acid (a reaction accelerated by carbonic anhydrase by 5,000 times). Carbonic acid dissociates freely into  $H^+$  and  $HCO_3^-$ .

**Carbon dioxide bound to proteins**  $CO_2$  combines with the amino groups of proteins to form carbamino compounds. The

combination between  $CO_2$  and amino groups of hemoglobin forms carbaminohemoglobin ( $CO_2Hb$ ).  $CO_2Hb$  contributes more to  $CO_2$  transport as hemoglobin is three times the quantity of plasma proteins.

**Carbon dioxide transport in tissues** Carbonic anhydrase present in the red blood cell catalyzes the formation of  $H_2CO_3$  which dissociates to form  $H^+$  and  $HCO_3^-$ . RBC membrane is impermeable to  $H^+$ , which is taken up by the reduced hemoglobin (through the imidazole group of histidine).  $HCO_3^-$  diffuses out of the cell while Cl diffuses inside to maintain electrical neutrality. The dissociation constant of the imidazole group of histidine is affected by the oxygenation state of hemoglobin. The oxygen bonding is weakened in the acidic state leading to unloading of oxygen in the tissues and buffering of  $H^+$  ions released from carbonic acid.

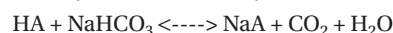
**Carbon dioxide transport in lungs** An increase in  $CO_2$  concentration in blood causes displacement of oxygen from the hemoglobin (Bohr's effect), with the reverse also true. Binding of oxygen to hemoglobin in the pulmonary capillaries augments  $CO_2$  unloading (Haldane effect).



### BUFFER SYSTEMS

Buffers are substances which maintain the pH in a narrow range despite addition of an acid or base to the body. Buffers are able to accept or donate protons ( $H^+$ ) to regulate pH. These buffers are able to maintain pH around normal but unable to remove the acid or alkali from the body. The pH at which the buffers (weak acids or bases) are in half dissociated form is known as the *dissociation constant* or pKa. As the physiologic buffers have their pKa close to systemic pH, they function best in these ranges.

The most important buffer system is the carbonic acid-bicarbonate buffer. Addition of any acid (HA, for example) leads to conversion of bicarbonate to  $CO_2$  via the following reaction mediated by the enzyme carbonic anhydrase:



$CO_2$  is eliminated by the lungs. Bicarbonate is consumed in this reaction to buffer the acid, thereby minimizing the change in pH. The ratio of bicarbonate to carbonic acid determines the systemic arterial pH. Normally, this ratio is about 20:1. The bicarbonate-carbonic acid buffer is extremely rapid and effective.

Other important buffers include plasma proteins, phosphates (organic and inorganic) and hemoglobin. Bones also attempt to buffer by acid-induced dissolution of bone-apatite releasing calcium salts and bicarbonate. Hemoglobin releases  $H^+$  after combining with  $O_2$ . In the peripheral capillaries with low  $O_2$  tension and exposure to acid, hemoglobin accepts  $H^+$  and releases  $O_2$ . This controls the pH in the peripheral capillaries despite a high  $PCO_2$ . A reverse of this happens in the lungs with high  $O_2$  partial pressure. The released  $H^+$  in the lungs combines with  $HCO_3^-$  to form  $CO_2$  which gets eliminated with respiration.

The bicarbonate buffer system is the most effective in the extracellular space, where proteins contribute to the intracellular buffering predominantly.

### HENDERSON-HASSELBALCH EQUATION

To understand the respiratory and metabolic components which regulate the systemic pH, it is important to understand the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log \left[ \frac{HCO_3^-}{(0.03 \times PaCO_2)} \right]$$

( $PaCO_2$  measured in mm Hg)

This equation suggests that the ratio of dissolved  $CO_2$  and  $HCO_3^-$  determines the pH. In other words, with primary problem being alterations in  $HCO_3^-$  or  $CO_2$ , the systemic pH can be regulated

by change in the same direction of the other component ( $\text{HCO}_3^-$  or  $\text{CO}_2$ ). The lungs eliminate or retain  $\text{CO}_2$  as necessary; similarly, kidneys optimize the  $\text{HCO}_3^-$  concentration as per situation. The clinical utility of this equation is that pH can be calculated if  $\text{PCO}_2$  and  $\text{HCO}_3^-$  concentrations are known. However, this equation is somewhat difficult for routine use; therefore to have an insight in the acid-base disorder, the equation can be interpreted as the following relationship:

$$\text{pH} \propto \text{HCO}_3^- / \text{PCO}_2$$

This relationship suggests that pH is positively related to  $\text{HCO}_3^-$ , and inversely related to  $\text{PCO}_2$ .

## Respiratory Regulation

The lungs participate in regulating pH by increasing or decreasing the elimination of  $\text{CO}_2$ . The respiratory compensation begins almost immediately within minutes and is fully established by 24 hours. Peripheral chemoreceptors respond to changes in pH,  $\text{PCO}_2$ , and  $\text{PO}_2$ , whereas central chemoreceptors respond only to  $\text{PCO}_2$ . With acidosis, pH changes around the brainstem stimulate hyperventilation, and the reverse is observed with alkalosis. However, the respiratory compensation is not completely effective in restoring pH as only volatile acids, i.e.,  $\text{CO}_2$  can be taken care of by the lungs.

## Renal Regulation

Kidneys are involved in the removal of nonvolatile acids/bases through several active transport systems in the tubules. Kidneys regulate the serum bicarbonate concentration by controlling  $\text{H}^+$  excretion, regulating bicarbonate reabsorption and generation of new bicarbonate. Renal compensation is a comparative slow process and may take up to 3–5 days for full compensation. Elimination of  $\text{H}^+$  in the renal tubule is facilitated by  $\text{Na}^+/\text{H}^+$  counter transport.  $\text{H}^+$  combines with  $\text{HCO}_3^-$  forming  $\text{CO}_2$  and water, where  $\text{CO}_2$  diffuses back into the tubular cell. Close to 85% of filtered bicarbonate is reabsorbed in the proximal tubule through these mechanisms for  $\text{H}^+$  secretion. Apart from this mechanism, secreted  $\text{H}^+$  is also excreted in combination with phosphate ( $\text{HPO}_4^{2-}$ ,  $\text{H}_2\text{PO}_4^-$ ) and ammonia (forming  $\text{NH}_4^+$ ). In this way, kidneys are able to excrete the nonvolatile or fixed acids, amounting to around 1 mmol/kg/day, generated in the body from various sources. Measurement of the amount of  $\text{H}^+$  excreted in the urine can be done by calculating the amount of alkali needed to neutralize the urine, referred to as *titratable acidity*. Normally urine pH is around 6.0 because of  $\text{H}^+$  and ammonium ions.

## ARTERIAL BLOOD GAS ANALYSIS

### Sample Collection

Radial artery is the preferred artery for arterial blood gas (ABG) because of its superficial location and ease of assessment of the collateral circulation. Other alternatives include posterior tibial, dorsalis pedis and femoral artery. Nondominant hand is selected for the radial/ulnar artery puncture. Umbilical artery can be utilized in the first week of life in neonates.

Modified Allen's test must be performed to assess collateral circulation. With the child's hand held high and fist clenched, both radial and ulnar arteries are compressed by the examiner. Once the fist appears blanched, the hand is lowered and pressure is released over the ulnar artery. Return of pink color of the hand within 6 seconds suggests a patent superficial palmar arch.

### General Precautions

- Prolonged storage of the sample (beyond 15 minutes at room temperature or 1 hour at  $4^\circ\text{C}$ ) underestimates  $\text{PO}_2$  especially in hyperleukocytosis, polycythemia, and thrombocytosis. If delay

is inevitable, sample should be kept at  $4^\circ\text{C}$  (not on ice!). With prolonged storage ongoing metabolism in RBCs reduces pH and  $\text{PO}_2$ , whereas  $\text{PCO}_2$  rises.

- Presence of air bubbles in the sample (especially if their volume exceeds 1% of the sample) underestimates  $\text{PCO}_2$ . Bubbles if any should be expelled immediately after sampling.
- Too much heparin may dilute the sample and measured values may be falsely low.
- *Temperature correction* With decrease in temperature,  $\text{PCO}_2$  decreases and pH increases. This is especially important in interpreting blood gases in a hypothermic child.
- Ensure proper mixing of the sample prior to analysis. The syringe should be rolled between the fingers and inverted many times to ensure proper mixing. This two-dimensional movement ensures proper mixing.
- While drawing sample from an arterial catheter, aspirate at least three to four times the volume of the dead space of the catheter before withdrawing ABG sample in another syringe. The aspirated blood can be pushed back into the catheter after sampling.
- Hemolysis of blood may lead to errors in measurement of electrolytes.

## Arterial Blood Gas Analyzer

Automated ABG analyzers have a complex electronic circuitry, electrolyte solutions to promote chemical reaction and electric current, and electrodes (pH,  $\text{PCO}_2$ , and  $\text{PO}_2$ ). pH is measured by determining the potential difference between the measuring electrode and the reference electrode. The  $\text{PCO}_2$  electrode (*Severinghaus electrode*) is a modification of the pH electrode.  $\text{CO}_2$  diffuses across a gas-permeable membrane to a bicarbonate solution and enters a chemical reaction to generate  $\text{H}^+$ . The change in pH is measured indirectly indicating  $\text{PCO}_2$ .  $\text{PO}_2$  is measured by the Clark electrode. Oxygen diffuses across a semipermeable membrane and gets reduced at the cathode generating a current which is proportional to  $\text{PO}_2$ . To ensure appropriate functioning of the analyzer, frequent calibration as recommended by the manufacturer should be performed.

In the routine blood gas analysis, pH,  $\text{PCO}_2$ , and  $\text{PO}_2$  are measured values, whereas rest are calculated values. It is therefore important to measure the electrolyte panel simultaneously which will provide the measured electrolytes needed to calculate anion gap (AG).

Common terms routinely used in blood gas reports are defined in **Box 1**.

## NORMAL BLOOD GAS VALUES

**Table 1** provides the normal blood gas values for arterial and mixed venous blood.

## Interpretation of Blood Gases

There are four major methods of identifying the acid-base disorders: the physiological approach, the base excess approach, the physicochemical approach (Stewart method), and nomograms. Physiological method utilizes the interpretation of pH,  $\text{PCO}_2$  and  $\text{HCO}_3^-$  using the Henderson-Hasselbalch method. Base excess approach is simple but less accurate. Stewart method utilizes the concepts of strong ions and weak acids in calculating strong-ion difference. Siggaard Anderson nomogram relates  $\text{PaCO}_2$  and pH to base excess. We will discuss the widely used and comprehensive physiological approach to interpret blood gases.

### Step 1: Is the pH acidic or alkalotic?

However, acidosis or alkalosis may even be present with a normal pH (i.e., in mixed disorders).

**BOX 1 Terminology in measurement of arterial blood gas**

- **pH:** pH is the negative logarithm of  $H^+$  concentration.
- **$PCO_2$ :**  $PCO_2$  is the partial pressure of  $CO_2$  in blood.
- **$PO_2$ :**  $PO_2$  is the partial pressure of  $O_2$  in blood.
- **Standard pH:** Standard pH is the pH adjusted for temperature of  $37^\circ C$  and  $CO_2$  of 40 mm Hg, that is, it purely reflects  $H^+$  concentration due to the metabolic derangements.
- **Actual bicarbonate (ABC):** Actual bicarbonate is the concentration of bicarbonate in the plasma which is calculated from measurements of  $PCO_2$  and pH.  $PCO_2$  falls by about 4.5% and pH rises by around 0.015 per  $^\circ C$  fall in temperature.
- **Standard bicarbonate (SBC):** Standard bicarbonate is defined as the bicarbonate concentration under standard conditions (temperature  $37^\circ C$ ,  $PCO_2$  40 mm Hg, saturated with oxygen). Hence, it reflects the change in  $HCO_3^-$  due to a nonrespiratory disorder. With respiratory acidosis, ABC is more than SBC, and converse in respiratory alkalosis.
- **Buffer base (BB):** Buffer base is defined as the total buffer capacity of the blood which includes bicarbonate, hemoglobin, plasma proteins and phosphate. Normal range is  $48 \pm 2$  mmol/L. This is estimated by the blood gas analyzer. It is important to feed in the hemoglobin value of the patient into the machine.
- **Actual base excess (ABE):** Actual base excess is defined as the concentration of titratable base when the blood is titrated with a strong acid or base to a plasma pH of 7.40,  $PCO_2$  of 40 mm Hg and  $37^\circ C$  at actual oxygen saturation. ABE is the deviation of the buffer base amount from the normal level. The normal range of base excess or base deficit is between +2 and -2. ABG analyzers calculate BE based on formulas including pH and  $HCO_3^-$  or pH and  $PCO_2$ . A positive base excess (above 2) suggests metabolic alkalosis, whereas negative base excess (below 2) suggests metabolic acidosis.
- **Standard base excess (SBE):** Standard base excess is a reflection of the base excess in the total ECF, of which blood represents approximately one-third. In a way, it is an in vivo expression of base excess. SBE is independent of the  $PCO_2$  and an indicator of the metabolic components in acid-base balance. Normal levels of SBC and SBE base excess excludes metabolic acid-base disorder, whereas an elevated SBC concentration and positive base excess indicates metabolic alkalosis.
- **Total  $CO_2$ :** Total  $CO_2$  value reflects  $CO_2$  in all forms present in the blood, i.e., sum of  $HCO_3^-$ ,  $H_2CO_3$ , carbonate, dissolved  $CO_2$ , and  $CO_2$  bound to amino acids.  $HCO_3^-$  constitutes nearly 95% of the total  $CO_2$ ; hence,  $tCO_2$  is nearly 2 mmol/L higher than  $HCO_3^-$ .

**Table 1** Normal blood gas values

Value	Arterial blood	Mixed venous
pH	7.40 (7.35–7.45)	7.36 (7.31–7.41)
$PO_2$	80–100 mm Hg	35–40 mm Hg
$O_2$ saturation	95%	70–75%
$PCO_2$	35–45 mm Hg	41–51 mm Hg
$HCO_3^-$	22–26 mEq/L	22–26 mEq/L
Base excess	-2 to +2	-2 to +2

**Step 2: Is the primary abnormality respiratory, metabolic or both?**

In primary respiratory disorders, change in pH and  $PCO_2$  is in opposite direction, whereas in primary metabolic disorders, change in pH and  $PCO_2$  is in same direction.

**Acidosis (pH < 7.35) with:**

- **Low  $PCO_2$  ( $PCO_2 < 35$  mm Hg):** Metabolic acidosis with respiratory compensation (respiratory alkalosis)
- **Normal  $PCO_2$ :** Uncompensated metabolic acidosis (uncommon)
- **High  $PCO_2$  ( $PCO_2 > 45$  mm Hg):** Primary respiratory acidosis

**Alkalosis (pH > 7.45) with:**

- **Low  $PCO_2$  ( $PCO_2 < 35$  mm Hg):** Primary respiratory alkalosis
- **Normal  $PCO_2$ :** Uncompensated metabolic alkalosis
- **High  $PCO_2$  ( $PCO_2 > 45$  mm Hg):** Primary metabolic alkalosis with respiratory compensation.

**Step 3: Assessment of hypoxemia and measures of oxygenation**

Assessment of oxygenation relative to ventilation may help in distinguishing respiratory from nonrespiratory causes of acid-base imbalance.

**Step 4: Calculate the AG and adjust the AG for hypoalbuminemia**

$$\text{Anion gap} = Na^+ - (HCO_3^- + Cl^-)$$

Normal AG is between 8 mEq/L and 14 mEq/L. Increased AG is usually associated with metabolic acidosis. There are a few causes of normal AG metabolic acidosis; these are discussed in the following chapter. The anion gap is influenced by the albumin concentration; so, in hypoalbuminemia, the AG has to be adjusted.

$$\text{Adjusted AG in hypoalbuminemia} = \text{observed AG} +$$

$$[2.5 \times (\text{normal albumin} - \text{observed albumin})]$$

**Step 5: What is the extent of compensation?**

Compensation usually does not normalize the pH. Respiratory compensation of metabolic disorders is usually rapid (within minutes to hours), but metabolic compensation of respiratory disorders take longer (hours to days). Extent of compensation depends on the duration of the underlying disorder (acute or chronic). Calculation of the expected compensation is also important to identify mixed acid-base disorder. **Table 2** depicts the extent of compensation in various disorders.

**Step 6: Calculate delta/delta or delta gap**

The ratio of change in anion gap to the change in bicarbonate ( $\Delta AG / \Delta HCO_3^-$ ) helps in assessing the contribution of process causing AG to the actual acidosis.

$$\text{Delta/delta} = (\text{Measured AG} - 12) / (24 - \text{measured bicarbonate})$$

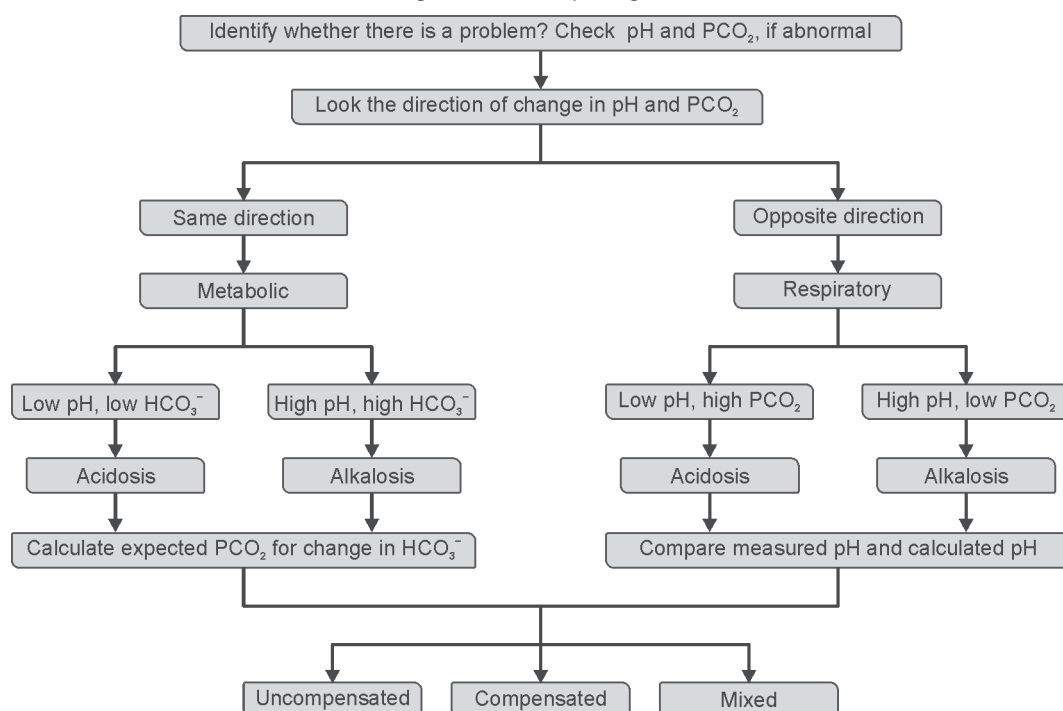
The ratio is usually around 1 if an uncomplicated metabolic acidosis is present. For every one unit increase in AG, the bicarbonate should decrease by 1 mmol/L, keeping the ratio at 1. If the change in the AG is more than the change in the serum bicarbonate, concomitant metabolic alkalosis is also likely to be present. Similarly, if the change in the AG is less than the change in the serum bicarbonate, a concomitant non-AG metabolic acidosis is also likely to be present.

The other parameter is delta gap. When an increased AG metabolic acidosis is present,  $\Delta AG - \Delta HCO_3^-$  is used to screen for mixed disorders. If  $\Delta AG - \Delta HCO_3^- \geq 6$  additional normal AG

**Table 2** Expected compensation in various acid-base disorders

Abnormality	Compensation
Metabolic acidosis	$PCO_2$ decreases due to hyperventilation (respiratory compensation) Expected $PCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$
Respiratory acidosis	Acute: $HCO_3^-$ increases by 1 mmol/L for every 10 mm Hg increase in $PCO_2$ Chronic: $HCO_3^-$ increases by 3.5 mmol/L for every 10 mm Hg increase in $PCO_2$
Metabolic alkalosis	$PCO_2$ increases by 7 mm Hg for every 10 mmol/L increase in $HCO_3^-$
Respiratory alkalosis	Acute: $HCO_3^-$ decreases by 2 mmol/L for every 10 mm Hg decrease in $PCO_2$ Chronic: $HCO_3^-$ decreases by 4 mmol/L for every 10 mm Hg decrease in $PCO_2$



**Flow chart 1** Algorithm for interpreting acid-base disorder

(hyperchloremic) metabolic acidosis is present. On the other hand, if  $\Delta AG - \Delta HCO_3^- \leq -6$ , additional metabolic alkalosis is present.

#### Step 7: Identify the cause for the acid-base disorder

A good history and examination is important to understand the likely underlying physiological disturbance which helps in interpreting the blood gas disorder. If the clinical setting does not correlate with the acid-base disorder, errors in ABG analysis must be considered. A thorough assessment of the respiratory, neurological, and renal status is necessary to understand the extent of compensation in blood gases.

**Flow chart 1** gives an algorithmic approach to identify and interpret acid-base disorder.

### MORE ON THIS TOPIC

- Al-Khadra E. Disorders of acid-base status. In: Kiessling SG, Goebel J, Somers MJG (Eds). *Pediatric Nephrology in the ICU*. Berlin Heidelberg: Springer; 2009. pp. 19-33.
- Arthurs GJ, Sudhakar M. Carbon dioxide transport. *Contin Educ Anaesth Crit Care Pain*. 2005;5:207-10.
- Berend K, de Vries AP, Gans RO. Physiological approach to assessment of acid-base disturbances. *N Engl J Med*. 2014;371:1434-45.
- Cowley NJ, Owen A, Bion JF. Interpreting arterial blood gas results. *BMJ*. 2013;346:f16.
- Deorari AK. Blood gas analysis. From [www.newbornwhocc.org/pdf/Blood-Gas-Book-workbook-2008.pdf](http://www.newbornwhocc.org/pdf/Blood-Gas-Book-workbook-2008.pdf). Accessed October 6, 2014.

### IN A NUTSHELL

1. Lungs are responsible for the disposal of volatile acids, whereas kidneys eliminate the nonvolatile acids from the body.
2. Increase in  $CO_2$  concentration in blood causes displacement of oxygen from the hemoglobin (Bohr's effect), and binding of oxygen to hemoglobin in the pulmonary capillaries augments  $CO_2$  unloading (Haldane effect).
3. Kidneys regulate the serum bicarbonate concentration by controlling  $H^+$  excretion, regulating bicarbonate reabsorption and generation of new bicarbonate.
4. Errors in ABG measurements can be avoided by keeping in mind general precautions.
5. In the routine blood gas analysis, pH,  $PCO_2$ , and  $PO_2$  are measured values, whereas rest are calculated values.
6. The assessment of the type of acid-base imbalance and the presence of a mixed acid-base disorder can be done by measurement of  $pCO_2$ , serum bicarbonate, and calculation of the AG.
7. Compensation usually doesn't normalize the pH. Respiratory compensation of metabolic disorders is usually rapid (within minutes to hours), but metabolic compensation of respiratory disorders takes longer (hours to days).
8. Mixed acid-base disorders can present with normal pH.
9. Assessment of oxygenation relative to ventilation may help in distinguishing respiratory from nonrespiratory causes of acid-base imbalance.
10. The ratio of change in AG to the change in bicarbonate ( $\Delta AG/\Delta HCO_3^-$ ) helps in assessing the contribution of process causing AG to the actual acidosis.

## Chapter 5.4

# Abnormalities of Acid-Base Balance

*Dinesh Raj, Rakesh Lodha*

Acid-base abnormalities are common in sick children. Timely recognition of the abnormalities and their causes can be lifesaving. In the respiratory disorders, the primary change is in  $\text{PCO}_2$ ; while in metabolic disorders, the bicarbonate ( $\text{HCO}_3^-$ ) concentrations are primarily affected. So, overall there are four simple acid-base disorders: metabolic acidosis, respiratory acidosis, metabolic alkalosis, and respiratory alkalosis. Mixed acid-base disorders have independently coexisting disorders, apart from the expected physiologic compensatory responses. This chapter reviews the pathophysiology, etiology and brief management of these various acid-base disorders.

## RESPIRATORY ACIDOSIS

Respiratory acidosis is characterized by an increase in  $\text{PaCO}_2$  and a decrease in pH. It can be either acute or chronic.

### Etiopathogenesis

Accumulation of  $\text{CO}_2$  can result from increased production or abnormalities in washing out  $\text{CO}_2$ ; the latter is usually the cause. Respiratory acidosis can be caused by hypoventilation due to decreased respiratory drive or respiratory muscle fatigue; these lead to a generalized fall in alveolar ventilation (**Table 1**). Severe lung diseases associated with ventilation-perfusion mismatch (pneumonia, pulmonary edema or ARDS), airway obstruction (foreign body, asthma or bronchiolitis) or diffusion abnormalities cause hypercarbia due to an imbalance between ventilation and perfusion. Excessive  $\text{CO}_2$  production, as in malignant hyperthermia, is a rare cause of respiratory acidosis.

Acute compensation of respiratory acidosis begins within a few hours with a rise in plasma bicarbonate by 1 mmol/L for every 10 mm Hg increase in  $\text{PCO}_2$ . This early response is due to the acid titration of nonbicarbonate buffers (hemoglobin, intracellular proteins, phosphate and plasma proteins). Chronic compensation is usually complete within 3–5 days with adaptive increase in renal acidification leading to new bicarbonate generation; for every 10 mm Hg increase in  $\text{PCO}_2$ , plasma bicarbonate increases by 3–4 mmol/L (up to a maximum of 38 mmol/L).

The various causes of respiratory acidosis are tabulated in **Table 1**.

### Clinical Features

The clinical features of respiratory acidosis are usually those of the underlying cause. Children with respiratory acidosis due to hypoventilation resulting from central nervous system depression or respiratory muscle fatigue and respiratory failure will have bradypnea, hypoxia and altered sensorium. On the other hand, child with respiratory acidosis due to pulmonary or airway obstruction manifests with tachycardia, tachypnea, respiratory difficulty and features of hypoxia.

Severe acute respiratory acidosis may lead to symptoms of restlessness, anxiety, headache, blurred vision and excessive sweating. Excessive  $\text{CO}_2$  retention may lead to  $\text{CO}_2$  narcosis as manifested by drowsiness, headache, confusion, hallucinations,

**Table 1** Causes of respiratory acidosis

Decreased respiratory drive	Drugs (anesthesia, sedatives) Head trauma Stroke Encephalitis Sleep-disordered breathing Hypothyroidism
Neuromuscular problems	Guillain-Barre syndrome Spinal cord injury Myasthenia gravis Poisonings causing neuromuscular blockade (curare, organophosphate) Myopathies and muscular dystrophies Diaphragmatic palsy
Severe lung disease	Severe pneumonia Acute respiratory distress syndrome Pulmonary edema Lung collapse Interstitial pneumonia Infiltrative disorders
Airway obstruction	Laryngospasm Angioedema Obstructive sleep apnea Foreign body Severe asthma Bronchiolitis
Miscellaneous	Flail chest Pneumothorax Hemothorax Massive ascites Obesity Kyphoscoliosis Permissive hypercapnia

stupor, and even coma. There may be features of raised intracranial pressure. The symptoms are more evident in acute respiratory acidosis compared to chronic respiratory acidosis.

Severe acidosis may also lead to significant vasodilatation and hypotension. With a significant fall in arterial pH, impairment in cardiac function, altered response to catecholamine and cardiac arrhythmia can also occur similar to metabolic acidosis. Rise in serum potassium is uncommon in children with respiratory acidosis as compared to those with metabolic acidosis.

### Diagnosis

The presence of acidemia and elevated  $\text{PCO}_2$  is diagnostic of respiratory acidosis. An accurate history and good examination are essential to help determine whether it is acute or chronic. It is essential to remember the expected compensations in acute and chronic respiratory acidosis to determine presence of mixed metabolic and respiratory abnormalities. Calculation of alveolar arterial oxygen gradient  $[(A-a) \text{DO}_2]$  can assist in determining the etiology. It is usually increased in patients with intrinsic pulmonary disease. A normal gradient usually excludes pulmonary disease and indicates central alveolar hypoventilation or abnormalities of chest wall or muscles of breathing.

### Treatment

Treatment of respiratory acidosis usually depends on the severity of the abnormality and the rapidity of development. Rapidly developing severe acidosis may need intubation for optimization of alveolar ventilation. Treatment of the underlying cause is the mainstay of management. Respiratory acidosis in a ventilated

child should warrant assessment of tracheal tube displacement or obstruction, air leaks, worsening of the lung/airway disease and/or ventilator malfunction. In the absence of these, a change in ventilator settings usually facilitates CO<sub>2</sub> removal.

As increased PCO<sub>2</sub> is associated with cerebral vasodilatation and increase in intracranial pressure. Children with CNS disorders especially meningoencephalitis, benefit with mechanical ventilation. Invasive mechanical ventilation should be avoided as far as possible in children with chronic respiratory acidosis. Measures to improve lung function usually result in improvement in respiratory acidosis. Ventilation of such patients should be cautious as rapid reduction in PCO<sub>2</sub> may lead to sudden elevation in pH which can be life-threatening. Such patients also tolerate extubation poorly with increasing acidosis in the absence of metabolic compensation. As these patients are poorly responsive to hypercarbia, and more sensitive to hypoxemia, the lowest possible FiO<sub>2</sub> to maintain adequate oxygenation is recommended. A high FiO<sub>2</sub> may decrease the respiratory drive, increasing the acidosis further.

## RESPIRATORY ALKALOSIS

Respiratory alkalosis is characterized by decrease in PCO<sub>2</sub> and an increase in pH.

### Etiopathogenesis

The causes of respiratory alkalosis include increased CO<sub>2</sub> elimination (hyperventilation) or uncommonly decreased CO<sub>2</sub> production. Respiratory alkalosis is often seen in mechanically ventilated children in the pediatric critical care setting. The various causes of respiratory alkalosis are summarized in **Table 2**. Hyperventilation often occurs as a response to hypoxemia via the peripheral chemoreceptors. Lung pathology may cause respiratory

alkalosis by stimulation of chemoreceptors or mechanoreceptors in the lung.

The immediate compensatory response to decrease in CO<sub>2</sub> is an acute decrease in plasma bicarbonate mediated by alkaline titration of nonbicarbonate buffers. Renal adaptation accounts for the further reduction in bicarbonate levels attributed to reduction in renal ammonium and titratable acid secretion and decrease in filtered bicarbonate reabsorption. For every 10 mm Hg decrease in PCO<sub>2</sub>, acute compensation reduces bicarbonate levels by 2 mmol/L, whereas chronic compensation (occurs over 2-3 days) reduces bicarbonate concentrations by 4 mmol/L.

### Clinical Features

Acute respiratory alkalosis is more often symptomatic than chronic respiratory alkalosis. The symptoms are secondary to decreased cerebral perfusion including light-headedness, confusion, and seizures. As respiratory alkalosis may lead to hypocalcemia due to decrease in ionic calcium, some of the symptoms attributed to hypocalcemia may be observed. They include perioral numbness, tetany, paresthesias, and laryngeal spasm. Uncommonly, cardiac arrhythmias may be observed.

### Treatment

Treatment is usually directed toward the underlying disorder. Chronic respiratory alkalosis is often asymptomatic, and treatment is usually not required. Rapid assessment of the cause of acute respiratory alkalosis should be made to reduce the acute symptoms. In case of anxiety or psychogenic hyperventilation, reassurance or rebreathing into a paper bag may help in increasing PaCO<sub>2</sub>. Children on mechanical ventilation benefit with reduction in rates, tidal volume or inspiratory pressures.

## METABOLIC ACIDOSIS

Metabolic acidosis is characterized by low systemic pH along with low bicarbonate concentration. An associated decrease in PCO<sub>2</sub> is observed due to respiratory compensation. Low PCO<sub>2</sub> may sometimes not be found in case of a mixed acid-base disorder with concurrent respiratory acidosis.

### Anion Gap

A calculation of anion gap helps in further characterizing the underlying problem leading to metabolic acidosis. The concept of anion gap rests on the fact that to maintain electrical neutrality in the blood, the total number of cations and anions must be equal. As the concentration of minor anions and cations does not change much, so anion gap can be described as the difference of major cations and major anions as follows:

$$\text{Anion gap} = \text{Na}^+ - [\text{Cl}^- + \text{HCO}_3^-]$$

Anion gap is hence the difference of unmeasured cations and unmeasured anions. The normal anion gap is 8-14, but can be up to 16 in sick neonates. With modern analyzers using ion specific electrodes estimating chloride levels very accurately, the anion gap could actually be low at  $6 \pm 3$ . Therefore, analyzer manufacturer's reference range should be kept in mind before interpreting anion gap. A major contribution to the anion gap is by serum albumin. Therefore, in certain situations with low albumin (nephrotic syndrome, liver failure, and malnutrition), the anion gap is low. Hypoalbuminemia can therefore mask the increase in anion gap needing a correction for the level of hypoalbuminemia. For every 1 g/dL decrease in albumin, anion gap decreases by 2.5.

**Table 2** Causes of respiratory alkalosis

Hypoxemia	Pneumonia Aspiration Pulmonary edema Severe anemia Circulatory failure Pulmonary edema Cyanotic heart disease Carbon monoxide poisoning
Increased respiratory drive	Pain Anxiety Psychogenic hyperventilation Fever Head trauma Encephalitis Stroke
Stimulation of chest receptors	Pneumonia Pulmonary edema Asthma Pneumothorax Hemothorax ARDS Flail chest
Miscellaneous	Drugs: Progesterone, salicylates, catecholamines Sepsis Hepatic failure Mechanical ventilation

## Etiopathogenesis

With loss of bicarbonate, pH decreases due to increase in  $H^+$ . If the anion accompanying  $H^+$  is chloride, then serum chloride levels increase matching bicarbonate, keeping the anion gap normal. This type of acidosis is known as *normal anion gap metabolic acidosis*. However, if the anion accompanying  $H^+$  is other than chloride, chloride levels remain normal and anion gap increases. The increased unmeasured anions balance the fall in bicarbonate. This type of acidosis is known as *increased anion gap metabolic acidosis*.

The normal anion gap metabolic acidosis could be either of renal origin (renal tubular acidosis) or extrarenal origin (diarrhea, chloride excess due to parenteral fluids). A commonly used mnemonic for increased anion gap metabolic acidosis is MUDPILES (Methanol; Uremia [renal failure]; Diabetic or starvation ketoacidosis; Paracetamol or Propylene glycol; Iron or Inborn error of metabolism; Lactic acidosis; Ethylene glycol; Salicylates).

Even in the setting of a normal pH and bicarbonate, a significantly elevated anion gap (above 20) is strongly suggestive of metabolic acidosis.

### Normal Anion Gap Metabolic Acidosis (Table 3)

To compensate for the bicarbonate loss, new bicarbonate generation resulting from net acid excretion in the form of ammonium ion is performed by the kidney. A useful method for evaluation of normal anion gap metabolic acidosis is assessment of urinary ammonia excretion. As direct measurement of urinary ammonia is not routinely available, indirect evidence can be obtained by calculation of urinary anion gap (UAG).

$$UAG = (U_{Na^+} + U_{K^+}) - U_{Cl^-}$$

UAG can be either positive or negative depending on urinary ammonia excretion. Negative UAG suggests presence of an unmeasured cation (usually  $NH_4^+$ ) in the urine. Whereas positive UAG is observed in renal tubular acidosis, renal failure, and hypoaldosteronism due to impaired urinary ammonia excretion. More than the magnitude of UAG, the direction of UAG (positive or negative) is of more clinical relevance. However, in certain scenarios UAG is not reliable. These include urine pH above 6.5, presence of polyuria, excretion of urinary ammonium with anions other than chloride (such as ketoacids, salicylates, D-lactate, and penicillins).

*Diarrhea* is commonly associated with normal anion gap metabolic acidosis. The diarrheal losses are usually rich in bicarbonate leading to metabolic acidosis. The volume depletion accompanying diarrhea increases renal NaCl reabsorption causing hyperchloremic metabolic acidosis with a normal anion gap. In response to acidosis, kidneys increase net acid excretion in the form of urinary ammonium.

*Proximal renal tubular acidosis* (Type 2 RTA) is characterized with decreased ability to reabsorb filtered bicarbonate. More commonly it presents as a diffuse proximal tubular dysfunction with impaired reabsorption of glucose, amino acids, phosphate, uric acid, and low molecular weight proteins. As distal acidification is intact in proximal RTA, children are able to acidify urine and urine pH is below 5.5. Some medications (trimethoprim-sulfamethoxazole, topiramate, spironolactone, and cyclosporine) can impact the kidneys and present with normal anion gap acidosis.

Children with *distal RTA* (Type 1) are unable to acidify urine and urine pH is above 5.5. The underlying problem could be reduced  $H^+$  secretion (secretory defect) in distal tubule or back-leak of protons (gradient defect) due to an abnormally permeable

distal tubule. Amphotericin B can also present as a distal RTA physiology by increasing the back-leak of protons.

*Glue sniffing* is an uncommon cause of acquired distal RTA. The fumes contain toluene which inhibits  $H^+$  secretion in collecting ducts. Metabolism of toluene leads to formation of hippuric acid and benzoic acid. With normal blood volume and urine output, these are eliminated in the urine and a normal anion gap metabolic acidosis is observed. In volume depleted state, urinary elimination is restricted and an increased anion gap is observed.

### Increased Anion Gap Metabolic Acidosis (Table 3)

Increased anion gap metabolic acidosis suggests the addition of an acid to the blood. This could be either secondary to increased production or decreased elimination of an endogenously produced acid (lactic acidosis, renal failure) or due to presence of an exogenous acid in the blood (as in poisoning).

*Lactic acidosis* is one of the commonest causes of increased anion gap metabolic acidosis. Most often it is due to tissue hypoxia causing anaerobic metabolism and excess formation of lactate. The cause underlying tissue hypoxia usually include shock (septic, cardiogenic, or hemorrhagic), severe anemia, hypoxemia (respiratory distress due to any cause), and carbon monoxide poisoning. A small amount of lactate normally produced by the body is metabolized by the liver. However, in some cases the excessive amounts produced in the body overwhelms the capacity of liver to metabolize. Once the underlying problem resolves, lactate is metabolized and converted in bicarbonate thereby normalizing the pH. Sometimes, lactic acidosis occurs without tissue hypoxia (as in inborn errors of metabolism, poisonings and liver failure).

*Diabetic ketoacidosis* is another common cause of increased anion gap metabolic acidosis. The excessive production of ketone bodies, i.e.,  $\beta$ -hydroxybutyrate and acetoacetate attribute to the unmeasured anions in the anion gap. A simultaneous presence of increased anion gap acidosis and hyperglycemia should suggest this diagnosis. As routine urine dip sticks for ketoacids detects acetone and acetoacetate but not  $\beta$ -hydroxybutyrate, this diagnosis is sometimes missed early on as the predominant ketoacid is  $\beta$ -hydroxybutyrate. With treatment, acetoacetate increases and the

**Table 3** Metabolic acidosis: causes

<i>Normal anion gap (hyperchloremic) metabolic acidosis</i>	<i>Increased anion gap metabolic acidosis</i>
<i>Gastrointestinal losses of bicarbonate</i>	<i>Lactic acidosis</i>
- Diarrhea	- Tissue hypoxia (shock)
- Ileostomy/jejunostomy/fistula	- Liver failure
- Ureterosigmoidostomy	- Inborn errors of metabolism
- Ileal conduit	- Medications—NNRTI, metformin, propofol
	- Short bowel with bacterial overgrowth
<i>Renal bicarbonate losses</i>	<i>Poisoning</i>
- RTA	- Salicylates
- Early renal failure	- Iron
- Carbonic anhydrase inhibitors	- Methanol
- Aldosterone inhibitor	- Paracetamol
	- Ethylene glycol
	- Toluene
	- Propylene glycol
<i>Excessive saline resuscitation</i>	<i>Ketoacidosis</i>
	- Diabetic
<i>Hyperalimentation</i>	- Starvation
	- Alcohol
	<i>Advanced renal failure</i>



strip test becomes strongly positive. Other causes of ketoacidosis include starvation, prolonged fasting and alcohol use.

*D-lactic acidosis* is an uncommon form of metabolic acidosis which occurs in children with small bowel syndrome with bacterial overgrowth. In these children, carbohydrates which normally get absorbed in the small intestine reach the colon in large amounts and get fermented by intestinal bacteria releasing D-lactic acidosis. The typical presentation is presence of neurological symptoms (in the form of confusion, slurred speech, and ataxia) after a carbohydrate rich meal. Serum lactate levels are fallaciously normal as the laboratory assays estimate the L-enantiomer. Supportive care, antibiotics, and low carbohydrate therapy is usually sufficient.

*Toxic ingestions* are frequent causes of increased anion gap metabolic acidosis. These include iron, paracetamol, salicylates, metformin, ibuprofen, methanol, ethylene glycol, toluene, paraldehyde and propylene glycol. Iatrogenic propylene glycol toxicity is observed in patients receiving large doses of intravenous benzodiazepines (as in lorazepam) which contain propylene glycol as solvent. Toxic alcohol ingestions can be identified by calculating the serum osmolar gap which is the difference between measured and calculated serum osmolality. As alcohols are osmotically active, an osmolar gap of above 20 mOsm is suggestive of toxic alcohol ingestion.

*Advanced renal failure* causes an increased anion gap acidosis due to decreased ability of urinary acidification and undersecretion of ammonium ion.

## Clinical Features

The clinical features of the underlying disorder causing metabolic acidosis are more prominent. The clinical manifestations due to metabolic acidosis depend on the severity of the acidosis and the respiratory function. Mild metabolic acidosis with appropriate respiratory compensation is characterized by rapid and deep breathing (Kussmaul respiration). Fall in blood pH below 7.2 may be associated with myocardial dysfunction with impaired contractility; the risk of ventricular arrhythmias increases if pH is less than 7.1. Severe acidosis attenuates the response to catecholamines. In neonates, metabolic acidosis can cause pulmonary vasoconstriction which aggravates persistent pulmonary hypertension.

Neurological symptoms, varying from lethargy to coma have been described in metabolic acidosis. Chronic acidemia, as with renal failure and renal tubular acidosis, can result in skeletal problems due to release of calcium ions and phosphate during bone buffering of the excess  $H^+$  ions; this contributes to impaired growth. Other metabolic impairments that may occur with metabolic acidosis are hyperkalemia, insulin resistance, increased protein catabolism and reduced ATP synthesis that are seen more commonly with long standing metabolic acidosis.

## Treatment

Though in most conditions, correction of the acidemia can be achieved by  $NaHCO_3$  infusion, it is more important to correct the underlying disorder. The initial therapeutic goal in patients with severe acidemia is to raise the systemic pH to above 7.0–7.1, a level at which arrhythmias become less likely. At this pH, the cardiac contractility and responsiveness to catecholamines is likely to be restored. Intravenous administration of sodium bicarbonate is indicated only in patients with severe metabolic acidosis; this should be done only if ventilation is adequate. Exogenous sodium bicarbonate is usually not required if the initial arterial pH is greater than 7.10, the child is asymptomatic and the underlying

process can be controlled. The amount of bicarbonate ( $HCO_3^-$ ) required to correct the acidemia can be estimated by the formula:

$$HCO_3^- \text{ required} = 0.6 \times \text{body weight} \times HCO_3^- \text{ deficit per liter.}$$

As the added  $HCO_3^-$  produces a large increase in the plasma  $HCO_3^-$  concentration within a few minutes, measurement of pH shortly after administration of  $HCO_3^-$  may overestimate the final effect of the treatment. Alkali therapy is usually not required in lactic acidosis or ketoacidosis where the metabolism of the organic anions will regenerate  $HCO_3^-$ . Similarly, citrate salts of sodium or potassium may be preferable in the chronic treatment of renal tubular acidosis.

Metabolic acidosis due to diarrheal losses should be corrected by expansion of extracellular fluid; in mild cases use of oral rehydration sachets for correction of dehydration suffices, while more severe cases are treated with intravenous Ringer's lactate solution. Correction of the underlying disorder is the primary therapy in lactic acidosis. For example, reversal of circulatory failure will reduce the output of lactate and allow metabolism of lactate to  $HCO_3^-$ . Current evidence does not support routine use of sodium bicarbonate in treatment of lactic acidosis. However, a small amount of sodium bicarbonate may be administered to patients with severe metabolic acidosis to raise the pH to 7.10.

In diabetic ketoacidosis, insulin is the mainstay of therapy. However, sodium bicarbonate therapy may be beneficial if there is marked acidemia (pH < 6.9).

In renal failure, exogenous alkali therapy is not used routinely. Usually in most patients, the arterial pH is maintained close to 7.3 because of respiratory compensation. If child has hypocalcemia, an increase in pH can precipitate tetany. There is also a risk of volume expansion. Sodium bicarbonate therapy may be considered if the plasma  $HCO_3^-$  is less than 12 mEq/L, the patients are symptomatic or there is persistent hyperkalemia. In children, alkali therapy is used more frequently, as acidemia interferes with growth. In renal failure, the alkali of choice is sodium bicarbonate. Citrate may increase aluminum absorption in children receiving aluminum hydroxide.

Sodium bicarbonate administration is helpful in poisoning due to salicylates, tricyclic antidepressant, ethylene glycol and methanol as they help in eliminating the poisonous agent through renal route. Long term sodium bicarbonate therapy may be necessary in cases of inborn error of metabolism.

Dialysis either peritoneal or hemodialysis may be required in treatment of severe metabolic acidosis due to renal failure or poisoning due to methanol or ethylene glycol.

## METABOLIC ALKALOSIS

Metabolic alkalosis is characterized by an increase in the systemic pH along with increased bicarbonate concentration. Hypoventilation occurs as respiratory compensation attempts to bring down pH by increasing  $PCO_2$ . With every 10 mmol/L increase in  $HCO_3^-$ ,  $PCO_2$  increases by 7 mm Hg. As kidneys have enormous capacity to eliminate bicarbonate, accumulation of bicarbonate must be accompanied by a decreased ability to eliminate bicarbonate, so as to sustain metabolic alkalosis.

## Etiopathogenesis

**Table 4** lists the causes of metabolic alkalosis.

Contraction alkalosis (or chloride depletion alkalosis) is the situation in which extracellular fluid contraction caused by chloride losses lead to metabolic alkalosis. The volume contraction in this setting alters the renal handling of electrolytes, bicarbonate

**Table 4** Metabolic alkalosis: causes

Chloride responsive	Chloride resistant
Vomiting	Primary hyperaldosteronism
Nasogastric drainage	Cushing syndrome
Diuretics (Thiazides, metolazone, loop diuretics)	ACTH or renin secreting tumor
Cystic fibrosis	Glucocorticoid remediable aldosteronism
Recovery from chronic hypercapnia	Adrenogenital syndrome
Congenital chloride diarrhea	Fludrocortisone treatment Bartter syndrome Gitelman syndrome Liddle syndrome Severe hypokalemia Severe hypercalcemia Severe hypomagnesemia

and acid excretion. Sodium and bicarbonate excretion increase initially but then decrease rapidly with a concomitant increase in potassium excretion. Hence, hypokalemia is a prominent feature of metabolic alkalosis. Hypokalemia stimulates  $H^+$  secretion and  $NH_4^+$  generation needing to sustain metabolic alkalosis. Chloride depletion affects  $HCO_3^-$  secretion through  $Cl^- - HCO_3^-$  exchanger. With severe hypokalemia, chloride reabsorption is also limited via the  $Na^+ - K^+ - 2Cl^-$  transporter. An understanding of this complex interplay of potassium, chloride, and bicarbonate handling of the kidneys in sustained metabolic alkalosis may help in identifying the likely cause and initiating appropriate therapy.

Broadly metabolic alkalosis can be divided into *chloride responsive* and *chloride resistant metabolic alkalosis*. The causes of *chloride responsive metabolic alkalosis* are persistent vomiting, nasogastric drainage, diuretics administration, recovery from chronic hypercapnia, and congenital chloride diarrhea. With vomiting and continuous nasogastric drainage,  $Cl^-$  and  $H^+$  are lost simultaneously. Hypokalemia occurs both due to gastric potassium losses and renal potassium wasting. A volume and chloride depleted state results, which persists unless resuscitation with chloride containing fluids is done to replenish chloride stores.

Children with *cystic fibrosis* can present with metabolic alkalosis, hypokalemia, and hyponatremia due to excessive losses in sweat. This is more often in hot summer months and occasionally they may be wrongly labelled as pseudo-Bartter syndrome due to such presentation.

An additional condition may be seen in ICU settings. In children with chronic respiratory acidosis, there is increase in the bicarbonate as a compensatory mechanism. If there is a rapid fall in the  $PCO_2$  due to initiation of mechanical ventilation or modification of settings of ventilator, the blood gas analysis will suggest metabolic alkalosis. This situation can easily be diagnosed if the clinical course and serial blood gas analysis reports are evaluated.

Urinary chloride excretion can differentiate between chloride responsive and chloride resistant metabolic alkalosis. A urinary chloride level below 25 mmol/L is suggestive of an appropriate response to alkalosis and indicates volume contraction and non-renal causes. A high urinary chloride (>40 mmol/L)

suggests an inappropriate renal excretion of NaCl probably due to mineralocorticoid excess or severe hypokalemia. A child on diuretics may have a high chloride excretion initially but decreased excretion once the diuretic effect is over. Patient with low urinary chloride respond to saline with improvement of ECF and correction of alkalosis. However, children with high urinary chloride do not benefit with chloride supplementation and continue to lose chloride in urine unless the underlying condition is corrected.

Diuretics (loop or thiazides) cause volume depletion stimulating angiotensin II, aldosterone and adrenergic pathways. Hypokalemia caused by these diuretics increases acid excretion. Enhanced delivery of sodium to distal tubules also facilitates acid excretion. An edematous child who may already be volume depleted is at increased risk of metabolic alkalosis due to diuretics.

The causes of chloride resistant metabolic alkalosis include mineralocorticoid excess, severe hypokalemia, severe hypercalcemia, severe hypomagnesemia, Bartter syndrome, Gitelman syndrome, and Liddle syndrome. Presence of hypertension and metabolic alkalosis suggests mineralocorticoid excess. In a child with normal or low blood pressure and metabolic alkalosis, the Bartter or Gitelman syndrome are likely. Measurements of plasma renin and aldosterone levels are useful in differentiating syndromes of mineralocorticoid excess from those with apparent mineralocorticoid excess. Children with severe  $K^+$  deficiency do not improve despite chloride supplementation, but a small increment in  $K^+$  levels lead to remarkable recovery. Refeeding after starvation may also lead to a sudden rise in  $HCO_3^-$  leading to mild metabolic alkalosis. The possible causes include bicarbonate formed from the metabolism of organic anions, and concomitant deficiency of  $K^+$  and  $Cl^-$ .

## Clinical Features

Mild to moderate metabolic alkalosis is usually asymptomatic. The symptoms of the underlying disorder leading to acid-base imbalance may be predominant. Altered sensorium can occur secondary to cerebral vasoconstriction due to alkalosis. Hypokalemia which usually accompanies metabolic alkalosis may cause cardiac arrhythmias. Hypocalcemia due to decreased ionized calcium may lead to tetany, muscle cramps, seizures and other neurologic manifestations. Polyuria and polydipsia may occur secondary to potassium depletion. Patients on digitalis are on higher risk of arrhythmia in a setting of hypokalemia and metabolic alkalosis.

## Treatment

The aim of treatment of metabolic alkalosis is to correct the volume,  $Cl^-$  and  $K^+$  deficits. Efforts should be directed at correction of the underlying disease/condition. Oral or intravenous administration of sodium chloride and water is indicated in chloride responsive causes of metabolic alkalosis. With the exception of hypotension or shock or severe metabolic derangement, gradual correction is preferable to avoid complications of volume overload. The efficacy of such treatment can be assessed bedside by monitoring the urine pH. Urine pH, which is often below 5.5 before therapy, increases to beyond 7.0 once volume and chloride are replaced.

The administration of saline is usually ineffective in chloride resistant causes of metabolic alkalosis and can worsen hypertension. In patients with edematous states, withholding diuretics is the corrective therapy. Acetazolamide may be used to treat both edema and alkalosis, where withholding diuretics alone does not help. Correction of severe hypokalemia (as in states of mineralocorticoid excess) leads to correction of alkalosis.

### IN A NUTSHELL

1. Respiratory acidosis can be caused by hypoventilation, severe lung disease associated with ventilation-perfusion mismatch, airway obstruction or diffusion abnormalities.
2. Respiratory alkalosis can be caused by either increased CO<sub>2</sub> elimination (hyperventilation) or less commonly decreased CO<sub>2</sub> production.
3. A calculation of anion gap helps in characterizing the underlying problem leading to metabolic acidosis.
4. Causes of normal anion gap metabolic acidosis include diarrhea, renal tubular acidosis, early renal failure and chloride excess.
5. A useful method for evaluation of normal anion gap metabolic acidosis is assessment of urinary ammonia excretion.
6. Causes of increased anion gap acidosis include lactic acidosis, ketoacidosis, poisonings, and advanced renal failure.
7. Causes of chloride responsive metabolic alkalosis are persistent vomiting, nasogastric drainage, diuretics administration, recovery from chronic hypercapnia, and congenital chloride diarrhea.
8. Causes of chloride resistant metabolic alkalosis include mineralocorticoid excess, severe hypokalemia, severe hypercalcemia, severe hypomagnesemia, Bartter syndrome, Gitelman syndrome, and Liddle syndrome.
9. Urinary chloride excretion can differentiate between chloride responsive and chloride resistant metabolic alkalosis.

### MORE ON THIS TOPIC

- Adrogué HJ, Madias NE. Disorders of Acid-Base Balance. Chapter in Atlas of the diseases in kidney. Schrier RW. From: [http://www.kidneyatlas.org/book1/adk1\\_06.pdf](http://www.kidneyatlas.org/book1/adk1_06.pdf). Accessed 14 October 2014.
- Al-Khadra E. Disorders of acid-base status. In: Kiessling SG, Goebel J, Somers MJG (Eds). *Pediatric Nephrology in the ICU*. Berlin Heidelberg: Springer; 2009. pp. 19-33.
- Berend K, de Vries AP, Gans RO. Physiological approach to assessment of acid-base disturbances. *N Engl J Med*. 2014;371:1434-45.
- Carmody JB, Norwood VF. A clinical approach to paediatric acid-base disorders. *Postgrad Med J*. 2012;88:143-51.

## Chapter 5.5

# Sodium and Related Disorders

Andrew C Argent, Mignon I McCulloch

Sodium is the dominant ion in the extracellular space and is extremely important in the maintenance of osmotic gradients and electrical neutrality in the body. Normally the human body has a remarkable capacity to deal with large loads of water and/or sodium, but under certain circumstances that capacity is limited and abnormalities of sodium concentrations occur. The renal control of sodium is integral to the understanding of these processes. Dysnatremia (where sodium levels are above or below the normal range) or rapid changes in sodium concentration are relatively common in sick children and both may have profound consequences, with major impact on the brain. There is a growing realization that even relatively mild dysnatremia may be associated with increased morbidity in sick adults.

Pediatricians have been aware of hyponatremia related to inadequate feeding in breastfed neonates or as a complication of gastroenteritis or salt overload. Symptomatic hyponatremia in hospitalized children has been reported in bronchiolitis, pneumonia and meningitis; and following surgery, together with a growing realization that this might have been iatrogenic. More recently, iatrogenic deaths and severe neurological morbidity have been attributed to hyponatremia related to administration of hypotonic fluids to previously normal children in hospital.

## ETIOLOGY

Dysnatremia may be the consequence of a primary illness affecting the child, but is frequently the consequence of inappropriate administration of fluids and electrolytes to sick or injured children.

Hypernatremia is seen most commonly in the setting of acute fluid loss, which may occur in a variety of settings. In preterm infants, hypernatremia may be related to excessive water losses through the skin, particularly in very low birthweight infants who are kept under radiant heaters and/or phototherapy units. Hypernatremia is also seen in breast-fed infants who have been receiving inadequate amounts of breast milk or if formula feeds have been overly concentrated. In older infants, gastroenteritis is the most common cause of hypernatremia, particularly those in whom oral rehydration fluid have been mixed incorrectly with a high concentration of salt.

Hyponatremia develops frequently in hospitalized children, particularly if they are treated with hypotonic intravenous fluids (the higher the proportion of fluids given intravenously, the higher the risk). These fluids can be either as prepackaged *maintenance fluid* solutions or as “*self-mixed*” cocktails of fluids. Particular clinical conditions which are more frequently associated with development of hyponatremia include cardiac diagnosis, pneumonia or respiratory infections, neurological disease or neurosurgical procedures, surgical reason for admission, or an underlying hematology/oncology diagnosis. Recently a number of authors and organizations have concluded that the incidence of hyponatremia could be substantially reduced by the use of intravenous fluids with 0.9% saline and not hypotonic fluids in sick children.

Hyponatremia is seen much less frequently in the context of endocrine abnormalities such as adrenal insufficiency, and more commonly in the context of children who have renal disease (transient acute kidney injury or chronic established disease) and those who have been on diuretic therapy (often in the context of underlying cardiac disease).

## PATHOGENESIS

### Normal Physiology

The concentration of sodium in the body is closely related to the water content of the body. In the infant, total body water constitutes approximately 70% of body weight (approximately 45% in the intracellular compartment, and about 25% in the extracellular compartment) and this changes during normal growth to the adult situation where body water constitutes 50–60% of body water (more in males).

Sodium is distributed throughout the body, with major differences in concentration between the intracellular and extracellular compartments (**Table 1**) and approximately 40% of total body sodium is within bone (in adults). Generally, water can move freely across cell membranes and does so in response to the osmotic pressure differences between the intracellular and extracellular spaces. As the intracellular space includes a wide number of osmotically active substances, the osmotic pressure within the cell is maintained by the active extrusion of sodium from the cell and normally there is little osmotic gradient across the cell membrane. As sodium is the major extracellular ion, significant changes in extracellular sodium may be associated with significant fluid shifts between the intracellular and extracellular spaces. Cells are able to respond in a variety of ways to changes in extracellular osmolality and change the intracellular osmolality. In hyperosmolar situations, they are able to increase the intracellular osmolality by degrading macromolecules such as proteins and glycogen to amino acids and glucose while forming other *osmolytes* such as polyols, methylamines and certain amino acids. The reverse process occurs in hypo-osmolar situations. Unfortunately these processes take time, and thus, rapid changes in electrolyte

**Table 1** Electrolyte concentrations in the body

Electrolyte	Intracellular concentration	Extracellular concentration	Plasma concentration
Sodium (Na <sup>+</sup> )	15 mmol/L	143 mmol/L	141 mmol/L
Potassium (K <sup>+</sup> )	140 mmol/L	4 mmol/L	4 mmol/L
Chloride (Cl <sup>-</sup> )	8 mmol/L	115 mmol/L	103 mmol/L
Calcium (Ca <sup>++</sup> )	0.1 μmol/L	1.3 mmol/L	2.5 mmol/L
Bicarbonate (HCO <sub>3</sub> <sup>-</sup> )	15 mmol/L	28 mmol/L	25 mmol/L
Magnesium (Mg <sup>++</sup> )	15 mmol/L	0.7 mmol/L	1 mmol/L
Phosphate (PO <sub>4</sub> <sup>-</sup> )	10 mmol/L	1 mmol/L	1 mmol/L

Source: Lang F. Mechanism and significance of cell volume regulation. J Am Coll Nutr. 2007;26:6135–235.

concentration (particularly sodium) may cause significant cell damage, particularly within the brain where changes may be exacerbated by thrombosis in the venous structures and by changes in intracranial pressure. These processes are often complicated by administration of various fluids and drugs.

Generally water moves freely through the endothelia between body compartments in response to the balance between oncotic pressures and hydrostatic pressures in those compartments. Fluid shifts between the intravascular and extracellular fluid compartments are largely driven by hydrostatic pressure and oncotic pressure related to macromolecules such as proteins.

Different body fluids have different concentrations of sodium (**Table 2**). Usually gastrointestinal fluids are secreted into the gut and mostly reabsorbed (leaving approximately 30 mmol/L sodium in relatively low volumes of normal stool), particularly in the large intestine. Thus, the normal gastrointestinal losses of sodium are low. However, in situations where there are abnormal gastrointestinal



**Table 2** Sodium concentration in different body fluids

Fluid	Sodium concentration (mmol/L)
<i>Gastrointestinal</i>	
Saliva	80
Gastric	60
Bile	140
Pancreatic fluids	140
Small bowel content	120
<i>Renal</i>	
GFR	140
Urine	< 1–300 dependent on situation
Sweat	5–80

Abbreviation: GFR, glomerular filtration rate.

Source: Lang F. Mechanism and significance of cell volume regulation. *J Am Coll Nutr.* 2007;26:613S–23S.

losses (vomiting; nasogastric tube drainage; presence of fistulae or stomas; diarrhea) there may be considerable losses of sodium. In gastroenteritis, the sodium losses may be related to specific pathogens with much higher sodium losses in gastroenteritis related to enteropathogenic *E. coli* or *Vibrio cholerae* than in rotavirus diarrhea. It is important to note that insensible fluid losses (from respiration and skin losses) do not contain sodium. While little sodium is generally lost through sweat, this may not be true in patients with cystic fibrosis who may lose significant amounts of sodium through sweat.

In the normal adult kidney, approximately 1.3 kg of sodium chloride (NaCl) is filtered through the glomeruli each day, together with some 180 liters of water. The vast majority of the NaCl and water are reabsorbed in the tubular system and both salt and water levels in the body are tightly regulated by a variety of endocrine systems. The urine output may vary substantially and urinary sodium concentration can vary between less than 1 mmol/L and 300 mmol/L. As a consequence the normal adult has a considerable capacity to deal with a wide range of both water and sodium intake without developing abnormal serum sodium levels. This is not true in premature babies and young infants who have limited renal concentrating capacity.

Water intake and output may vary considerably throughout the day and from day to day. The excretion of sodium and water by the kidney are controlled by the renin-angiotensin system via the adrenal glands (increased angiotensin II production causes the retention of sodium and associated water), the arginine vasopressin system via the posterior pituitary gland (increased secretion increases water retention by the body) and the natriuretic peptides secreted by the brain and the heart (**Flow chart 1**). The arginine vasopressin system may also stimulate thirst with subsequent changes in fluid intake in patient who are able to seek additional fluid and drink.

## Pathophysiology

Dysnatremia may arise in a number of situations (**Table 3**). Changes in the sodium concentrations significantly alter the osmolality of the extracellular fluid compartment, and this may be exacerbated if there are concomitant changes in the glucose concentration (as in diabetes mellitus, or not uncommonly in severe hyponatremia related to gastroenteritis). This change in osmolality may cause fluid shifts between the intracellular and extracellular spaces with subsequent damage, particularly to the brain. In addition, hyponatremic states may be associated with hypercoagulability. Thus, cerebral sinus and venous thrombosis have been associated with hyponatremia in children of all ages. Complications of dysnatremia have been described both in response to the primary

condition, and in response to rapid iatrogenic correction of the dysnatremia.

## Hypernatremia

Hypernatremia may be related to either water loss, sodium overload or a combination of both of these (**Table 3**). Severe hypernatremia in the neonatal period may be a complication of inadequate breast-feeding, of inappropriate mixing of formula feeds or less frequently underlying gastrointestinal problems or renal disease. The condition may have a range of presentations, but may have severe complications including cerebral venous and venous sinus thrombosis with severe long-term neurological consequences.

Hypernatremia in gastroenteritis may be relatively common in developing countries, particularly if there have been errors with the constitution of rehydration fluids. In this setting, the hypernatremia is primarily related to gastrointestinal fluid losses, but may also be exacerbated by renal tubular dysfunction with inadequate urinary concentration. This will only become obvious if urine output is specifically monitored using a urinary catheter.

Hypernatremia is also seen in neurological conditions where it may be the result of diabetes insipidus related to damage to the posterior pituitary, or it may be the consequence of iatrogenic administration of hypertonic saline. Although hypertonic saline has been extensively used to try and reduce brain swelling in neurological or neurosurgical situations, there is evidence that hypernatremia in this setting may be associated with adverse outcomes.

## Hyponatremia

During illness or injury there may be substantial changes in the endocrine environment which generally tend toward retention of water (with or without sodium). Arginine vasopressin levels are frequently elevated in patients with pneumonia and meningitis (including tuberculous meningitis, following surgery or other procedures or following therapy with vasopressin). The elevation of vasopressin may reflect relative hypovolemia or an attempt to improve cerebral perfusion. In some situations administration of a fluid bolus has been shown to cause normalization of the vasopressin levels, but administration of hypotonic fluids—which used to be common clinical practice—to these children will almost invariably result in the development of hyponatremia.

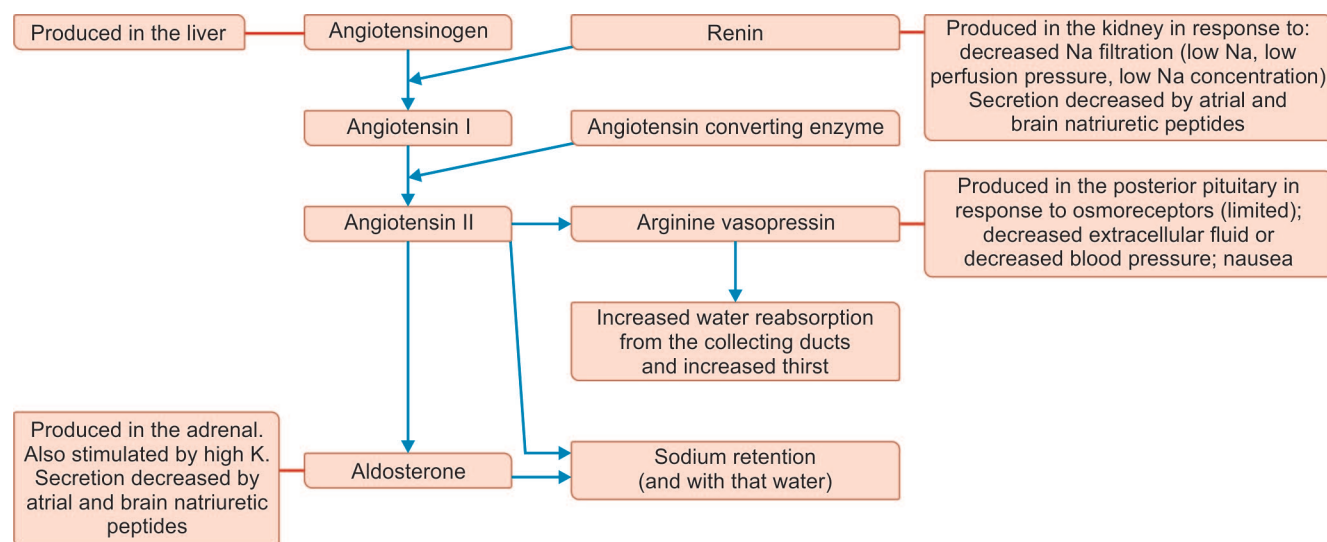
There is considerable debate as to whether the hyponatremia that may occur in hospitalized children on hypotonic intravenous fluids is related to excessive fluid intake, or the hypotonic fluids administered (or possibly both). Some children may still become hyponatremic despite the administration of 0.9% NaCl. There is however, a consensus that *maintenance intravenous fluid* in sick children or following surgical procedures should be given at a rate less than that initially recommended by Holliday and Segar. Fluid overload is increasingly seen to have adverse clinical outcomes.

Following surgical procedures, particularly neurosurgical and spinal procedures there is a high incidence of hyponatremia which may be related to high arginine vasopressin levels, but has also been related to the entity of cerebral salt wasting. While the entity of cerebral salt wasting may be controversial, it is clear that in this setting, fluid restriction alone may be inadequate to improve sodium levels and administration of 0.9% NaCl (or higher concentrations) may be necessary in order to normalize dysnatremia.

While primary endocrine causes of hyponatremia are relatively rare, it is important to be aware of this possibility. The full clinical picture of adrenal insufficiency may take time to develop and may not be obvious. However, the association of low sodium levels together with high potassium levels should alert the clinician to this possibility.

**Table 3** Hyponatremia—real or not?

	Problem	Correction
Spurious hyponatremia	Contamination of the specimen with fluid that has a low sodium concentration—may occur if specimen collected from vein into which an intravenous infusion with low sodium concentration is running	Not possible, need to repeat specimen collection
Pseudohyponatremia	Specimen has high concentration of lipid (particularly seen if patient is on total parenteral nutrition) or protein	The concentration of sodium in water is normal, but each liter of serum contains less water. [True sodium] (mEq/L) = [reported sodium (mEq/L)] $\times$ [0.021 $\times$ (triglycerides in mg/dL) + 0.994]
Fictitious hyponatremia	Sodium content of the serum is normal, but concentration is decreased by the osmotic impact of hyperglycemia	Measured sodium levels decrease by approximately 1.6 mmol/L for every 100 mg/dL (approximately 5.5 mmol/L) increase in glucose concentration. Alternatively [Corrected Na] = [measured Na] + 2[(plasma glucose - 5.6)/5.6] (mmol/L)

**Flow chart 1** Regulation of sodium and water excretion

## CLINICAL FEATURES

The most common clinical features of acute dysnatremia in children relate to the central nervous system with symptoms ranging from altered behavior, changes in level of consciousness and irritability to convulsions and features of raised intracranial pressure. Although these signs and symptoms are very nonspecific, they should be taken as warning signs in any clinical situation where there are (or potentially have been) significant fluid shifts, either with loss of fluid or with administration of significant fluid volumes.

### Hyponatremia

Mild symptoms of hyponatremia include headache, nausea, vomiting and anorexia. There may be development of altered sensorium, abnormal behavior, hallucinations, seizures and respiratory depression. Severe cerebral edema may manifest with abnormal posturing, abnormal blood pressure, prolonged seizures, and coma.

### Hypertnatremia

Symptoms of hypertnatremia include high-pitched cry, irritability, lethargy, abnormal sensorium, seizures and hypertonia. Few children may have rhabdomyolysis.

There are high-risk situations which include:

- Children with renal disease, cardiac disease (particularly with use of diuretics), infections (particularly of the central nervous

system or the respiratory system) or following either injury or surgical procedures

- Children who are receiving significant volumes (> 24% of total daily fluid intake) of intravenous fluids
- Children have been given hypertonic saline infusions or other osmotically active solutions such as mannitol.
- Children with skin conditions that are related to excessive fluid losses (including burns, Stevens Johnson syndrome, extreme prematurity, etc.)
- Situations in which there are marked elevations in glucose levels—as may happen in diabetes mellitus.

One of the challenges with the diagnosis of dysnatremia in children is the overlap of the clinical features with the clinical features of the underlying and contributory conditions. Thus the diagnosis is likely to be missed unless the possibility is frequently considered. Chronic dysnatremia may develop in children on diuretic therapy and with cirrhosis, and correction of the dysnatremia has been associated with improved quality of life.

## APPROACH TO DIAGNOSIS

Dysnatremia should be considered within the clinical context mentioned above, but particularly when patients present with altered level of consciousness, irritability and/or seizures. The diagnosis is made by direct measurement of serum sodium levels. As shown in **Table 4**, there are a number of situations where the

reported value of sodium may be lower than the actual level, and this may be important both in the diagnosis of hyponatremia, and when considering the severity of hypernatremia. Total fluid overload since admission can be determined by careful input and output measurements.

## MANAGEMENT

As soon as the diagnosis of dysnatremia has been made, measures should be taken to provide an understanding of the etiology of the condition and to correct sodium levels to normal. An underlying principle is that if dysnatremia is associated with severe symptoms such as seizures, the initial correction should be relatively rapid. In all other settings the sodium concentration should be corrected at a rate that does not exceed 0.5–1 mmol/L per hour.

### Hypernatremia

Ongoing hypernatremia is associated with ongoing brain injury. If the patient is hypovolemic, then fluid boluses with approximately 150 mmol/L of Na should be given until the patient is normovolemic. Thereafter, the fluid administration would depend on the cause of the hypernatremia. In settings where excessive fluid losses are ongoing and dehydration is part of the cause, therapy should focus on limiting ongoing losses where possible (this may include the administration of vasopressin in diabetes insipidus, obtaining skin cover for burns, etc.).

If the patient is dehydrated, then maintenance fluids together with rehydration fluids should be administered. As it may be impossible to predict ongoing fluid losses, it is reasonable to estimate the fluid requirements (planning to provide rehydration over approximately 48 hours) and then monitor the patient at regular intervals (using weight, urine output and serum electrolyte levels) to ensure that the patient is actually being rehydrated. The sodium content of the fluid to be administered would depend to some extent on the underlying pathology. Some authors have recommended fluid replacement with isotonic saline, while other studies have shown that patients with severe hypernatremic dehydration related to gastroenteritis can be safely rehydrated using a 0.45% saline solution. Measurement of the sodium content of the fluids that are being lost may provide some insight into what replacement fluids can be administered. In a child with diabetes insipidus, the child's hyponatremia will respond to administration

of vasopressin or its analog—1-deamino-8-D-arginine vasopressin; however, one should be careful about intake of electrolyte-free water during this period as there may be rapid fall in serum sodium.

Some patients can have oral fluid administration for correction of hypernatremia, but great care should be exercised if there is a depressed level of consciousness.

### Hyponatremia

If there is hyponatremic encephalopathy, then emergency therapy with 2 mL/kg bolus of 3% NaCl (maximum 100 mL) can be given (a similar sodium load could be used if only 5% solutions are available), and be repeated 1–2 times if symptoms persist. Once acute symptoms have resolved sodium concentrations should be corrected at a rate of 0.5–1 mmol/L per hour.

Again the principles in achieving that rate of correction depend on adjusting fluid intake (if fluid overload is a component of the problem then restriction of fluid intake would be appropriate).

## OUTCOMES/ PROGNOSTIC FACTORS

There is increasing recognition that dysnatremia is associated with adverse outcomes in adults, in children and in neonates. In many of these settings, it is difficult to separate the prognosis related to dysnatremia from the prognosis of the underlying illness, but there is evidence that the outcomes are related to the severity of the dysnatremia. However, there is data from adult intensive care studies to show that correction of dysnatremia is associated with improved outcome.

## PREVENTION

Within the healthcare environment, prevention needs to be focussed on identification of high-risk patients, careful management of intravenous fluid administration and appropriate monitoring. In general hypotonic intravenous solutions with [Na] of less than 70 mmol/L should not be given to hospitalized children or those following surgical interventions (in the early neonatal period there may still be a place for hypotonic intravenous fluids particularly in infants with high insensible fluid losses). A number of international guidelines have recommended the removal of such hypotonic fluids from pediatric clinical areas. Several authors have recommended the use of intravenous fluids containing at least 130 mmol/L of Na for maintenance fluids in children. There are even

**Table 4** Causes of dysnatremia

	Hypernatremia	Hyponatremia
Sodium related	<p><i>Acute sodium overload</i></p> <ul style="list-style-type: none"> <li>• Oral or parenteral</li> <li>• Iatrogenic or accidental</li> </ul>	<p><i>Acute sodium loss</i></p> <ul style="list-style-type: none"> <li>• Gastrointestinal losses</li> <li>• Renal losses               <ul style="list-style-type: none"> <li>– Tubular dysfunction</li> <li>– Cerebral salt wasting syndromes</li> <li>– Adrenal dysfunction</li> </ul> </li> </ul> <p><i>Chronic sodium loss</i></p> <ul style="list-style-type: none"> <li>• Diuretic use</li> </ul>
Water related	<p><i>Water loss</i></p> <p><i>With polyuria</i></p> <ul style="list-style-type: none"> <li>• Diabetes insipidus (cranial or nephrogenic)</li> <li>• Diabetes mellitus</li> </ul> <p><i>Without polyuria</i></p> <ul style="list-style-type: none"> <li>• Neonatal hypernatremia related to inadequate breast-feeding with limited renal concentrating capacity</li> <li>• Gastroenteritis</li> <li>• Evaporation via the skin in situations of loss of integumentary integrity (preterm infants, burns)</li> <li>• Inadequate intake related to confusion, depressed level of consciousness, patient unable to access fluids, rare hypodipsic hypernatremic syndromes</li> </ul>	<p><i>Water overload</i></p> <ul style="list-style-type: none"> <li>• Administration of excessive free water</li> <li>• Administration of hypotonic intravenous fluids</li> </ul>

recommendations that children with dehydrating diarrhea should be rehydrated with intravenous fluids containing 0.9% saline, but these recommendations have not been tested in settings with a high incidence of severe dehydrating gastroenteritis.

Children on enteral feeds are at less risk of developing dysnatremia than those given significant volumes of intravenous fluids, so enteral feeds should be provided to children where at all possible. When intravenous fluids are given in volumes exceeding 30% of recommended daily fluids, then serum sodium levels should be checked at least daily.

Probably the most important consideration in the prevention of dysnatremia is the recognition that the condition is common in hospitalized children, particularly those on intravenous fluids and can be largely avoided by careful monitoring of fluid and electrolyte intake of children at risk, and regular monitoring of serum sodium levels.

Outside the hospital environment, dysnatremia is probably best addressed by general education (particularly directed at mothers) of the risks associated with water and electrolyte imbalance in children.

### IN A NUTSHELL

1. Dysnatremia (serum sodium < 135 mmol/L or > 145 mmol/L) is common in sick children of all ages and is associated with increased morbidity and mortality.
2. Children are at particular risk of dysnatremia in the settings of: significant fluid administration (particularly intravenous) or losses, renal disease, cardiac disease (particularly with diuretic therapy) or in the setting of acute respiratory or neurological disease.
3. Children are at significant risk of hyponatremia if given hypotonic fluids as *maintenance fluid* in the perioperative period particularly if surgery has involved the spine and the brain.
4. Dysnatremia may have devastating effects on the brain with acute presentations of seizures and long-term adverse consequences.
5. Most cases of hyponatremia could be avoided by careful implementation of fluid guidelines together with careful monitoring of children at risk.

### MORE ON THIS TOPIC

- Blum D, Brasseur D, Kahn A, Brachet E. Safe oral rehydration of hypertonic dehydration. *J Pediatr Gastroenterol Nutr.* 1986;5:232-5.
- Bussmann C, Bast T, Rating D. Hyponatraemia in children with acute CNS disease: SIADH or cerebral salt wasting? *Childs Nerv Syst.* 2001;17:58-62.
- Carandang F, Anglemeyer A, Longhurst CA, et al. Association between maintenance fluid tonicity and hospital-acquired hyponatremia. *J Pediatr.* 2013;163:1646-51.
- Easley D, Tillman E. Hospital-acquired hyponatremia in pediatric patients: a review of the literature. *J Pediatr Pharmacol Ther.* 2013;18:105-11.
- Foster BA, Tom D, Hill V. Hypotonic versus isotonic fluids in hospitalized children: a systematic review and meta-analysis. *J Pediatr.* 2014;165:163-9.
- Halberthal M, Halperin ML, Bohn D. Lesson of the week: Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. *BMJ.* 2001;322:780-2.
- Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics.* 1957;19:823-32.
- Kanakriyeh M, Carvajal HF, Vallone AM. Initial fluid therapy for children with meningitis with consideration of the syndrome of inappropriate antidiuretic hormone. *Clin Pediatr (Phila).* 1987;26:126-30.
- Lim YJ, Park EK, Koh HC, Lee YH. Syndrome of inappropriate secretion of antidiuretic hormone as a leading cause of hyponatremia in children who underwent chemotherapy or stem cell transplantation. *Pediatr Blood Cancer.* 2010;54:734-7.
- Rivkees SA. Differentiating appropriate antidiuretic hormone secretion, inappropriate antidiuretic hormone secretion and cerebral salt wasting: the common, uncommon, and misnamed. *Curr Opin Pediatr.* 2008;20:448-52.
- Robertson G, Carrihill M, Hatherill M, et al. Relationship between fluid management, changes in serum sodium and outcome in hypernatraemia associated with gastroenteritis. *J Paediatr Child Health.* 2007;43:291-6.
- Wang J, Xu E, Xiao Y. Isotonic versus hypotonic maintenance IV fluids in hospitalized children: a meta-analysis. *Pediatrics.* 2014;133:105-13.
- Wrotek A, Jackowska T. Hyponatremia in children hospitalized due to pneumonia. *Adv Exp Med Biol.* 2013;788:103-8.
- Yaseen H, Salem M, Darwich M. Clinical presentation of hypernatremic dehydration in exclusively breast-fed neonates. *Indian J Pediatr.* 2004; 71:1059-62.
- Zilberberg MD, Exuzides A, Spalding J, et al. Epidemiology, clinical and economic outcomes of admission hyponatremia among hospitalized patients. *Curr Med Res Opin.* 2008;24:1601-8.



## Chapter 5.6

# Potassium

Virendra Kumar

Potassium, an essential cation for cellular functions, is widely distributed in body. It is one of the most commonly affected ions in sick children. The spectrum of disorders related to the potassium homeostasis may vary from asymptomatic to serious life-threatening state, requiring immediate intervention. This section will deal with the physiological aspects of potassium homeostasis and disorders related to them.

### BASICS OF POTASSIUM PHYSIOLOGY

The total body content of potassium may vary from person to person depending upon the muscle mass. In an average person it is approximately 50 mEq/kg body weight. Nearly 98% of potassium is distributed in the intracellular compartment with a concentration of 140–150 mEq/L. Three-fourths of intracellular potassium is in muscles. Only 2% of the potassium is in the extracellular compartment, mostly in bones. Normal plasma concentration of 3.5–5.2 mEq/L represents about 0.4% of total body potassium.

The intracellular to extracellular potassium gradient (38:1) is maintained by sodium potassium adenosine triphosphatase (Na-K-ATPase) and selective potassium channels located in the cell membrane. Na-K-ATPase allows active transport of potassium into the cells whereas selective channels allow passive diffusion of potassium out of cells. Potassium gradient across the cell membrane helps in maintaining resting membrane potential. Potassium is also required for generation of action potential and depolarization.

*Potassium homeostasis* depends on a number of renal and extrarenal factors, such as intake, gastrointestinal and urinary losses and transcellular shift. Daily requirement of potassium is about 1–2 mEq/kg. Nearly 90% is absorbed in small intestine and eliminated through kidney; 5–10% is excreted in stool and less than 5% in sweat. Potassium losses in stool may be increased in diarrhea and other related disorders. Colonic secretion of potassium in response to hyperkalemia is also increased under the influence of aldosterone and glucocorticoids.

Transcellular shift of potassium is an early protective measure against loss of excess of potassium and helps maintaining the electroneutrality between intracellular and extracellular compartment without altering the total body potassium. Major factors which influence transcellular shift are metabolic acidosis, alkalosis, insulin, glucagon, catecholamine, hyperosmolality, failure of Na-K-ATPase pump, and cellular injury. Insulin and  $\beta$ -adrenergic receptor agonist activate Na-K-ATPase and promote potassium uptake by the cells. Acidosis promotes extracellular movement of potassium, whereas alkalosis leads to potassium uptake by the cells. Extracellular increase in osmolality results in water movement from intracellular to extracellular space and potassium moves out of cells passively as dragging effect. Hyperkalemia itself stimulate insulin secretion and thereby intracellular movement of potassium.

### Excretion of Potassium

Kidney is the primary organ responsible for excretion of 90% of the potassium. Colonic secretion may contribute to a small amount. In persons with normal renal function, potassium is filtered freely from the glomerulus. Nearly 85–90% of the potassium is reabsorbed up to distal tubules and only 10–15% reaches cortical and outer

medullary collecting duct, which is the principle site of regulation of potassium excretion. They have the capacity to reabsorb and secrete as well into the lumen. In case of potassium depletion, absorption exceeds the secretion and urinary  $K^+$  levels of less than 15 mEq/day suggest renal potassium conservation.

Potassium secretion in cortical collecting duct (CCD) is regulated mainly by the aldosterone secreted from adrenal cortex. Plasma concentration of potassium and sodium and water delivery to *distal convoluted tubule* also influences the regulation of potassium secretion by activating the Na-K-ATPase pump. *Antidiuretic hormone* does not contribute much to the overall potassium excretion.

Aldosterone facilitates the movement of sodium into the peripheral cells of CCD through sodium channels. Increased intracellular sodium concentration stimulates Na-K-ATPase activity and potassium is secreted into the lumen to balance the negative luminal charges. Intracellular concentration gradient also allows the passive diffusion of potassium from the cells through potassium channels.

The net  $K^+$  secretion at CCD level can be evaluated by transtubular  $K^+$  concentration gradient (TTKG), which is the ratio of  $K^+$  concentration in the lumen of CCD to that of plasma.  $K^+$  concentration in CCD lumen can be calculated by urinary  $K^+$  concentration divided by the ratio of urinary and plasma osmolality (Uosm and Posm).

$(K^+)_{CCD} = (K^+)_{urine} / (Uosm/Posm)$ ;  $TTKG = (K^+)_{CCD} / (K^+)_{plasma}$ . In hypokalemic children TTKG of more than 4, indicates renal loss of  $K^+$ , whereas in hyperkalemic children TTKG of less than 8, suggests impaired renal secretion of potassium.

### HYPOKALEMIA

Hypokalemia is defined as plasma potassium concentration of less than 3.5 mEq/L. It is reported in 20–68% of hospitalized patients in different clinical settings. In addition to plasma potassium concentration, intracellular to extracellular potassium ratio and concentration gradient across the membrane also effect the polarization of cell membrane and its function. Hypokalemia possesses a greater risk of complications in cases with pre-existing heart disease, liver disease, severe acute malnutrition, respiratory disease or on ventilatory support.

### Etiology

Reduction of plasma potassium levels may broadly be attributed to inadequate intake of some duration, result of transcellular shift, or renal and extrarenal losses. However, in day to day practice, errors related to sample collection, processing or estimation causing spurious hypokalemia are also common.

*Inadequate oral intake* or intravenous supplementation of potassium may result in hypokalemia, though renal conservation of potassium helps preventing it unless the net intake is less than 15 mEq/day. However, it takes 3–5 days for effective renal conservation.

*Transcellular shift* of potassium can give rise to hypokalemia without total body potassium depletion. Beta-adrenergic receptor agonist (catecholamine, bronchodilators), insulin and alkalosis are commonly associated with intracellular shift. Theophylline by blocking the degradation of cyclic *adenosine monophosphate* and barium by blocking the potassium channels can also lead to hypokalemia. Hypokalemic periodic paralysis and thyrotoxicosis are rare causes but may be associated with massive shift of potassium into the cells.

*Gastrointestinal (GI) losses of potassium* in children are commonly observed with large volume diarrhea. Fecal content of potassium in diarrhea is usually 30–35 mEq/L; in severe diarrhea

the losses may exceed 100 mEq in a day. Persistent vomiting or nasogastric aspirates, losses from GI fistula and congenital chloride losing diarrhea are the other causes which can lead to GI losses. Potassium content of gastric fluid is not more than 10 mEq/L and hypokalemia observed with upper GI losses is also contributed by urinary loss of potassium in response to hypovolemic stimulation of aldosterone.

*Increased urinary loss of potassium ( $K^+$ )* alone or in addition to other losses is a common cause of hypokalemia in children. Hypokalemia due to renal loss can be categorized on the basis of acid-base status. *Hypokalemia with normal acid-base status or metabolic acidosis* is seen in diuretic phase of acute tubular necrosis, postobstructive uropathy, renal tubular acidosis type I and II, osmotic diuresis, hypomagnesemia and drugs. Commonly associated drugs are diuretics, aminoglycosides, and amphotericin B. Children having *hypokalemia with alkalosis* require estimation of urinary chloride. Normal urinary chloride varies from 10 mEq/L to 20 mEq/L. Cases presenting with *hypokalemia, alkalosis and low urinary chloride* are generally secondary to conditions resulting in chloride loss, such as postdiuretic phase, chloride losing diarrhea, persistent vomiting or cystic fibrosis.

*Hypokalemia, alkalosis and high urinary chloride with normal blood pressure* is usually associated with diuretics, Bartter or Gitelman syndrome. In thick ascending limb of loop of Henle [thick ascending limb (TAL)], defect in  $Na^+-K^+-Cl^-$  co-transport results in poor sodium reabsorption, salt wasting, and elevated renin and aldosterone levels in Bartter syndrome. A significant proportion of filtered calcium is also reabsorbed in TAL; defect in TAL also results in poor calcium absorption and hypercalciuria. Loop diuretics act on  $Na^+-K^+-Cl^-$  co-transporter in TAL and prolonged use of them can give rise to Bartter like picture. Mutations in gene encoding for thiazide-sensitive  $Na^+-Cl^-$  co-transporter in distal tubule are responsible for Gitelman syndrome. Since calcium absorption is normal hypercalciuria is not seen. Hypocalciuria, hypomagnesemia and late presentation are distinguishing feature of Gitelman syndrome.

A similar combination of metabolic alkalosis, hypomagnesemia and hypocalciuria is also seen in epilepsy, ataxia, sensorineural hearing loss and tubulopathy (EAST) syndrome. Defect in gene encoding for potassium channels present in kidney, ear and brain results in EAST.

Cases with *hypokalemia, alkalosis and hypertension* are classified on the basis of mineralocorticoid activity. Aldosterone, being a primary regulator of potassium loss in urine, raised levels increases  $Na^+-K^+-ATPase$  activity, resulting in sodium retention and potassium secretion into the tubular lumen and excretion in urine. This leads to the development of hypokalemia and hypertension. Primary hyperaldosteronism is seen in adrenal hyperplasia, adenoma or glucocorticoids remediable aldosteronism. In all these cases, PRA activity is low. Secondary hyperaldosteronism may result from decreased intravascular volume or increased renin activity. Elevated levels of mineralocorticoids other than aldosterone such as cortisol, deoxycorticosterone and exogenous steroids can also produce hypertension and hypokalemia.

Similarly, nonaldosterone upregulation of sodium ( $Na^+$ ) channels is seen in cases with Liddle syndrome. Mutations of  $\beta$  or  $\gamma$  subunit of intracellular carboxyl terminal of  $Na^+$  channels of distal tubules increases  $Na^+$  conductance resulting in more of  $Na^+$  absorption and  $K^+$  secretion into the tubular lumen and hypokalemia.

### Pathological Changes Observed With Hypokalemia

Reversible epithelial vacuolization of proximal tubules are early changes observed with hypokalemia. In cases with persistent hypokalemia, interstitial lymphocytic infiltration, scarring and

tubular atrophy may be seen. Rarely, rhabdomyolysis may be seen with severe persistent hypokalemia.

### Clinical Features

Clinical manifestations are primarily dependent on the extracellular potassium concentration and the gradient across the membrane. Acute changes in plasma potassium may affect neuromuscular, cardiac, renal and GI system. Hypokalemia may be graded on the basis of plasma potassium concentration as mild (3.5–3 mEq/L), moderate (3–2.5 mEq/L) or severe (< 2.5 mEq/L). Mild hypokalemia is generally asymptomatic, however worsening of pre-existing heart disease, liver disease or ventilatory functions is known to occur even with mild hypokalemia.

Moderate hypokalemia results in muscle weakness, hypotonia, hyporeflexia, decrease bowel movements (distension, feed intolerance). Severe hypokalemia may lead to ascending paralysis, respiratory failure, and cardiac dysrhythmia. Consciousness remains normal unless there is some other cause to affect it. Persistent hypokalemia may present with polyuria and polydipsia similar to diabetes insipidus. Inability of the kidney to excrete bicarbonate, increased collecting duct secretion of  $H^+$  ion and increased chloride loss in urine contribute to metabolic alkalosis in hypokalemia, which can further reduce the plasma potassium levels.

### Electrocardiographic Changes

All cases with hypokalemia may not show electrocardiographic (ECG) changes. Appearance of U wave with amplitude more than that of T wave, ST segment depression and flattening of T wave are commonly seen in moderate hypokalemia. Prolongation of PR interval, QRS widening and ectopic rhythm usually suggests severe hypokalemia.

### Management

All children should be clinically evaluated for the underlying disease, clinical features, ECG changes, nutritional status, hydration, hypertension and status of respiratory, cardiac, liver and renal functions. Exposure to drugs especially digoxin, insulin,  $\beta$  agonist, amphotericin B, diuretics and steroids in the recent past should also be checked. Initial investigations required, in addition to plasma/serum  $K^+$  are *arterial blood gas*, electrolytes, blood glucose, osmolality and urinary potassium and chloride.

Most of the children with plasma potassium levels between 3 mEq/L and 3.5 mEq/L are asymptomatic and many have spurious hypokalemia. True asymptomatic hypokalemia may be managed with dietary or oral potassium supplementation, 2–4 meq/kg/day mixed with feed to avoid GI irritation. If oral potassium cannot be given, intravenous fluid concentration of potassium may be increased from maintenance of 20 mEq/L to 40 mEq/L and then reassess every 6–8 hours for further need. Each milliliter of injection potassium chloride (KCl), 15% solution provides 2 mEq of potassium and should be diluted at least 50 times of its volume. Simultaneously appropriate replacement of ongoing losses and correction of underlying cause should also be considered.

Children with severe hypokalemia with respiratory failure or cardiac dysrhythmia should initially be supported for airway, breathing and circulation. Hypokalemia should be treated either with increasing the intravenous fluid concentration of potassium to 60 mEq/L or with a rapid infusion of 0.5–1 mEq/kg (maximum 40 mEq) of KCl diluted in 5–10 mL/kg of saline (dextrose may stimulate insulin secretion and shift of  $K^+$  into the cells) to be given over 30–60 minutes under strict monitoring in pediatric intensive care unit (PICU). As the plasma  $K^+$  concentration improves the rate of infusion should be reduced to maintenance. Children who respond poorly to potassium replacement should also be checked and corrected for hypomagnesemia and hypophosphatemia.

## HYPERKALEMIA

Hyperkalemia is defined as plasma potassium levels of greater than 5.5 mEq/L. Though less common than hypokalemia, the serious consequences such as arrhythmia and sudden death are more common. Based on the plasma  $K^+$  concentration hyperkalemia can be categorized as mild, (5.5–6.5 mEq/L), moderate (6.6–8 mEq/L) or severe ( $> 8$  mEq/L). Rapidly rising potassium levels, presence of hypoxia or acidosis and compromised cardiac status are other contributory factors for complications.

### Etiology

*Spuriously raised levels* may be due to release of potassium from hemolyzed RBCs at the time of sampling or due to delay of more than 3 hours in sample processing at room temperature. Release of potassium during clot formation may result in about 0.4 mEq/L higher potassium level in serum compared to plasma. This may become significant if there is marked leukocytosis or thrombocytosis.

*True hyperkalemia* may either be due to increased load of potassium, impaired renal excretion or transcellular shift of potassium. In a given case there may be more than one mechanism responsible for hyperkalemia. Since kidneys have potential of excreting large amount of potassium, generally there is some degree of renal impairment associated with increased potassium load to cause hyperkalemia.

An excess load of  $K^+$  from exogenous source (potassium salt supplements, stored blood transfusion) or endogenous source (intravascular hemolysis, resolving hematoma, rhabdomyolysis and tumor lysis) may result in hyperkalemia.

Renal excretion of potassium is influenced mainly by the sodium and water delivery to distal cortical tubules and functional aldosterone. Potassium excretion is generally maintained within normal range unless GFR falls below 10 mL/min; however, their ability to handle excess load is seriously compromised at GFR less than 20 mL/min. Reduction of GFR is primarily a part of acute kidney injury or chronic kidney disease due to a number of renal or systemic diseases. Reduced sodium and water delivery may either be due advanced kidney disease or volume depletion as a result of dehydration, shock, or cardiac failure.

Aldosterone helps in sodium reabsorption and potassium excretion in urine and hypoaldosteronism usually results in hyperkalemia. Hypoaldosteronism with high renin levels indicate primary adrenal disease, aldosterone synthase deficiency or use of drugs (angiotensin converting enzyme inhibitor or receptor blockers). Renin produced from kidney converts angiotensinogen to angiotensin I which is then converted to angiotensin II with the help of converting enzyme. Angiotensin-II stimulates adrenals for aldosterone synthesis. If this stimulus is lost (low renin state), aldosterone levels are also reduced. This is commonly seen in *systemic lupus erythematosus* (SLE), interstitial nephritis, obstructive uropathy, and nonsteroidal anti-inflammatory drugs. End organ failure to aldosterone causes functional hypoaldosteronism which is seen in SLE, sickle cell disease, postrenal transplant and use of potassium sparing diuretics.

Transcellular shift of  $K^+$  from intracellular to extracellular space is commonly seen in acidosis, hypertonicity, exercise, diabetes, myolysis, and drugs such as digoxin,  $\beta$ -blockers, and succinylcholine. Extensive muscles or cellular injury may result in shift of intracellular potassium to plasma. Hyperkalemia due to cellular damage is also commonly associated with hyperphosphatemia.

### Clinical Features

In children, hyperkalemia is often asymptomatic and picked up on ECG monitoring or routine testing. Some of the nonspecific

symptoms of hyperkalemia include paresthesiae, muscle cramps, muscle weakness, paralysis and symptoms related to cardiac rhythm disturbances (palpitation, missed beat, syncope).

### Electrocardiographic Changes

These correlate well with plasma  $K^+$  levels. However, cases even with early ECG changes may suddenly develop fatal cardiac rhythm disturbances. Earliest ECG changes with hyperkalemia (plasma potassium 6–7 mEq/L) are tall ( $> 50\%$  of QRS) and peaked T waves, best observed in chest leads. With increasing levels of potassium, flat P waves, prolonged PR interval and wide QRS complex become evident (plasma potassium 7–8 mEq/L). Absence of P waves, wide QRS complex to appear as *sine wave* or progressing to asystole or ventricular fibrillation indicate severe hyperkalemia.

### Management

Clinical evaluation of children with hyperkalemia should include detailed history and examination, especially for hydration, hypertension, hyperpyrexia, hyperglycemia, hypoxia, acidosis, and cardiac and renal status. ECG should be done for changes in cardiac rhythm. If plasma  $K^+$  is more than 6.5 mEq/L or ECG abnormalities are detected, emergency treatment should be initiated.

The priority of treatment execution should be: (1) withdrawal of source of excess  $K^+$  if any. In case blood transfusion is urgently needed use of fresh and washed RBCs are recommended; (2) stabilization of myocardial cells; (3) rapid reduction of plasma  $K^+$  levels with transcellular shift; (4) enhance  $K^+$  elimination from body; and (5) treatment of the underlying cause.

For membrane stabilization, calcium gluconate is used as 10% solution, 0.5–1 mL/kg (maximum 10 mL) 1:1 diluted with saline over 10 min under cardiac monitoring. If slowing of heart rate is observed then slow the rate of infusion. If patient is taking digitalis, give infusion over 30 min. Onset of action is within 1 min and lasts up to 20–60 min.

Transcellular shift may be achieved by using glucose insulin infusion. Infants and young children should receive 2 mL/kg of 25% dextrose with 0.1 unit/kg of regular insulin to be infused over 30 min. For older children use 50 mL of 50% dextrose with 10 units of regular insulin to be infused over 30 min. If blood glucose level is more than 300 mg/dL, insulin may be given alone. All cases should be monitored for hypoglycemia.

Short acting  $\beta$ -agonist is also useful in intracellular shift of potassium. Salbutamol, 2.5–5 mg in 3–4 mL of saline may be nebulized over 20 min and may be repeated if required. It has onset within 30 min and effect lasts for about 2 hours.

If there is nonanion gap metabolic acidosis, 1–2 mEq/kg of sodium bicarbonate may be given intravenously; onset occurs within 30 min and lasts for 60 min.

Elimination of  $K^+$  may be achieved by using ion-exchange resin, such as sodium polystyrene sulfonate (Kayexalate), 1–2 g/kg orally or per rectally as retention enema. Onset of action takes about 60–90 min. Each gram of kayexalate will exchange 1 mEq of potassium with 2 mEq of sodium. The dose may be repeated after 2–4 hours.

Intravenous furosemide 1–2 mg/kg may also help in excretion of  $K^+$  if kidney functions are normal.

Hemodialysis can lower the  $K^+$  levels by 1.2–1.5 mEq/h. Peritoneal dialysis with potassium-free fluid is also an effective alternative especially if hemodialysis is not possible. It removes  $K^+$  slowly and chances of rebound hyperkalemia are much lesser than hemodialysis. A variable degree of renal dysfunction coupled with excess load of potassium, infection, medications, decreased renal perfusion or obstruction may also be contributing to hyperkalemia and should be addressed appropriately.

### IN A NUTSHELL

1. Normal plasma  $K^+$  levels of 3.5–5.2 mEq/L represents about 0.4% of total body potassium; intracellular fluid to extracellular fluid potassium gradient (38:1) is maintained by (Na-K-ATPase) and selective potassium channels located in the cell membrane.
2. Hypokalemia (plasma  $K^+ < 3.5$  mEq/L) may be graded as mild (3.5–3 mEq/L), moderate (3–2.5 mEq/L) or severe ( $< 2.5$  mEq/L).
3. Electrocardiographic changes of hypokalemia include U wave with amplitude more than that of T wave, ST depression and flat T wave
4. Transcellular shift, GI and renal loss of potassium contribute to hypokalemia in most cases.
5. Slow correction of hypokalemia with 40–60 mEq/L of  $K^+$  in maintenance fluid is safe. Injection KCl, 15% solution (2 mEq/mL) should be diluted at least 50 times of its volume. Rapid infusion of 0.5–1 mEq/kg (maximum 40 mEq) of KCl diluted in 100 mL of saline (dextrose stimulate insulin secretion and shift of  $K^+$  into the cells) may be given over 30–60 min under strict monitoring in PICU in cases of severe hypokalemia.
6. Hyperkalemia ( $K^+ > 5.5$  mEq/L) can be categorized as mild (5.5–6.5 mEq/L), moderate (6.6–8 mEq/L) or severe ( $> 8$  mEq/L).
7. Rapidly rising potassium levels, presence of hypoxia or acidosis and compromised cardiac status are other contributory factors for complications.
8. ECG changes of hyperkalemia include tall ( $> 50\%$  of QRS) T waves, flat P waves, prolonged PR interval and wide QRS.
9. Potassium excretion is maintained within normal range unless GFR falls below 10 mL/min; however, their ability to handle excess load is seriously compromised at GFR less than 20 mL/min.
10. Treatment of hyperkalemia should aim at stabilization of myocardium, reduction of plasma  $K^+$  levels, enhance elimination and treatment of underlying cause.

### MORE ON THIS TOPIC

- Ahee P, Crowe AV. The management of hyperkalemia in the emergency department. *J Accid Emerg Med.* 2000;17:188-91.
- Bockenhauer D, Feather S, Stanescu HC, et al. Epilepsy, ataxia, sensorineural deafness, tubulopathy and KCNJ10 mutations. *N Engl J Med.* 2009;360:1960-70.
- Brewster UC, Perazella MA. The renin-angiotensin-aldosterone system and the kidney: effects on kidney disease. *Am J Med.* 2004;116:263-72.
- Cohn JN, Kowey PR, Whelton PK, et al. New guidelines for potassium replacement in clinical practice. *Arch Intern Med.* 2000;160:2429-36.
- Gennari FJ. Disorders of potassium homeostasis: hypokalemia and hyperkalemia. *Crit Care Clin.* 2002;18:273-88.
- Lin SH, Halperin ML. Hypokalemia: a practical approach to diagnosis and its genetic basis. *Curr Med Chem.* 2007;14:1551-65.
- MacDonald JS, Atkinson CC, Mooney DP. Hypokalemia in acutely injured children: a benign laboratory abnormality. *J Trauma.* 2003;54:197-8.
- Montague BT, Ouellette JR, Buller GK. Retrospective review of the frequency of ECG changes in hyperkalemia. *Clin J Am Soc Nephrol.* 2008;3:324-30.
- Schaefer TJ, Wolford RW. Disorders of potassium. *Emerg Med Clin N Am.* 2005;23:723-47.
- Wiederkehr MR, Moe OW. Factitious hyperkalemia. *Am J Kidney Dis.* 2000;36:1049-53.



## Chapter 5.7

# Magnesium Balance

Virendra Kumar

Magnesium is an important intracellular cation, which is widely distributed in body. Though isolated disorders of magnesium are less frequently observed in clinical practice, the association with disorders of potassium, sodium, calcium and phosphate are not uncommon. Primary manifestations of magnesium abnormalities are often subtle and easily get confused with disorders of potassium and calcium. This section will deal with the physiological aspect of magnesium homeostasis and disorder related to them.

### Basics of Magnesium Physiology

Magnesium is the second most common intracellular cation, required for enzymatic activity of ATPase, kinases, and cyclases. It also influences the cell membrane stabilization, neuromuscular functions, cardiac conduction and parathyroid hormone (PTH) regulation. Total body contents of magnesium are approximately 22–26 g in adults, distributed largely in intracellular space (bones, muscles, liver and soft tissues). Only 1% is distributed in extracellular space. Nearly 30% of plasma magnesium is protein bound and only 70% of magnesium is exchangeable and filtered in the kidney. Most of the filtered magnesium (60–70%) is reabsorbed in loop of Henle and only 5–10% is reabsorbed in distal collecting ducts.

The normal plasma levels of magnesium range from 1.2 mEq/L to 1.9 mEq/L (1.5–2.3 mg/dL). Daily requirement of magnesium is about 4–5 mg/kg/day. Children with chronic illnesses or severe malnutrition require higher amount of magnesium. Magnesium is available in green leafy vegetables, cereals, pulses and animal foods. Dairy products and processed food are poor source. About 40% of dietary magnesium is absorbed primarily in the jejunum and ileum. Intestinal absorption is increased in deficient state with low magnesium intake. PTH and vitamin D may also help gut absorption. Increased intestinal mobility and presence of phosphate, oxalate and high fiber may reduce the net absorption. Magnesium balance is maintained by intake, gut absorption and renal excretion. There is no known hormonal control of renal absorption or excretion though PTH and insulin may play some role. Among all, renal regulation plays a crucial role in most cases. Higher levels of magnesium in the plasma facilitate renal excretion. Alkalosis, excess catecholamine state (trauma, tumor, infusion of catecholamines) and insulin therapy can cause intracellular shift of magnesium.

### Therapeutic Uses of Magnesium

Magnesium has been used as a therapeutic agent in the treatment of many disorders. It has been used as a cathartic agent for long time. The other known uses are in asthma, long QT syndrome and other refractory arrhythmias.

### HYPOMAGNESEMIA

Hypomagnesemia is defined as plasma magnesium levels less than 1.2 mEq/L. The reported prevalence of hypomagnesemia varies from 7% to 11% in hospitalized patients. In critically sick patients and those with other electrolyte abnormality, prevalence of hypomagnesemia is even higher. Hypomagnesemia may either be caused by low intake, intracellular redistribution or excessive loss from the gut or kidney.

### Etiology

Hypomagnesemia should always be suspected in children with severe acute malnutrition, chronic diarrhea, refractory hypokalemia

and hypocalcemia, and ventricular arrhythmias. Other important causes include major resection of bowel, acute pancreatitis, diabetes mellitus, hyperthyroidism, primary hyperparathyroidism and hyperaldosteronism. Prolong use of diuretics, aminoglycosides, amphotericin B, pentamidine, and cisplatin are also known to cause hypomagnesemia. Primary renal disorders such as Bartter's and Gitelman's syndrome, familial hypomagnesemia, postobstructive and post-transplant nephropathy may also be associated with hypomagnesemia.

### Clinical Manifestations

Most of the clinical manifestations are nonspecific and indistinguishable from hypocalcemia and hypokalemia, including lethargy, tremors, confusion, fasciculation, tetany, seizures, and cardiac arrhythmias. However, persistence of these symptoms even after correction of calcium and potassium levels or failure to correct their levels should be taken as an indicator of hypomagnesemia.

### Diagnosis

High index of suspicion of hypomagnesemia in a given suggestive background is the most crucial part of evaluation. Estimation of serum and urinary magnesium, fractional excretion of magnesium may help to support the diagnosis. In presence of hypomagnesemia (serum magnesium < 1.2 mEq/L), 24-hour urinary excretion of magnesium of more than 2 mEq/day or fractional excretion of more than 2% suggest a renal loss of magnesium. Fractional excretion can be calculated as  $[U Mg \times Pcr \div (0.7 \times P Mg) \times U cr] \times 100$ . Plasma concentration of magnesium is multiplied by 0.7 as 30% is protein bound and only 70% of magnesium is in unbound form and filtered in the kidney.

### Electrocardiographic Changes

These include prolong PR and QT interval, T wave flattening wide QRS complex or ventricular arrhythmia.

### Treatment

#### Symptomatic Cases

Children with ECG abnormalities should be treated with IV infusion of magnesium sulfate 25–50 mg/kg (0.05–0.1 mL/kg of 50% solution) over 30 min. Infusion may be repeated every 6 hourly for 2–3 doses if serum levels remain less than 1 mEq/L or symptoms/ECG abnormalities persist. To restore the body stores, slow infusion with maintenance fluids may be continued for 3–5 days. Serum Mg levels should be checked to keep the serum magnesium levels less than 2.5 mEq/L. Higher doses or rapid infusion may increase the serum levels more than 2.5 mEq/L which can promote renal excretion without contributing much to body stores. Deep tendon reflexes should also be checked and recorded with the start of infusion. If signs of hypermagnesemia (hypotension, bradycardia or loss of deep tendon reflexes) develop, therapy should be discontinued and serum magnesium levels should be checked.

#### Asymptomatic Cases

Those without ECG abnormalities and gastrointestinal disorders should be treated with magnesium rich diet and oral magnesium supplementation. Magnesium is available as a salt with sulfate, gluconate, hydroxide and chloride. Magnesium gluconate is preferred for oral supplementation as it is better absorbed and causes fewer diarrheal episodes. Oral magnesium is usually started with 30 mg/day in 3–4 divided doses and gradually increasing to 120 mg/day. Concomitant deficit of calcium and potassium should also be corrected. Care should be taken in cases with renal impairment to use lower doses and frequent monitoring.

## Prophylaxis

High-risk children for magnesium deficiency such as patients receiving total parenteral nutrition, long-term diuretic therapy and those with chronic diarrhea or severe malnutrition should have serum magnesium checked regularly and supplemented with magnesium in the doses of 4–5 mg/kg/day.

## HYPERMAGNESEMIA

Hypermagnesemia is defined as serum Mg levels more than 2.2 mEq/L.

### Etiology

Excessive intake and reduced glomerular filtration rate to less than 30 mL/min are most common factors implicated in hypermagnesemia. In children hypermagnesemia is rare with normal renal functions as higher serum levels promote renal excretion. However, excessive intake of magnesium can result in hypermagnesemia in neonates and young infants because of their reduced renal ability to excrete the excess load. Babies born to mothers with eclampsia who have received higher doses of magnesium are also at a higher risk. Excessive intake of cathartics has also been reported to cause hypermagnesemia in children. Addison's disease, hypothyroidism, extensive tissue injury or tumor lysis and acute acidosis (transcellular shift) are other conditions may be associated with hypermagnesemia.

### Pathogenesis

Hypermagnesemia prevents the release of presynaptic acetylcholine and blocks the neuromuscular transmission. It also depresses the conduction system of the heart and the sympathetic ganglia. Hypermagnesemia per se can reduce the serum calcium levels partly due to its suppressive effect on PTH secretion. Calcium is a natural antagonist of magnesium at the neuromuscular junction; hypocalcemia therefore can exaggerate the effects of hypermagnesemia.

### Clinical Manifestations

These depend on serum levels. Cases with serum magnesium levels less than 4.5 mg/dL (< 3.7 mEq/L) are mostly asymptomatic. Levels between 4.5 mg/dL and 7 mg/dL (3.7–5.7 mEq/L) manifest with lethargy, poor feeding, nausea, flushing and poorly elicitable deep tendon reflexes. Levels between 7 mg/dL and 11 mg/dL (5.7–9 mEq/L) manifest with absent tendon reflexes, hypotension and ECG abnormalities (prolong PR and QT interval and wide QRS). Heart block, respiratory failure and cardiac arrest can occur if levels are more than 11 mg/dL (9 mEq/L).

### Treatment

High index of suspicion in any patient receiving magnesium therapy, especially with impaired renal functions generally form the basis for testing for magnesium in most of the cases.

### Symptomatic Cases

Symptomatic cases with neurological, cardiac or respiratory compromise should be managed with ventilatory support and

cardiac stabilization using intravenous 10% calcium gluconate 0.5–1 mL/kg (maximum 10 mL) 1:1 diluted with saline over 10 min under cardiac monitoring. The dose may be repeated if required. Glucose insulin infusion as used in hyperkalemia can also help in transient reduction of serum levels. Cases with kidney disease should be considered for hemodialysis or peritoneal dialysis. Neonates may also be considered for exchange transfusion.

### Asymptomatic Cases

Asymptomatic cases with normal renal functions can be managed with withdrawal of source of magnesium, correction of hydration and loop diuretics to promote renal excretion. Diuretics however, can also cause loss of calcium in urine and hypocalcemia which can potentiate the manifestations of hypermagnesemia.

## MORE ON THIS TOPIC

Chang WT, Radin B, McCurdy MT. Calcium, magnesium, and phosphate abnormalities in the emergency department. *Emerg Med Clin N Am*. 2014;32:349–66.

Jahnen-Dechent W, Ketteler M. Magnesium basics. *Clin Kidney J*. 2012;5:i3–14.

Kutsal E, Aydemir C, Eldes N, et al. Severe hypermagnesemia as a result of excessive cathartic ingestion in a child without renal failure. *Pediatr Emerg Care*. 2007;23:570–2.

Martin KJ, Gonza'lez EA, Slatopolsky E. Clinical consequences and management of hypomagnesemia. *J Am Soc Nephrol*. 2009;20:2291–5.

Moe SM. Disorders involving calcium phosphorus and magnesium. *Prim Care*. 2008;35:215–37.

Swaminathan R. Magnesium metabolism and its disorders. *Clin Biochem Rev*. 2003;24:47–66.

## IN A NUTSHELL

1. Normal serum levels of magnesium range from 1.2 mEq/L to 1.9 mEq/L (1.5–2.3 mg/dL). Hypomagnesemia is defined as serum magnesium levels of less than 1.2 mEq/L.
2. Electrocardiographic changes of hypomagnesemia includes prolonged PR and QT interval, T wave flattening wide QRS complex or ventricular arrhythmia.
3. Symptomatic hypomagnesemia with ECG abnormalities should be treated with IV infusion of magnesium sulfate 25–50 mg/kg (0.05–0.1 mL/kg of 50% solution) over 30 min.
4. Asymptomatic children without ECG abnormalities and gastrointestinal disorders should be treated with magnesium rich diet and oral magnesium supplementation.
5. Hypermagnesemia is defined as serum Mg levels more than 2.2 mEq/L.
6. Electrocardiographic changes of hypermagnesemia include prolong PR and QT interval and wide QRS.
7. Symptomatic hypermagnesemia with neurological, cardiac or respiratory compromise should be managed with ventilatory support and cardiac stabilization and measures to enhance elimination of magnesium and treatment of underlying cause.
8. Asymptomatic cases with normal renal functions can be managed with withdrawal of source of magnesium, correction of hydration and loop diuretics to promote renal excretion.

# Section 6 DRUGS AND THERAPEUTICS

**Section Editor** Sandeep B Bavdekar

## Chapter 6.1

### Principles of Drug Therapy

*Sandeep B Bavdekar*

Parents bring their children to doctors for multiple reasons. These include seeking advice regarding health-protective and health promotive strategies (e.g., vaccines, dietary advice); growth monitoring, undergoing a screening procedure, seeking treatment of an ongoing illness, receiving prophylaxis and follow-up for chronic illnesses. Drugs constitute the most important therapeutic tool for most of the objectives for contact; either as the primary modality or as an adjunct to another modality. This chapter discusses the general principles of drug therapy in children.

#### SPECIAL ASPECTS OF PEDIATRIC PHARMACOLOGY

Although, the pharmacological principles governing the absorption, distribution, metabolism and elimination are universal and apply to children and adults, alike; differences in body composition and in the absorptive, metabolic and excretory capabilities; pharmacokinetics and pharmacodynamics in the pediatric age group differ to an extent. Also, the pediatric age-group is not a homogeneous population: neonates, infants, young children and adolescents vary in their capabilities as well. This has implications for therapeutic indications, dose and dosage schedules, and effectiveness and safety of medicines.

#### Pharmacokinetics

##### *Drug Absorption*

Absorption from the gastrointestinal (GI) tract is dependent on gastric acid secretion, bile salt formation, gastric emptying time, intestinal motility, bowel length and microbial flora. However, newborns and children differ from adults in several aspects. These differences are responsible for the dissimilarity in the absorption of drugs in children (**Table 1**).

Children receive drugs through various parenteral routes: intravenous, intramuscular (IM), subcutaneous, intradermal, per-rectal, into the cerebrospinal fluid, etc. Intravenous route is considered the most ideal route for administering drugs with assured bioavailability. IM route is generally not preferred as neonates have hardly any muscle mass and the absorption is erratic. IM injections are painful and there is greater possibility of injury. In addition, variability in the depth of injection, muscle mass and circulatory status contributes to erratic absorption from the IM site. Per-rectal route is employed in emergency situations when quick intravenous access is not available. For example, diazepam is used to control convulsions in infants and children for a quick action. This route is quite efficient in neonates and infants.

##### *Drug Distribution*

The distribution of a drug in the body is dependent upon the physicochemical properties such as protein binding and pH. Age-dependent variables such as relative size of the total and extracellular body water compartments and fat compartment and the amount and composition of plasma proteins influence the drug distribution and are responsible for the differences in drug distribution in children and adults.

Preterm neonates (80%), full-term babies (70%) and infants (61%) have a higher percentage of their body weight in the form of water as compared to adults (50–60%). The higher total body water is almost entirely due to higher extracellular fluid (ECF) compartment and as concentrations of drugs in the ECF determine the concentrations at the receptor sites, water-soluble drugs need to be prescribed in comparatively higher (per kg body weight) doses in neonates and infants so that the desired concentrations can be achieved. The body fat composition also changes throughout childhood and adolescence and there are gender-linked differences in the body fat composition during the pubertal years. Thus, age influences the pharmacokinetic properties of the lipophilic drugs (**Table 1**).

Albumin, alpha-glycoprotein and lipoprotein are the most important circulating proteins responsible for drug binding in plasma. The concentrations of most of these proteins are lower in neonates and approach adult levels by 10–12 months of age. In addition, neonates have higher levels of fatty acids and bilirubin in the blood; which compete with drugs for protein binding sites. The net result of this reduced protein binding is that comparatively larger proportion of the drug is available in the free form and for binding to receptor sites, thereby exposing the infant to toxicity at comparatively lower drug doses.

The transport of drugs across membranes is influenced by transporters like P-glycoprotein. Although, there is only limited data; their generally lower levels in neonates and infants could influence distribution and therapeutic capabilities of those drugs that need to cross membranes to reach their site of action.

##### *Drug Metabolism*

Liver is the primary organ for drug metabolism, although the kidneys, lungs, intestines, adrenals and skin also biotransform drugs. Drug metabolism is primarily carried out through two types of reactions, viz. phase I (nonsynthetic processes consisting of oxidation, reduction, hydrolysis and hydroxylation reactions) and phase II (synthetic processes involving conjugation with glucuronide, glycine, glutathione or sulfate). All the enzyme systems have lower than adult activity in the neonatal period and the various enzyme systems mature at different age. For example, the cytochrome P450 monooxygenase system appears to mature rapidly, with metabolic activity similar to adults being achieved by 6 months of age. In contrast, glucuronide formation reaches adult values between 3rd and 4th years of life. Although, infants are regularly characterized as being slow metabolizers of drugs, some

**Table 1** Examples of effect of age on the pharmacokinetic properties of drugs

<i>Alteration as compared to adults</i>	<i>Implications with examples</i>
<b>Absorption</b>	
Neonates and infants have reduced acid-secreting capacity. The adult values (gastric pH: 2–3) are reached only by 3–7 years of age	Increased bioavailability of acid-labile drugs such as penicillin Decreased absorption and consequent reduced serum concentrations of weakly acidic drugs like phenobarbitone, requiring higher per unit body weight doses
Infants have delayed gastric emptying	Adverse effect on the absorption of less water-soluble drugs absorbed in intestine (phenytoin, carbamazepine)
Increased intestinal motility in infants	Reduction in the time of contact with absorptive surfaces results in decreased bioavailability of sustained-release preparations
Neonates have thinner and better hydrated stratum corneum and relatively larger skin surface for body weight	Enhanced transcutaneous absorption of medicines applied locally (e.g., silver sulfadiazine and topical corticosteroids)
Delayed development of intestinal flora	Impact on the bioavailability of digoxin
<b>Distribution</b>	
Higher total body water and extracellular body water in neonates	Water-soluble drugs like aminoglycosides need to be prescribed in higher per kg body weight doses so that desired drug concentrations can be achieved in the ECF and at receptor sites
Neonates and infants have lower total body fat content	Lower volume of distribution of fat-soluble drugs such as diazepam
Comparatively higher proportion of body fat in the CNS in neonates	Higher effects of lipophilic drugs such as propranolol
Presence of fetal albumin present in neonates has lower affinity for acidic drugs	Lowered affinity to phenytoin results in greater proportion of the total drug being free, higher probability of toxicity even when total plasma phenytoin levels are within the therapeutic range
<b>Metabolism</b>	
Lower activity of hepatic oxidizing systems in neonates	Slower metabolism and longer action of phenytoin, diazepam and caffeine
Reduced activity of hydrolytic enzymes in neonates	Prolonged action of local anesthetic agents in neonates Prenatal exposure to cocaine has prolonged action in neonates
<b>Excretion</b>	
The renal mechanisms are not fully developed in neonates and reach adult levels later in life	In neonates, drugs such as gentamicin are administered once a day and the frequency of administration is increased progressively to twice and then thrice a day

Abbreviations: ECF, extracellular fluid; CNS, central nervous system.

drugs (for example, theophylline, phenytoin, phenobarbitone) are more rapidly metabolized by infants than adults. There are qualitative differences, too. A drug may be preferentially metabolized by one pathway during the neonatal period (e.g., theophylline) as compared to adulthood. All these have practical implications (**Table 1**). While determining dosages of drugs that undergo hepatic biotransformation, sequence of maturation of process of drug metabolism has to be taken into account. The drugs that are metabolized at a rapid rate are required to be administered in higher doses. Thus, theophylline is administered at much higher dose and frequency during infancy than in adulthood.

### Drug Excretion

Kidney is the predominant organ concerned with drug excretion and all renal mechanisms (filtration, secretion and reabsorption) are reduced in neonates. Although, drugs are also eliminated through the GI tract, biliary tract, respiratory tract and sweat glands, these are important routes of excretion only for a few drugs. Renal excretion is dependent upon glomerular filtration rate (GFR), renal blood flow (RBF) and rate of active tubular secretion. These are dependent on age and maturity. A term infant has GFR and RBF that approximates 30% of adult values. In premature neonates, these renal capabilities are only 15% or less, depending on the degree of prematurity. The renal capacity to excrete solutes improves quickly to reach 50% of adult value by 4 weeks and equals that of adults by 9–12 months of age.

### Pharmacodynamics

Drugs act through receptors and the most receptors and basic physiological processes are present in children. Hence, generally children's responses to drugs are quite similar to adult responses. But, there are examples where these could be different. For example, despite having similar plasma warfarin concentrations, prepubertal children show significantly lower plasma concentrations of protein C and higher INR values than adults. Similarly, in vitro, the peripheral blood monocytes from infants cultured in the presence of cyclosporine, show significantly lower peripheral blood monocyte proliferation and interleukin-2 expression than peripheral blood monocytes from adults. Evidence generated mainly from animal studies indicates that differences in receptor number, density, distribution, function and affinity to ligands could be responsible for the pharmacodynamic differences between children and adults.

### Pediatric Drug Dosages

From the description above, it is amply clear that pharmacokinetic and (to some extent) pharmacodynamic profiles of drugs in children and adults differ. The organs, systems and functions mature in a nonlinear or nonuniform fashion and various functions mature at different age. Hence, a simple proportionate reduction in the adult dose is not adequate to determine a safe and effective pediatric dose. Formulae or rules providing calculations based on age or weight of the child are mere approximations and would



be applicable to some extent only in older children over the age of 8 years. The most reliable pediatric dose information, wherein the dose is given in terms of weight or surface area, is usually that provided in the package insert, the pharmacopeia, established guidelines or pediatric textbooks. For some drugs whose apparent volume of distribution is less than ECF space (less than 0.3 L/kg), a body-surface-area-based approach is preferable. For other drugs, a body-weight-based approach is more suitable and is the most frequently used method for describing pediatric doses.

### Other Considerations

**Compliance and adherence** It is obvious that drug therapy can be successful only if it is administered as per advice. Depending upon their maturity and abilities, children can take responsibility for self-administration after 8–14 years of age. Prior to this age, this responsibility is assumed by parents and guardians in the home setting and by doctors and nurses in the hospital setting. When the child is in day care or in school, other adults might share this responsibility. The administration of drugs to adolescents brings in different challenges. Although, they are definitely capable of self-administering drugs; incomplete understanding and altered perceptions regarding disease process, need for treatment and health maintenance, and defiant behavior can lead to disruption of therapeutic schedules. Education combined with periodic reinforcement of advice and vigilance can help minimize and eliminate these disruptions.

**Off-label and extemporaneous drug use** For several decades, the society, regulators and pharmaceutical industry have been reluctant to conduct clinical trials in children. Hence, the drugs get marketed for use in adults. However, when an indication exists for use of drugs in children; the health-care providers are required to prescribe these drugs although data regarding the efficacy, dose, dose regimen and safety in children have not been generated. This use is called as off-label or off-license use; and given the complexity of pharmacokinetic changes such prescriptions have the potential of causing harm. On the other hand, it is also unethical not to prescribe an available indicated drug, just because it is off-label. It is advisable that when an off-label drug is to be used, the use is rational, the caregiver bases his decision on evidence or guidelines, records the indication and dose used and parents are informed about such use. The regulators have woken up to the need for ensuring the availability of pediatric labeling information and have implemented initiatives, such as providing a financial benefit, including data from experiences to alter label (licensing information) and mandating industry to include children in clinical trials when the drug is likely to have a pediatric indication.

The other challenge faced by children is the non-availability of appropriate liquid formulations. Neonates, infants and young children cannot swallow tablets and when tablets and capsules are split for providing the drug, there is always a possibility of the child receiving an inaccurate dose raising the prospect of undertreatment (ineffective therapy) or overdosing (toxicity).

**Adverse drug reactions (ADRs)** These are defined as a noxious, unintended responses to a drug that occur at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function. Although, children suffer from ADRs similar to those in adults, they could be different because of differences in pharmacokinetics, pharmacodynamics, or age-related alterations in the maturation of systems. In addition, newborn babies and infants can get affected due to drugs that they received transplacentally during the fetal period or through breastfeeding. As the ADRs in infants and children could be different from adults in terms of frequency and manifestations, health-care providers need to be more alert in diagnosing them (**Box 1**).

#### BOX 1 List of some adverse drug reactions that are common in or unique to children

- Aspirin-associated Reye syndrome
- Chronic corticosteroid therapy inhibiting growth
- Serum sickness-like reaction associated with cefaclor
- Tetracyclines associated with staining of developing enamel
- Lamotrigine-induced cutaneous toxicity
- Dystonia associated with metoclopramide (more frequent than in adults)
- Valproate-associated hepatotoxicity in children aged less than 2 years
- Hepatotoxicity associated with nimesulide use
- Multiple anticonvulsant hypersensitivity syndrome associated with exposure to phenobarbitone, phenytoin and carbamazepine.

**Drugs and breastfeeding** Virtually every drug that enters maternal circulation will appear in the breastmilk. However, such transfer is not always a harbinger of harm. As the breastmilk is slightly acidic, weak alkaline drugs that are lipid soluble and have low molecular weight are more easily transported into the breastmilk. In most instances, the drugs are not transported in pharmacological amounts; although hypersensitivity reactions can occur even with these lower doses in infants.

When a nursing mother is on medications, a three-way classification of drugs is useful. One group consists of drugs that are commonly prescribed to newborn babies and infants (e.g., ampicillin and gentamicin). If the mother is on any of these drugs, there is hardly any concern. The second group consists of drugs that are prescribed to newborns and infants, but for very limited number of indications and with great caution. If the maternal drug belongs to this group, an acceptable alternative needs to be looked for and if not available; the risks and benefits of continued breastfeeding need to be assessed. If it is decided to continue with breastfeeding, the mother can be given the lowest possible dose for the shortest period of time and schedule of drug administration and breastfeeding can be adjusted so that drug exposure can be minimized. The third category of drugs includes those (such as antimetabolites, ergotamine and lithium) that are never given to neonates and appear in the breastmilk in significant amounts. If such therapy is necessary, breastfeeding would be contraindicated.

**Pharmacogenetics and personalized therapy** Pharmacogenetics has underlined the role of human genes in defining the pharmacokinetics and drug responses in individuals. This would make personalized care (wherein drugs would be selected on the basis of genetic profile of an individual patient) possible. Children would derive significant benefits in terms of improved pharmacotherapeutics only if technology is also employed to determine the changing patterns of gene expression that have bearing on pharmacokinetics and pharmacodynamics through the pediatric age-group.

### STEPS IN INITIATION OF THERAPY

It is usually believed that every illness should be treated. This principle of therapeutic enthusiasm is clearly appropriate in severe and life-threatening illnesses. It, however, does not apply to all clinical situations. Infants, children and adolescents have intrinsic recuperative capacities. Therefore, therapeutic intervention may not be required in many conditions. It should be borne in mind that drug therapy is not synonymous with good health-care. While initiating drug therapy, the treating doctor should undertake the following steps:

#### Reach an Initial Working Diagnosis

Reaching a provisional or working clinical diagnosis with the help of detailed history and examination constitutes an important

initial step in this process. Appropriate treatment can be started depending on the clinical status of the child. A critically ill child would require immediate therapy aimed at stabilization of vital signs. In this situation, it would not be appropriate to wait for the specific confirmation of the etiological agent. Therapy can be initiated taking into consideration the patient's age, likely etiological agent and the pattern of resistance likely to be encountered. The treatment can be changed subsequently on the basis of results of investigations and response to therapy.

### Define Therapeutic Objectives

In this step, the caregiver should specify what intends to be achieved through therapy and in what time interval. It might include symptomatic treatment, therapy directed amelioration or eradication of cause of illness and steps to prevent the occurrence of complications. For example, when the patient presents with fever and vomiting and is diagnosed to have typhoid fever, therapeutic objectives would include symptomatic relief (control of fever and vomiting), and eradication of the infectious agent (with anti-salmonella antimicrobial agent).

### Assess Effectiveness of Therapy

Comparative efficacy of different therapeutic regimens should be assessed. There is hardly any therapeutic regimen that is completely effective in all cases. Efficacy is dependent on several factors, which include patient's own defenses, drug's pharmacokinetic properties and stage of illness.

### Assess Risk to the Patient

Every effective drug has adverse effects. This is the second sieve (after efficacy) in the process of selecting suitable drug.

### Plan Strategies to Ensure Compliance

As adults take the responsibility of administering drugs to infants and children at home, the caregiver must explain to them the importance of administering the drug, the symptoms it would help control or the manifestations that it might ameliorate and when this is expected to happen, and the importance of completing the course. However, infants and young children are unlikely to ingest drugs that are unpalatable or have unpleasant smell. Thus, the doctor should be familiar with the available preparations, their flavors and unpleasant characteristics.

### Consider Costs Involved

Cost of therapy is a major determinant. However, this consideration should come after drugs are shortlisted on the basis of efficacy and safety. If a therapy is selected just because it is least expensive, the ultimate cost of therapy is likely to be higher as it is likely to prove inefficacious in many patients; who will then require a course of another effective drug. Costs could be reduced by using the appropriate formulation (avoiding injections when oral medications would suffice) and prescribing good quality generic drugs in preference to the branded ones. When time-honored inexpensive but effective medications are available, one should not push the parents to buy newer drugs that are usually more expensive.

### Enquire about Previous Experience

The treating physician should inquire about what has worked or failed in the child in the past. This should include questions about allergy, side effects and problems with compliance. Obviously, if a child has had an allergic reaction or serious side effects, the physician should avoid exposing the child to the same drug, again.

## PREScribing DRUGS FOR CHILDREN: PRACTICAL SUGGESTIONS

The following issues need to be kept in mind while prescribing drugs to children:

- Prescribe drugs only when required. Consider benefits, potential risks and costs of therapy. Monitor for response and undesirable events. Review therapy based on clinical and laboratory data.
- It is necessary to keep abreast with the advances in the medical field, especially those related to diagnostics and therapeutics. It is unwise to rush to prescribe new drugs just because they are recently discovered. Do not succumb to pressures of prescribing newly marketed drugs, unless a clear indication exists. Therapy should continue to be based on information, experience and judgment. Prescribe minimum number of appropriate, inexpensive drugs of good quality, one is familiar with.
- Write prescriptions clearly and legibly. State the name of the drug, preparation, dose, frequency and duration of treatment. Sign the paper prescription. It is desirable to provide the prescriber's contact details. Adhere to all legal requirements.
- To ensure compliance, explain the nature of the disease and the likely benefits to be obtained from the therapy to the parents. Provide clear written instructions to avoid misinterpretation. Clarify regarding drugs that need to be stopped after the child becomes asymptomatic and those that need to be given for a predetermined duration.
- Consult product insert guidelines or standard pediatric textbooks while prescribing drug doses.
- Prescribe medications for a complete course in appropriate formulations.
- *Direct parents to discard all remaining doses* This avoids accidental poisoning or improper self-medication at a later date.
- Explain the adverse effects of the drug. Explain the need for periodical clinical and/or laboratory monitoring. Instruct them to report an unexpected untoward event.
- Drug combinations should be used only when they are combined in the right and proportionate doses and when they are required to be administered at similar frequencies during the day (For example, amoxicillin plus clavulanic acid combination).

### IN A NUTSHELL

1. The pharmacokinetic profile of drugs is dissimilar in adults and children because of differences in distribution of drugs and absorptive, metabolic and elimination capabilities of children.
2. Various processes concerned with handling of drugs mature at different age.
3. Determination of dose and dosage frequency is a complex process, as several age- and maturity-related factors play a role. Hence, pediatric dosages should not be derived only on the basis of proportional reduction of adult doses.
4. Making a working diagnosis, enlisting therapeutic objectives, assessing comparative efficacy and safety of drugs, taking steps to enhance compliance, considering expenses of therapy and reviewing previous experiences are important steps while initiating drug therapy.
5. Monitor patient for effectiveness of therapy and look for untoward and unexpected events. The adverse drug reactions in children could be different from those in adults.

## MORE ON THIS TOPIC

- Bavdekar SB, Gogtay NJ. Unlicensed and off-label drug use in children. *J Postgrad Med.* 2005;51:249-52.
- de Vries TPGM, Henning RH, Hogerzeil HV, Fresle DA. *Guide to Good Prescribing.* Geneva: World Health Organization; 2000.
- Langerová P, Vrtal J, Urbánek K. Incidence of unlicensed and off-label prescription in children. *Ital J Pediatr.* 2014;40:12.
- Loebstein R, Vohra S, Koren G. Drug therapy in pediatric patients. In: Carruthers SG, Hoffman BB, Melmon KL, Nierenburg DW. *Melman and Morrelli's Clinical Pharmacology: Basic Principles in Therapeutics.* 4<sup>th</sup> ed. New York: McGraw Hill Medical Publishing Division; 2000. pp. 1143-49.
- Lowry JA, Jones BL, Sandritter T, Liewer S, Kearns GL, et al. Principles of drug therapy. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, Behrman RE. *Nelson Textbook of Pediatrics.* 19<sup>th</sup> ed. Philadelphia: Elsevier Saunders; 2011.
- Nunn T, Williams J. Formulation of medicines for children. *Br J Clin Pharmacol.* 2005;59:74-6.
- Ritter JM, Lewis LD, Mant T GK, Ferro A. *A Textbook of Clinical Pharmacology and Therapeutics.* 5<sup>th</sup> ed. London: Hodder Arnold; 2008.
- Rose K. Better medicines for children—where are we now, and where do we want to be? *Br J Clin Pharmacol.* 2005;59:657-9.
- Stephenson T. How children's responses to drugs differ from adults. *Br J Clin Pharmacol.* 2005;59:670-3.

## Chapter 6.2

# Administration of Medications

Jeeson C Unni

This chapter discusses the various challenges faced while administering drugs to neonates, infants and children. For example, children need different types of formulations as compared to adults. Similarly, the way oral drugs can be administered in adults is quite different from that in children. Even pediatric population does not represent a homogeneous population. Infants require drops while young children require liquids and dispersible tablets and adolescents can be expected to take tablets and capsules. Much more care is required to be taken while administering intravenous (IV) fluids to neonates and infants, as they require smaller volumes of fluids to be given over longer durations.

## ISSUES REGARDING MEDICATIONS FOR CHILDREN

- Administering oral liquid medications to infants and young children is a challenge and the doctor should educate the caregiver in this regard.
- Doctors should clearly explain the indication dose and frequency of administration of each and every prescribed drug. It is also worthwhile explaining the time it might take for clinical response to appear. This would help scale down the parental expectations to realistic levels and would enhance compliance. In addition to the expected drug effect, the caregivers should educate guardians about the side effects.
- Children are extremely choosy about taste and recognize even minor alterations in taste when a medicine is mixed in food for administration.
- Forcing a medicine down the throat of an angry and reluctant child heightens the child's resistance to have any medicine.
- Formulations which are not appealing to children (e.g., due to initial bad taste, its odor or color) also add to child's reluctance. Religious, cultural, local and personal beliefs are often important determinants of medication acceptance.
- Nonavailability of sugar-free liquid/dispersible medicines in child prone to caries.

A pediatrician should be able to tackle each of these aforementioned issues. Reinforcement and elaboration of the physician's instructions by the pharmacist and other members of the health-care team is important. Proper education of the parents, grandparents and the adolescent child regarding the prescribed medications including need to report red flag signs may improve compliance, increase possibility of reporting concerns during treatment and decrease chances of discontinuation of therapy.

## ROUTES OF ADMINISTRATION

Medicines vary in form and are given by different routes.

- *By mouth*
  - *Liquid* Solutions, suspensions, syrups, elixirs, emulsions and oils
  - *Solid* Tablets, capsules, granules and lozenges
- *Inhaled* Metered-dose inhalers (MDI), powder devices and compressed air nebulizers
- *Into the ear* Solutions, suspensions, drops and ointments
- *Into the eye* Solutions, suspensions, drops and ointments
- *Into the nose* Solutions, suspensions, drops, ointments and sprays

- *On the skin* Solutions, suspensions, drops, ointments, sprays, creams, lotions, pastes, powders, shampoos and soaps
- *In the mouth* Lozenges, chewing gum and sublingual tablets (rarely)
- *Injected* Water solutions, suspensions and oil in water emulsions, depending on the route—subcutaneous (SC), intramuscular (IM), IV, intrathecal or intraosseous (IO)
- *Into the rectum* Enema, suspensions, oils, suppositories and ointments.

## Oral Administration

### Liquids

Though a child less than 5 years of age would swallow or chew on solids, they cannot be depended upon to take tablets. Older children also often prefer liquids. Taste, as mentioned earlier, is a factor that determines compliance with liquid formulations. Taste (unpleasant or otherwise) may be masked by adding acceptable flavoring agent or by mixing them in foods or drinks that the child likes. There is always the possibility that a child could recognize the change in taste of the foodstuff thus served and refuse any further feeds thinking the medicine would be added again. The dosage and absorption of medications may also be affected when it is mixed with food. It is important to check literature including drug monographs to ensure that mixing with food does not affect absorption/bioavailability of the drug and advice accordingly. As a general rule, it is advisable to avoid mixing drugs in feeding bottles.

Excipients are added to liquid medications to provide stability and taste. Preparations containing sugar, salt and alcohol need to be identified. Permissible alcohol content in medication intended for adults and children less than 12 years, 6–12 years and more than 6 years is 10%, 5% and 0.5%, respectively. Sugar-free preparations are preferable. The amount of lactose in most medications is too small to produce any symptoms in those with primary or secondary disaccharidase deficiency. Nevertheless, the lactose-containing preparations need to be administered cautiously to children with severe lactose intolerance. The child may be occasionally sensitive to oils used as emulsifiers. Propylene glycol is generally considered safe but large amounts can cause lactic acidosis, if its elimination is impaired, e.g., in renal failure, in neonates and young children, and in slow metabolizers. It may interact with metronidazole.

Teaspoon size varies and therefore it is not a reliable measure of the desired quantity of liquid medication that a child is prescribed. Time spent in explaining (and demonstrating, whenever possible) how a quantity may be measured using a dropper, plastic syringe or medicinal bottle cap with markings for different volumes, is time well spent.

Liquids are limited by their short shelf life. In addition, they are heavy and bulky requiring greater storage space in pharmacy and while transporting. Many liquid preparations also require refrigeration. Powders for suspension are affected by humidity and need to be mixed with sterile fluids.

### Tablets

Tablets are cheaper than most other preparations; one can carry them around easily; and they are stable. It is generally felt that children in the schoolgoing age can swallow tablets. However, there are exceptions to the rule and many are uncomfortable with swallowing tablets even till adolescence. A liquid *chaser* could follow immediately after the tablet is swallowed. Most tablets can be crushed and most capsules may be emptied to make a suspension in something acceptable to the child. But crushing certain tablets to mix them with food or water may change the rate or extent of drug absorption, e.g., drugs like lopinavir/ritonavir used in antiretroviral therapy. Crushing drugs with a narrow therapeutic index, such as levothyroxine, could also result in considerable variability



between doses. It is not advisable to break or crush slow-release or enteric-coated tablets. When cutting a tablet, it is necessary to follow specific instructions on the process, including the proper use of a tablet splitter. And whatever method is used to cut or crush a tablet, it is near to impossible to provide an accurate dose where small doses are required as in the neonate, infant or small sized toddler. Splitting tablets is easier when scored tablets are available. Tablets that *melt* on the tongue in a small amount of saliva or the tablets that can be dispersed in a small amount of liquid on a spoon, are easy to administer and ensure accurate dose provided their taste is acceptable. Sublingual administration of drugs is difficult in young children. It is definitely not advisable to open a capsule and administer the powder, if the reason for having a capsule formulation is to avoid its degradation or neutralization by gastric juices. Advances in pharmaceutical technology have resulted in the development of many different types of tablets, those that melt in the mouth; chewable and orodispersible tablets and films.

### Administration through a Feeding Tube

Children with feeding tubes in place, can be encouraged to take medicines by mouth. This may not be possible if, for example, the tube is in place because of a problem with swallowing or if the child is unconscious. Liquid medicines can be given via the tube, provided special precautions are taken to avoid the tube being blocked by the medicine. The liquid formulation should flow easily down the tube and the medicine should be *washed* through with warm water. If medicines are given to a newborn infant via a nasogastric tube, then sterile water must be used. Medicines may be mixed with enteric feeds provided the two are compatible. In general, continuous feeding should be discontinued for 15 minutes before giving a medicine down the tube, unless otherwise specified.

### Inhalational Route

For respiratory ailments, administering medicines through inhalation is the most logical method of delivering medicines directly to the lungs, the target organ. The dose required to achieve the necessary drug levels in the lungs is miniscule when this method is used and hence the side effects (both local and systemic) are also minimal. These advantages need to be explained to the caregivers and the adolescent patient, to ensure compliance.

The child needs to be provided information on various available devices and should be allowed to decide the device of her/his choice. Long-term compliance is poor in young children who are uncooperative and in those whose caregivers force the procedure on them.

The teaching of technique (using MDI, MDI with spacer, dry-powder inhalers) and good care of the devices are essential for success (**Box 1**). Regular review is necessary to ensure that the devices are functional and effective and to check if the child is using them in an appropriate way. Because products and delivery systems vary, it is important that the manufacturer's directions are followed precisely.

Nebulizers can be used in children of all ages. The child breathes an aerosol through a facemask or preferably, a mouthpiece. A mouthpiece gives better deposition. In acute asthma, oxygen and not air should be used as a driving gas while administering drugs such as salbutamol, terbutaline or ipratropium to minimize the possibility of exacerbating hypoxia.

Breath-activated inhalers do not require coordination but the child must be able to take a deep breath. MDI require a child to press and breathe in at the same time. Most school children cannot manage them and their use without spacers is not encouraged. A spacer should always be used if a corticosteroid is being administered via a MDI.

#### BOX 1 Administration of inhalational drugs

##### A. With metered-dose inhalers

- Remove the mouthpiece cover
- Shake the inhaler
- Breathe out as much air as is possible, gently
- Place the inhaler mouthpiece in the mouth between the teeth. Seal lips around it
- As the child begins breath in slowly through the mouth, press the canister and continue breathing. This coordination is vital for ensuring appropriate delivery of the drug
- Remove the inhaler from the mouth and hold breath for about 10 seconds
- Wait for at least 1 minute if another dose needs to be taken.

##### B. Metered-dose inhalers with spacer device

- Remove the mouthpiece cover
- Shake the inhaler
- Fix the mouthpiece of the inhaler in an upright position into the slot provided on the spacer
- Put the spacer mouthpiece between teeth without biting and close lips to form a good seal
- Breathe out gently through the nose
- Press the canister firmly once to instill the spray into the spacer
- Breathe through mouth, in and out, gently and slowly
- The inspiratory breath must be sufficient to visibly or audibly open the valve
- Remove the spacer from the mouth and hold the breath for 10 seconds or as long as comfortable
- Dismantle the assembly of spacer and metered-dose inhalers
- If an extra dose is required, wait for a minute and repeat the steps. Instilling two or more doses simultaneously results in droplets crash/colliding against each other and settling at the bottom of the spacer. These are then not available for inhalation
- Spacer should be cleaned weekly by washing. It should be allowed to dry and should not be wiped. It should be replaced annually.

##### C. Dry powder inhalers

- To use these correctly, children need to be able to take a good deep breath in, to draw the powder into the airways
- They need to be able to hold their breath and not to blow out first.

### Ophthalmic Preparations

Medicines meant for ophthalmic use should be kept sterile. An ophthalmic preparation should be discarded 28 days after it is opened as the probability of bacterial contamination is high beyond this period. The ideal is to drop the solution or squeeze the ointment into a gully formed by pressure of a finger on the lower lid. Tilt the head back or lie the child down and direct the gaze of the child upward. Avoid touching the eye. Alternatively, lay the infant on his or her back, drop the solution or ointment into the corner, wait until the infant's eyes open and then gently mop away the excess. In neonates and infants, it is more appropriate to instill into the inner angle of the open eye. Gentle finger pressure on the inner corner of the eye to occlude the tear duct enhances the effect of the eye drop. Massage the ointment into the upper and lower conjunctival sacs with finger massage on the upper and lower lids. Eye ointment may be applied either at night (if eye drops used during the day) or 3–4 times daily (if eye ointment used alone).

One drop is all that is needed; instillation of more than one drop at a time should be discouraged because it may result in an overflow and wastage of medicine or increase the probability of occurrence of systemic side effects, and results in an overflow. A small amount of eye ointment is applied similarly; the ointment melts rapidly and blinking helps to spread it. If multiple drugs are to be instilled, to avoid dilution and overflow it is recommended to

maintain an interval of at least 5 minutes between the two; interval may be extended for eye drops with a prolonged contact time, such as gels and suspensions. Application of an eye ointment should follow that of eye drops, if both need to be administered at the same time.

### Contact Lenses and Ophthalmic Preparations

Drugs and preservatives in eye preparations can accumulate in hydrogel lenses and can cause adverse reactions. Therefore, unless medically indicated, the lenses should be removed before instillation of the eye preparation and not worn during the period of treatment. Eye drops may, however, be instilled while patients are wearing rigid corneal contact lenses. Ointment preparations should never be used in conjunction with contact lens wear; oily eye drops should also be avoided.

### Aural Medications

These are used to treat conditions of the external auditory canal, which is not sterile. The method of administering medications into the external auditory canal is described in **Box 2**.

### Delivering into the Nostrils

The lining of the nose is very vascular, so the intranasal route offers an alternative to an injection to achieve a systemic effect. This is the chosen route for some peptides (e.g., desmopressin). Currently however, most nose drops are given for the treatment of local conditions. Some children might not like having liquid squirted into the nose. Because the nasal passage connects to the throat, there is a tendency for the saline solution to drip down the back of the throat, giving rise to a bad taste. The method of administration of intranasal drops and sprays is described in **Box 3**.

### Topical Application

Topical applications are mainly used for treating disorders of the skin. However, it can be used as a route for drugs with systemic effect, and it must always be remembered that topical drugs may cause systemic toxicity, particularly if applied to damaged skin or to preterm infants. Generally the skin is left exposed, but a wet dressing may facilitate absorption, and a dry dressing may be used for protection.

*Creams* are a semisolid emulsion with equal amounts of oil and water. They are easy to spread and wash off with water. The active ingredient gets well absorbed and creams promote hydration of the skin. Lotions are thinner than creams and feel very light on the skin. The ingredients in lotions are absorbed very quickly. They are preferred for hairy areas. *Ointments* are 80% oil and 20% water. Although the ingredients are not absorbed well quickly, the ointment remains in contact with skin for longer periods due to its occlusive properties. In this manner, ointments promote absorption of the ingredients. This makes them more potent than when packaged as cream or lotion. *Gels* are emulsions that contain oil-in-water. They usually have an alcohol base. They dry into a thin, greaseless, nonstaining film. They may be used on hairy areas and when large areas need to be treated. Because they dry the skin they may be used for those with oily skin. *Pastes* are a mixture of powder and ointment (e.g., zinc oxide 20% paste)—powder improves porosity (breathability).

It is important therefore to keep in mind the type of vehicle used for topical medications. An occlusive vehicle like an ointment enhances penetration of the active ingredient and improves efficacy. The vehicle itself may have a cooling, drying, emollient, or protective action. It can also cause side effects by being excessively drying or occlusive. The type of preparation used can be determined

#### BOX 2 Administration of aural medications

- Warm the bottle of ear drops if the weather or the room is cold. Rub the bottle back and forth between the palms to let the warmth thus generated heat the bottle
- Place the head on one side
- Pull the ear back and down for the infant and back and up for the older child
- Place the number of drops prescribed in the ear so that they hit the side of the ear canal and roll into the ear
- Wipe any excess drops off the outside of the ear
- Have the child remain with her head tilted or lying on her side for a few minutes to allow the drops to flow all the way into the ear
- Do not put the drops directly into the ear canal without allowing it to hit the side as this could cause pain or dizziness
- Gentle massage immediately in front of the ear helps the drops to descend into the ear and relax the child.

#### BOX 3 Administration of medications by nasal route

##### Intranasal Administration

##### A. Administration of nasal drops

- Lay the child on his or her back with neck extended
- Instill the prescribed drops
- Tilt head forward

##### B. Administering nasal spray to infants

- Make sure to have a nasal spray, small towel, and tissues on hand
- Lay the baby on the lap, with head resting gently on the knees and feet pointed toward caregiver's waist
- Gently spray one or two nasal drops in one nostril and allow a few seconds for the solution to moisturize the nasal passage and loosen the excess mucus
- Use a tissue to wipe any drainage from the nose or face
- Avoid touching the applicator to your baby's nose to prevent the spread of germs.

##### C. Administering nasal spray to older child

- Hold child in sitting position and support him with one arm. Use the other arm to squirt the nasal drops
- Tilt the child's head back slightly. As child takes in a breath, administer one saline nasal dose to each nostril
- After the spray has had time to moisten the nasal passage and loosen excess mucus, help the child gently blow his nose to remove mucus
- Avoid touching the applicator to your baby's nose to prevent the spread of germs.

by the type and site of lesions. For example, greasy ointments should not be preferred for acute weepy dermatitis, and powder in the paste is useful when treating diaper rash. Gel or lotion should be preferred for hairy areas. The irritation or sensitization potential should also be taken into consideration. Generally, ointments and water-in-oil creams are less irritating, while gels are irritating. Ointments do not contain preservatives or emulsifiers, and can be preferred when allergy to preservatives is a concern.

### Parenteral Administration

Drugs may be injected into most of the body spaces. The drugs must be sterile and pyrogen-free. The skin may be washed and then cleaned with antiseptic (70% isopropyl alcohol) or in children not sensitive to iodine, with an iodophor. If alcohol is not allowed to evaporate, this may add to the pain of injection. A topical anesthetic cream may also be used. Neither is common practice when insulin is self-administered or vaccines are given. Children less than 5 years of age should be held firmly; older children should be well-supported but not overpowered; those over 12 years of age, like many adults, may be frightened of needles and their feelings need to be recognized and addressed. Many parents are a great

help and will assist with restraining and comforting their child, but others find the experience upsetting and should not be forced to hold their child during the procedure, but encouraged to comfort afterward. Adolescents need to be told to lie down for a while after a parenteral drug administration to avoid possible vasovagal syncope (e.g., human papillomavirus vaccine).

### Subcutaneous Route

Small volumes (under 2 mL) of isotonic solutions are usually given into the SC tissue using short needles with narrow bore and regular bevel. The SC route is used for insulin self-injection. There is a possibility of fat atrophy or hypertrophy occurring. This can be minimized by rotating the injection sites, over the outer aspect of the upper arm, the anterior or lateral thigh, and the abdomen. In thinner children, it may help to pick-up the skin gently between the fingers to create a pocket in which to inject vertically.

### Intramuscular Route

Most drugs can be injected into the muscle. However, the IM route should be avoided, whenever possible. In practice, the route is used for administering concentrated and irritating solutions, which may cause local pain if injected subcutaneously. Volumes of 1–2 mL can be administered through the IM route in infants, while older and bigger children can receive volumes up to 5 mL. The shorter and the narrower the needle, the less pain it will cause. Some draw up the fluid with one needle and inject with another, to avoid the solution on the wet needle irritating the needle track. Using a single needle saves time and for most drugs leads to no extra reaction. Before injecting the solution, the plunger should be slightly withdrawn to check whether the needle has entered a blood vessel. If blood is withdrawn, another site must be chosen. IM injections should not be given to children on anticoagulants or to those with thrombocytopenia. As IM injections can damage muscles and leave deep scars, injection sites should be regularly inspected, particularly in the immobile and very sick.

### Intravenous Route

This route is generally chosen when a medicine cannot be given by mouth and one requires faster onset of action. Reliable access, often a central vein, should be used for children whose treatment involves irritant or inotropic drugs or who need to receive the medicine over a long period. The IV may be given as intermittent bolus, continuous or intermittent infusion. IV administration is used for administering intravenous fluids (maintenance fluids and for correction of fluid, electrolyte and acid-base disturbances), blood and blood products and medications.

Administration of IV drugs and fluids at slower rates and in small volumes required in neonates, infants and small children requires special equipment. The micro-drip set is useful in these situations as the narrow tubing produces smaller drops enabling precise adjustment of slow flow rates. Infusion pumps can administer fluids at rates as little as 0.1 mL per hour; administer injections every minute or as repeated boluses; and amounts that vary at different times of the day. Fluids can be pumped in at high pressures and hence these pumps may be used for giving accurate amounts of fluids via SC or epidural routes.

### Per-rectal Administration

This route is used when drugs cannot be given orally or intravenously or when a local effect is desired. Presence of diarrhea, impacted feces and fissure *in ano* are contraindications to the use of this route. The child should be lying on his side, with legs curled

up in a fetal position. With babies, it is possible to administer drugs per-rectally by lifting her legs and flexing the knees (as for changing a nappy). The suppository should be gently inserted into the anus, just beyond the anal sphincter. It may be necessary to hold the buttocks together for several minutes to prevent the immediate expulsion of the suppository.

### Intraosseous Route

Intraosseous access is resorted to, if vascular access is not rapidly achieved in any infant or child requiring IV drugs or fluids, especially in a life-threatening emergency. Those trained in the procedure can achieve access successfully in around 80% of attempts, within 1–2 minutes. In infants and children, proximal tibia is the most commonly chosen site for IO catheter insertion. The recommended site is the flat area approximately 1–2 cm distal to the tibial tuberosity. The needle may be angled 10–15° caudally to avoid injury to the epiphyseal growth plate. Disadvantages of this route include extravasation and rarely osteomyelitis.

### Endotracheal Route

The endotracheal route may be used for administering drugs when IV or IO access is not achieved especially in a life-threatening or serious condition. Medications are absorbed through this route but the blood levels attained may not be equivalent to those produced by IV/IO administration. Further, for most drugs the optimal doses for endotracheal use are unknown. Drugs that can be given by this route include surfactant, lidocaine, epinephrine, atropine and naloxone.

## METHODS OF GIVING MEDICINES

Young children and infants who cannot understand will usually take medicine from someone they know and trust, a parent or the main caregiver. It is important that those who give medicines know about the medicine and how to give it. Occasionally, a medicine has to be disguised or masked with small quantities of food. Rarely, a child has to be restrained for the medicine to be administered. Then, especially, the child should be comforted and reassured. They must not be left with the impression that being given medicine is a punishment for being sick. The approach depends on the child's understanding and the circumstances:

- Under 2 years of age: Administration by parents if possible, using an approach which they believe is most likely to succeed.
- Two to five years old need a calm, gentle, firm and efficient approach after they have been told what is happening. Play and acting out may help them understand. Rewards and an acceptable *chaser* (drink) encourage further collaboration.
- Five to twelve years old also need encouragement, respect for their trust, and an explanation attuned to their understanding.
- Children over 12 years of age: At this age children must have a proper understanding of what is happening. They should be having a share in the decision-making process as well as the responsibility for adhering to the agreed plan. They must feel in control.

### Ensuring Safety of Medicines

Children and neonates are extremely vulnerable to harm due to errors while prescribing, administering and storing medicines. The doctors, parents and caregivers need to be extremely vigilant to ensure that children do not suffer from undue harm. All of them need to take coordinated steps to ensure this safety. Some of the steps are enlisted in **Box 4**.

**BOX 4 Steps to avoid undue harm during prescribing and administration of drugs to children***Doctors*

- Prescribe suitable formulation based on the child's age, development and ability
- Calculate doses diligently. Do not hesitate to use calculators. It is better to have another independent check
- Check the concentration of active ingredient in the formulation
- Prescribe oral medications in terms of mL and not in terms of teaspoon/tablespoons. The volume in spoons is highly variable
- Avoid the use of decimal points by prescribing in whole units, i.e., 100 µg rather than 0.1 mg
- If a decimal point is required, always use a leading zero, i.e., 0.5 mL
- Avoid using a trailing zero. For example do not write 5 mg as 5.0 mg. The latter can lead to a tenfold error
- Remember to account for any administration issues such as displacement volume for IV medicines, the correct diluent and administration method
- Provide complete information regarding the dose, frequency, side effects, possibility of response and action to be taken if any untoward event is noticed
- Instruct parents/caregivers regarding appropriate storage of medicines, keeping them away from children and discarding them
- Ensure that parents/caregivers have understood the instructions. Encourage them to get doubts clarified.

*Parents/caregivers*

- While buying drugs, ensure that the preparation is the same as prescribed. Check for the expiry date
- Follow instructions regarding administration, storage and discarding of medicines provided diligently
- If something is not understood, do not hesitate to get doubts clarified
- If there is an unexpected event, contact the doctor. It could be due to progression of disease or due to an unrelated event. It could also be due to a side effect of the drug.

*General*

- Report adverse events
- Advocacy for the conduct of clinical trials in children and for availability of formulations appropriate for children.

**IN A NUTSHELL**

1. Administering medicines to children is a challenge and requires special attention. It needs the cooperation of the child and understanding of the parents/caregivers.
2. Depending upon their age and developmental abilities, children require different types of oral formulations: drops, syrups, suspensions and dispersible tablets. Tablets and capsules are suitable for older children.
3. Lack of appropriate formulations compromises the right of children to safe medicines.
4. Caregivers need to be informed about the medicines and way to administer them. It is advisable to demonstrate the method of measuring actual volume of oral liquid preparations to them to avoid under or overdosing.
5. Additional specific equipment may be necessary to ensure that correct dose is administered. For administering aerosol medicines, young children might need a spacer device in addition to a MDI. To ensure that the correct volume is delivered while providing IV fluids and drugs, doctor may have to use syringe infusion pump. The syringe infusion pump allows measured delivery of small volumes over a longer time period.
6. Well-coordinated actions by doctors, pharmacists and parents are required to ensure that children receive their medicines in the right amount, at the right frequency, for the right duration without exposing them to undue risks.

**MORE ON THIS TOPIC**

Unni J. Indian Academy of Pediatrics Drug Formulary 2012. Cochin: Indian Academy of Pediatrics; 2013.



# PART III Intensive Care and Emergencies

## Section 7 ACUTELY ILL CHILD AND RESUSCITATION

Section Editor Rakesh Lodha

### Chapter 7.1

### Assessment and Triage

Jayashree M, Sunit Singh

Most cardiac arrests in infants and children result from progressive respiratory failure, shock, or both. Sometimes, they can occur due to sudden cardiac events such as arrhythmia. The outcome of out-of-hospital cardiac arrest despite optimal resuscitation is only 4–13%. Therefore, quick recognition and timely intervention in respiratory and/or circulatory failure is paramount to prevent progression to cardiac arrest. The biological response to any initiating illness, e.g., trauma, infection, surgery, burns, etc., involves activation of immune system that further triggers an inflammatory cascade, which if untreated can spiral into sequential organ failure called the *physiological domino effect*. The longer the process, the more advanced and irreversible the physiological derangements become, resulting in a high mortality. Therefore, the key to emergency management is to identify and stabilize the physiological or functional impairments irrespective of whatever may be the primary etiology.

Triage refers to assessment of a patient in the *emergency room* with a view to define urgency of care and priorities in management, and also helping in the rational allocation of limited resources when the demand exceeds the availability. This system is a structured framework within which a patient is classified according to the acuity and severity of illness. Those who need acute care in the *emergency department* (ED), are attended to immediately in order of priority while those needing less acute care wait in the triage room. There are many international triage systems devised for acute care in emergency departments such as Emergency Triage and Treatment (ETAT) guidelines, Emergency Severity Index (ESI), Canadian Triage and Acuity System (CTAS) and the Australian Triage Scale. Goals of triage are summarized in **Box 1**.

#### BOX 1 Goals of Triage System

- To rapidly assess and identify children with life-threatening illness
- To determine appropriate cause and initiate timely interventions
- Order immediate investigations and procedures as per the need
- To provide safe and quality care to patients
- To perform ongoing assessments, keeping in mind the dynamicity of illness and progression
- To utilize the limited resources in an efficient manner.

### PEDIATRIC TRIAGE

The rules of “Rights” have to be followed in every patient who presents to the emergency: *Get the right patient to the right provider, in the right moment of time, to receive the right care, to achieve the right outcome.*

The pediatric triage assessment is a rapid 3–5 min clinical evaluation of a child with an aim to determine the severity of illness by means of subjective and objective parameters. Also, it is particularly important to triage each child according to the age, symptomatology and acuity of illness. What is assigned a high level of acuity differs with age and associated symptoms and signs, e.g., abdominal pain or fever less than 39°C in older child may be non urgent but an emergency for a one month old infant. Once the patients are triaged, they are classified into 5 levels of category (discussed here) and prioritized accordingly.

### Triage Assessment

Triage evaluation can be completed in an organized and systematic manner using the general assessment, i.e., Pediatric Assessment Triangle (PAT) and primary assessment (ABCDE approach). This assessment is different from diagnostic evaluation and is based and modified from Pediatric Advanced Life Support (PALS) guidelines. The objective is to identify anatomical or functional abnormality, its severity, and to plan and guide initial emergency treatment and stabilization. The assessment and treatment always go hand in hand.

### General Assessment

The PAT (**Fig. 1**) comprises of the immediate visual and auditory impression of a sick child who is wheeled into an ER based on the triad of appearance, breathing and circulation. The process is rapid and hardly takes 30–40s at the end of which the provider is able to identify children with acute life-threatening problems requiring

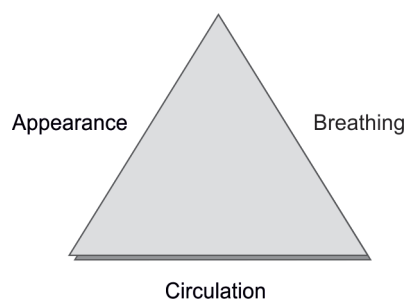
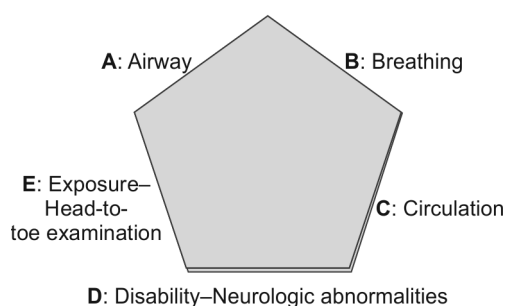


Figure 1 Pediatric assessment triangle



**Figure 2** Pediatric assessment pentagon

immediate life-saving interventions, e.g., a child who is brought gasping.

**Appearance** Muscle tone, interaction, consolability, look/gaze or speech/cry are assessed.

**Work of breathing** Increased work of breathing (nasal flaring, retractions), decreased or absent efforts or abnormal sounds (wheeze, grunt, and stridor).

**Circulation** Abnormal skin color (pale or cyanosed) or bleeding.

Based on PAT assessment, patient's illness is categorized as either stable or unstable. The unstable ones are further classified into life-threatening and non-life-threatening. Patients in the former category, e.g., cardiac arrest, cardiorespiratory failure, hypotensive shock, deep coma, severe stridor, etc., need immediate treatment or resuscitation before proceeding to primary assessment.

## Primary Assessment

The primary assessment [assessment pentagon (**Fig. 2**)] involves a more detailed physical examination/assessment of airway (**A**), breathing (**B**), circulation (**C**), neurologic abnormalities (**D**) and head-to-toe examination (**Exposure**). Primary assessment should be completed in 1–3 minutes. Besides clinical parameters, primary assessment also involves recording of SpO<sub>2</sub>, ECG and blood glucose.

## Airway

The anatomical part of respiratory tract which acts as a conduit for carrying atmospheric air to lungs but does not participate in gas exchange is called the airway. The goal is to determine the patency of airway which can be determined by *look, listen* and *feel* maneuvers.

*Look:* for chest rise.

*Listen:* for breath sounds and air movement.

*Feel:* the movement of air at the nose and mouth.

**Status classification** Normal or obstructed airway. Signs that suggest airway obstruction are inability to speak, a silent cough, breathing difficulty, poor chest rise, gurgling noises, pooling of secretions or paradoxical chest movements.

**Stabilization** Some airway problems respond to simple maneuvers such as positioning (chin-lift head-tilt) or suction while some require adjuncts such as oropharyngeal airway, endotracheal tubes or laryngeal mask airway to maintain patency. In suspected cervical spine injuries, the airway should be opened with the jaw thrust maneuver.

## Breathing

The goal is to determine the adequacy of gas exchange (oxygenation and ventilation). The assessment of breathing includes an evaluation of the respiratory rate and effort, lung sounds, and pulse oximetry. Normal respiratory rates are age dependent (**Table 1**) and hence respiratory rates more or slower than normal for age are defined as tachypnea and bradypnea, respectively. Apnea is defined as a complete cessation of breathing for 20 sec or more.

Increased work of breathing (WOB) manifests in the form of nasal flaring, retractions, accessory muscle use, or irregular respirations. The adequacy of tidal ventilation is determined by the chest wall excursion, and auscultation of air movement. Abnormal lung sounds include stridor, grunting, gurgling, wheezing, and crackles. O<sub>2</sub> saturation more than 94% at room air is surrogate for adequate oxygenation.

**Status classification** Based on the above assessment, a child's respiratory status can be classified into two severity groups: 1. Respiratory distress and 2. Respiratory failure. The following combinations can give a reasonable idea about the level of respiratory problem:

Retractions + stridor = Upper airway obstruction

Retractions + wheeze = Lower airway obstruction

Retraction + Grunt/labored breathing + crepitations = Parenchymal disease

Increased rates without recessions = Acidosis or neurogenic hyperventilation

Paradoxical breathing/see-saw breathing = Neuromuscular weakness

**Stabilization** O<sub>2</sub> saturations less than 92% qualifies for hypoxemia and warrant oxygen support through nasal prongs, facemask, partial re-breathing or non-rebreathing mask provided, the patient is breathing spontaneously. Patients having hypoxemia with poor respiratory efforts, require assisted breathing with bag and mask or bag and tube immediately.

**Table 1** Normal respiratory rates (breath/min), according to age

Age range Years	Neonates	0–1	1–2	2–3	3–4	4–5	5–6	6–12	12–13	13–18
APLS	30–40	30–40	25–35	25–30	25–30	25–30	20–25	20–25	15–20	15–20
PALS <sup>a</sup>	30–60	30–60	24–40	24–40	24–40	22–34	22–34	18–30	18–30	12–16
EPLS <sup>b</sup>	30–40	30–40	26–34	24–30	24–30	24–30	20–24	20–24	12–20	12–20
PHTLS <sup>c</sup>	30–50	20–30	20–30	20–30	20–30	20–30	20–30	12–20	12–20	12–20
ATLS		<60	<40	<40	<35	<35	<35	<30	<30	<30

a: PALS and EPLS provide separate range for infants up to 3 months, and for those between 3 months and 2 years of age.

b: PALS and EPLS provide multiple ranges—ranges for awake children are tabulated

c: PHTLS provides separate ranges for infants up to 6 weeks, and for those between 7 weeks and 1 year of age

**Abbreviations:** PALS, Pediatric Advanced Life Support; EPLS, European Pediatric Life Support; APLS Advanced Pediatric Life Support; PHTLS Pre Hospital Traumatic Life Support; ATLS Advanced Trauma Life Support.

**Table 2** Normal heart rates (beats/minute), according to age

Age, Years	Neonate	0–1	1–2	2–3	3–5	5–6	6–10	10–12	12–13	13–18
APLS	110–160	110–160	100–150	95–140	95–140	80–120	80–120	80–120	60–100	60–100
PALS	85–205	100–190	100–190	60–140	60–140	60–140	60–140	60–100	60–100	60–100
EPLS	85–205	100–180	100–180	60–140	60–140	60–140	60–140	60–100	60–100	60–100
PHTLS	120–160	80–140	80–130	80–120	80–120	80–120	(60–80) >100	(60–80) >100	(60–80) 100	60–100 <100
ATLS	<160	<160	<150	<150	<140	<140	<120	<120	<100	

PALS and EPLS provide separate ranges for infants upto 3 months, and for those between 3 months and 2 years of age

PALS and EPLS provide multiple ranges—ranges for awake children are tabulated

PHTLS does not provide ranges for adolescents over 16 years of age

Abbreviations: PALS, Pediatric Advanced Life Support; EPLS, European Pediatric Life Support; APLS, Advanced Pediatric Life Support; PHTLS, Pre Hospital Traumatic Life Support; ATLS, Advanced Trauma Life Support.

### Circulation

The goal is to determine the adequacy of cardiac output (pre-load, myocardial contractility and afterload) and tissue perfusion. The assessment of cardiovascular function is basically divided into direct parameters which include heart rate and rhythm, peripheral and central pulses, blood pressure, and capillary refill time and indirect parameters which indicate adequacy of end organ perfusion such as skin color and temperature, urine output and level of consciousness. Heart rate is also age dependent as shown in **Table 2**. Normally, the rate will be slower in a sleeping or an athletic child. Labeling as tachycardia or bradycardia will depend on age-based cut-offs.

Similarly, blood pressures also vary according to age (**Table 3**). Hypotension is defined as BP below the fifth percentile for age. In children who are not hypotensive, an observed fall of 10 mm Hg in systemic blood pressure from baseline should prompt careful evaluations.

The heart rhythm should always be determined during circulatory assessment by attaching to a monitor or taking a three-lead ECG so as to rule out or rule in rhythm disturbance as a cause for circulatory instability. The important dysrhythmias to recognize are supraventricular tachycardia, ventricular fibrillation, ventricular tachycardia, pulseless electrical activity (PEA) and asystole. Once recognized, appropriate interventions need to be initiated. Adequacy of end organ perfusion can be

determined by measuring the urine output which is normally maintained at 1 mL/kg/hour.

**Status classification** Based on the above assessment the severity of child's circulatory status can be classified into two groups: 1. Compensated shock (poor perfusion with maintained BP); 2. Hypotensive shock (poor perfusion with less than 5th centile BP). The mechanism of shock may be one or combination of hypovolemic, distributive and cardiogenic.

**Stabilization** O<sub>2</sub> with a non re-breathing mask (FiO<sub>2</sub> 100%) should be started in all children with shock. The first priority in shock stabilization is to optimize the preload with help of isotonic fluids (20 mL/kg of isotonic saline). The rapidity of administration is determined by the severity of shock. Fluid refractory shock (after 40–60 mL/kg) is treated with vasoactives. First dose of antibiotics should be given in suspected septic shock. Early inotropes should be initiated in cardiogenic shock.

### Disability

It involves a quick evaluation of cortical and brainstem functions. Standard evaluation includes the level of consciousness using an AVPU scale (Awake, Voice, Pain, Unresponsive), or Glasgow Coma Score (GCS), muscle tone, pupillary response to light, motor activity and symmetry/asymmetry of movements. A change of at least 2 points in the GCS score from one assessment to the next indicates a clinically important change in neurological status.

**Status classification** Based on the above assessment the disability status can be classified into two groups: 1. Primary brain dysfunction (e.g. encephalitis, meningitis, acute stroke or traumatic brain injury); and 2. Systemic dysfunction (altered sensorium secondary to systemic changes such as shock, sepsis, hypoxia, etc.).

### Exposure

Examine for evidence of trauma, unusual markings of abuse, rashes, bleeds and core temperature.

At the end of the primary assessment, patient's physiological status is classified as; stable, respiratory distress or respiratory failure, shock compensated or hypotensive, primary brain/systemic dysfunction, cardiorespiratory failure or cardiorespiratory arrest and further triaged into 5 levels.

### Triage Classification

Patients' illness severity can be triaged into 5 levels depending on the physiological abnormalities (**Table 4**).

**Table 3** Normal systolic and diastolic blood pressures according to age

Age	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
0 day	60–76	30–45
1–4 days	67–84	35–53
1 month	73–94	36–56
3 months	78–103	44–65
6 months	82–105	46–68
1 year	67–104	20–60
2 years	70–106	25–65
7 years	79–115	38–78
15 years	93–131	45–85

Females have slightly lower systolic blood pressures, and higher diastolic blood pressures than males of the same age.

(Adapted from Fourth Report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents: NHLBI; May 2004)

**Table 4** Triage classification

<i>Triage Level</i>	<i>Acuity</i>	<i>Description</i>	<i>Target time to Treatment and Reassessment</i>	<i>Examples</i>	<i>Remarks</i>
Level 1	Resuscitation	Patient with life-threatening disease or injury requiring immediate treatment	Immediate and continuous (1–5 minutes)	Cardiac arrest, seizure, unresponsive, airway obstruction, hypothermia, coma, Glasgow Coma Score (GCS) < 10, major burns, severe trauma, severe respiratory distress, shock	Need continuous assessment and intervention to maintain physiological stability
Level 2	Emergent	Patient with significant health problems that could become life threatening or disabling	15 minutes	Moderate respiratory distress, stridor, GCS < 13 Severe dehydration, febrile child < 3 months old and temperature > 38°C, inhalation or ingestion of toxic substance, acute bleeding, purpuric rash, burns > 10%, abdominal pain with vomiting/diarrhea or abnormal vitals	Any infant/child who require multiple interventions to prevent further deterioration
Level 3	Urgent	Patient with significant health problems that are not immediately life-threatening or disabling	30 minutes	Alert, oriented, with minor alteration in vitals Febrile child > 3 months old with temperature > 38.5°C, minor head injury	Level 3 patients need carefully planned reassessments while awaiting care, since critical illness may present with common symptoms and may evolve rapidly
Level 4	Less urgent	Patient with stable health conditions; to be evaluated in the ED	1 hour	Diarrhea with no dehydration, lacerations, pain, sore throat	
Level 5	Non-urgent	Patient with stable health conditions; to be evaluated in ED/OPD	2 hours	Afebrile, alert, well oriented, euhydrated, normal vitals	These patients may be referred to other areas of hospital for management

(Adapted from Canadian pediatric triage and acuity scale)

Abbreviations: ED, emergency department; OPD, outpatient department.

### IN A NUTSHELL

1. The key to emergency management is to identify and stabilize the physiological or functional impairments irrespective of the primary etiology.
2. Triage refers to rapid assessment of children with the objective to define urgency and prioritize management.
3. A patient is classified according to the acuity and severity of illness. Those who need acute care in the emergency department (ED) are attended to immediately while those needing less acute care wait in the triage room.
4. The assessments are systematic and organized using PAT triangle and ABCDE pentagon.
5. Patient's illness severity is triaged into 5 levels of acuity based on physiological abnormalities: Resuscitation, Emergent care, Urgent care, less urgent and non-urgent care.
6. Patients in cardiac arrest, cardiorespiratory failure, hypotensive shock, deep coma, and severe upper airway obstruction are categorized as life-threatening problems and resuscitated immediately.

### MORE ON THIS TOPIC

- Australian College of Emergency Medicine 2000. The Australian Triage Scale. Carlton Vic; 2011. pp.1-13. Available from: [www.wacebnm.curtin.edu.au/workshops/triage.pdf](http://www.wacebnm.curtin.edu.au/workshops/triage.pdf). Accessed July 1, 2014.
- Beveridge R, Clark B, Janes L, et al. Canadian emergency department triage and acuity scale: implementation guidelines. *Can J Emerg Med.* 1999;1(3 suppl):1-40.
- Canadian Association of Emergency Physicians. Canadian Pediatric triage and acuity scale: implementation guidelines for emergency departments. *Can J Emerg Med.* 2001;3(4 suppl):1-40.
- Emergency Triage Assessment and Treatment (ETAT) Course: WHO Manual for Participants. Geneva:WHO; 2005.
- Fuchs S, Gausche-Hill M, Yamamoto L. The Pediatric Emergency Medicine Resource, Advanced Pediatric Life Support (APLS) Manual, American College of Emergency Physicians, 4<sup>th</sup> ed. Dallas: Jones & Bartlett; 2004. pp. 2-19.
- Shelton R. The emergency severity index 5-level triage system. *Dimens Crit Care Nurs.* 2009;28:9-12.



## Chapter 7.2

# Cardiopulmonary Resuscitation

*Utpal Bhalala, Vijay Srinivasan*

Cardiac arrest (CA) in children is a global public health problem that tragically cuts short the life and potential of a child with important emotional and economic consequences to family and society at large. Modern cardiopulmonary resuscitation (CPR) was developed approximately 65 years ago by Kouwenhoven, Jude, Knickerbocker and Safar at the Johns Hopkins Medical Center in the USA. Subsequent advances in resuscitation science and coordinated emphasis on the science of education and implementation have substantially improved survival outcomes for pediatric CA, particularly for in-hospital CA. Certain groups of children (such as those who undergo cardiac surgery) are at much greater risk for CA but also have improved potential for good survival outcome. Unfortunately, good neurologic outcome and quality of life is frequently unattainable, especially following pediatric out-of-hospital CA. This chapter will review the etiology of pediatric CA (both in-hospital and out-of-hospital), mechanisms of blood flow during CA, techniques and quality of CPR, and post-resuscitation care that can save the lives of children and improve their subsequent quality of life.

## HISTORY

The problem of CA has occupied the minds of scientists and investigators over several millennia. Several methods to restart the heart have been described over centuries ranging from comical to dangerous, betraying a lack of understanding of cardiopulmonary physiology. The discovery of electricity greatly aided efforts to treat CA. The first successful case of open-chest defibrillation in humans was reported in 1947 by Beck. However, open-chest CPR is impractical for obvious reasons and can only be used in limited circumstances. In the 1950s, investigators observed that application of pressure to the sternum and sides of the chest resulted in increase in intra-arterial pressure. This sparked the discovery of chest compressions and resulted in the first instance of external compressions and defibrillation being employed in a 2-year-old child. Subsequently, this technique was employed successfully in over a 100 patients who experienced CA. Following these efforts, Safar incorporated oxygenation and ventilation with closed chest compressions, resulting in the birth of CPR as we know it. Over the last 65 years, significant advances in our knowledge of CA and science of CPR have enhanced the widespread use of this technique to save countless lives. Notably, national and regional resuscitation council societies [American Heart Association (AHA), Heart and Stroke Foundation of Canada, European Resuscitation Council, Australia and New Zealand Committee on Resuscitation, Resuscitation Councils of Southern Africa, Inter American Heart Foundation, and Resuscitation Council of Asia] have come together to coordinate efforts through the International Liaison Committee on Resuscitation to develop and revise guidelines for CPR every 5 years that are widely published in leading medical journals and available free of cost to health-care providers. This has hugely helped standardize the technique of CPR and enabled providers to speak a common language during detection of CA and delivery of CPR.

## EPIDEMIOLOGY

Estimates of pediatric CA and subsequent survival vary widely between different countries and regions across the world, largely due to limitation in reporting mechanisms and lack of registry style datasets as well as differences in resources for CPR and post-resuscitation care. Additionally, incidence and outcomes differ between in-hospital CA and out-of-hospital CA groups, with generally worse outcomes for the latter. A study of in-hospital CA from a single center in Taiwan demonstrated hospital survival of 21% with favorable neurological outcome in 16%. Another study of in-hospital pediatric CA from a single center in Pakistan demonstrated a low incidence of CA of all admissions (0.4%), likely reflecting that the majority of deaths due to CA occur prior to admission. Most CA occurred in the pediatric intensive care unit (PICU) with return of spontaneous circulation (ROSC) in 55% of patients with CA and survival to discharge in 11% of patients. In a mixed population of adults and children in a single 2,300 bed hospital in Thailand, the overall survival to discharge was 6.9%. A single study from Kenya in 2001 demonstrated that survival to discharge following in-hospital pediatric CA was 0%.

A 2009 study in multiple sites in North America observed the incidence of pediatric out-of-hospital CA to be 8 per 100,000 person years (72.7 in infants, 3.7 in children and 6.4 in adolescents). In the same study, survival for all pediatric out-of-hospital CA was 6.4% (3.3% for infants, 9.1% for children and 8.9% for adolescents). A 2010 study in Korea observed the incidence of pediatric out-of-hospital CA to be 4 per 100,000 person years (67 in infants, 3 in children and 4 in adolescents). In the same study, survival for all pediatric out-of-hospital CA was 4.9% (2.9% for infants, 4.7% for children and 7.2% for adolescents). Data from a single center in Singapore between 1997 and 2001 demonstrated that survival to discharge following pediatric out-of-hospital CA was 4.7%.

## ETIOLOGY

The majority of pediatric CA (whether in-hospital or out-of-hospital) result from respiratory failure leading to hypoxemia and bradycardia with subsequent loss of circulation and pulseless electrical activity (PEA). Typical disease states when untreated that predispose to CA include pneumonia, sepsis, diarrhea, trauma and poisonings. Primary arrhythmias are generally less common in children, but can occur postoperatively in children with congenital cardiac disease or in the setting of myocarditis and/or cardiomyopathy as well as ingestions. Ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) can result in sudden death in older children due to previously unrecognized channelopathies and metabolic disorders of fatty acid metabolism.

## PATHOPHYSIOLOGY

The pathophysiology of CA in children differs significantly from that in adults. Adults more frequently experience CA due to VF from underlying coronary artery disease and myocardial infarction. Pediatric CA usually stems from severe hypoxia or asphyxia as a result of respiratory failure and/or circulatory shock. Refractory hypoxia and/or tissue hypoperfusion favors anaerobic metabolism with resulting lactic acidosis. Both hypoxia and acidosis lead to myocardial depression, which ultimately leads to CA. In South Asia and Africa, pneumonia, diarrhea, sepsis and trauma are the leading causes of both out-of-hospital and in-hospital CA in children.

In contrast to adults, children have unique physiologic characteristics that impact their pre-arrest states, mechanisms of arrest and post-arrest outcomes. Children exhibit rapid developmental changes that affect cardiac and respiratory physiology during pre-arrest, intra-arrest and post-arrest phases. Neonates undergo transitional physiological changes from the in utero environment to an external, gaseous environment at the time of birth. Neonates and infants have much lower cardiac and respiratory reserve, and higher pulmonary vascular resistance compared to older children. Certain children have pre-existing developmental defects and other organ dysfunction, which significantly increase their risk for CA and pose additional challenges to successful CPR following CA. Additionally, due to developmental differences, neurologic assessment scales and tools that are suitable for one age group may not be accurate or valid at other age groups.

There are four well-described phases of CA: (1) pre-arrest, (2) no-flow (untreated CA), (3) low-flow (CPR), and (4) post-arrest phase. The *pre-arrest phase* includes pre-existing conditions (e.g., neurologic, cardiac, respiratory, or metabolic abnormalities), developmental status (e.g., preterm neonate, term neonate, infant, child, or adolescent), and precipitating events (e.g., respiratory failure or shock). It may represent a period of low, normal, or high blood flow. During the *no-flow or arrest phase*, there is no blood flow to vital organs, including the brain and the heart. Depending upon the duration of no-flow state, neurons suffer varying degrees of primary damage. During *low-flow or CPR phase*, external chest compressions provide approximately 20% of baseline cardiac output. The provision of high-quality CPR during this phase determines vital organ perfusion. The delivery of CPR to achieve adequate cerebral and myocardial perfusion pressures is essential for ROSC and overall survival, including neurological outcome. The *post-arrest phase* can be divided into an immediate post-arrest phase and a late post-arrest phase. In the immediate post-arrest phase, ischemia-reperfusion leads to a cascade of pathophysiologic changes in vital organs. Ischemia-reperfusion induces systemic inflammatory response with release of cytokines and chemokines that lead to multiple organ dysfunction (MOD). Similarly, a neuroinflammatory response due to ischemia-reperfusion leads to secondary neuronal injury leading to encephalopathy. In the late post-arrest phase, recovery is characterized by neurologic deficits of varying degrees depending upon the severity of encephalopathy (**Fig. 1**).

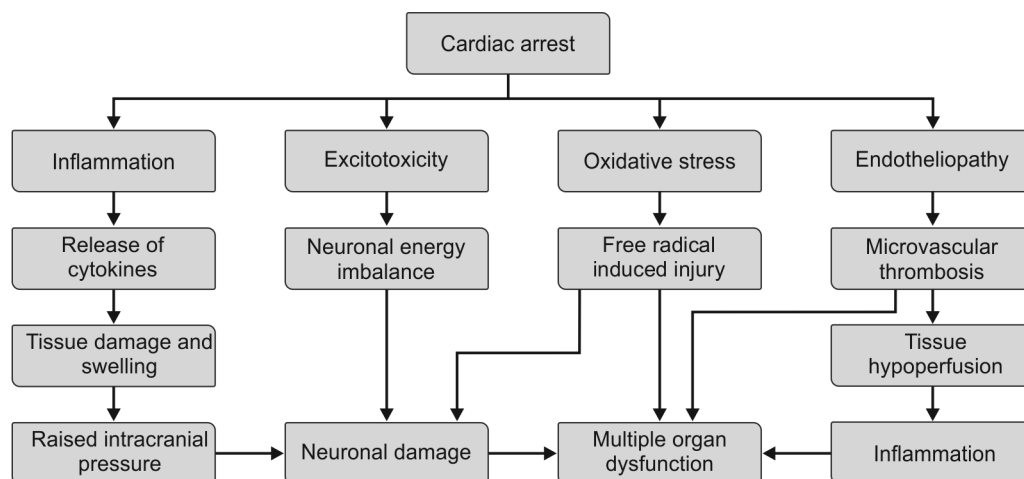
## CLINICAL FEATURES

While recognition of a child in CA is fairly straightforward due to lack of signs of life, it is very important to recognize children at risk for progression to CA so that prompt measures can be instituted to stabilize the child and prevent CA. Laypersons often mistake agonal respirations for good breathing efforts and fail to provide CPR when indicated. Changes in mental status can often be difficult to discern in a tired child that is progressively getting sicker. Fevers can mask signs of dehydration with mistakes in assessment and treatment. In general, during the pre-arrest phase, the child usually has significant derangements in vital signs and organ dysfunction with associated laboratory abnormalities.

## MANAGEMENT

The goal of CPR for CA is not only ROSC and survival, but importantly favorable neurological outcome. The key to successful CPR is early recognition of CA and prompt institution and maintenance of high-quality CPR with adjunct measures.

During the pre-arrest phase, management strategies should focus on early recognition and aggressive management of respiratory failure and shock to prevent an arrest. For example, public health education to identify warning signs of respiratory failure and dehydration can result in parents seeking help before progression to CA. The development of hospital code teams and monitoring systems in hospitals can help identify children that are progressing toward CA and help institute measures to stabilize them prior to CA. Another important but frequently overlooked aspect of pre-arrest care in children with refractory hypoxia and shock is anticipating and preparing for CA during stabilization. Lack of preparation and anticipation can result in precious seconds ticking away while efforts are made to scramble to respond to CA. For example, a child with septic shock and refractory hypotension from intravascular volume depletion and poor cardiac output is at very high risk of experiencing CA during intubation and/or line placement attempt. Preparation for such situations would include administering fluid bolus, correcting electrolyte abnormalities and intubating under controlled, titrated sedation but also importantly being ready with all medications (epinephrine, atropine, dextrose, electrolytes), equipment (backboard under the patient, step stool for chest compression provider and defibrillator) and personnel (chest compressions, administration of medications, and documentation) for managing an impending CA. Since there is a clear evidence that early institution of high-quality CPR improves



**Figure 1** Pathophysiology of cardiac arrest leading to neuronal damage and multiple organ dysfunction

outcome from CA, every effort should be made to avoid delay in recognition of CA and prompt institution of high-quality CPR. For example, refractory hypoxia and shock frequently lead to bradycardia in children which in turn leads to pulseless state and CA. Since there is clear evidence of improved outcome in children who receive CPR for bradycardia with a weak pulse compared to pulseless CA, one should commence CPR in children with bradycardia with a weak pulse immediately upon recognition.

During the no-flow or arrest phase, high-quality CPR is warranted and together with early defibrillation (when indicated) possibly the only measures definitely shown to improve outcome from CA. Providers should follow pediatric advanced life support (PALS) algorithm for CPR and focus on monitoring and delivering high-quality CPR. For high-quality chest compressions, one should follow the AHA mantra of *push hard, push fast, avoid interruptions and allow full recoil*. Every component of high-quality CPR has strong physiologic basis supported by good quality evidence through animal and human research. Through the studies using CPR quality-sensing devices, it is well established that quality of in-hospital CPR is often suboptimal and can be associated with worse patient outcomes. In a study on adult in-hospital CA, 23% of chest compressions were found to be associated with incorrect rates and 36% of the chest compressions were too shallow. In a porcine model of asphyxia CA, deeper chest compressions resulted in improved hemodynamic and short-term survival outcomes. Use of step stool by chest compression providers and a backboard under the patient have been shown to improve the quality of chest compressions. Adequate coronary perfusion pressure during CPR is essential for myocardial preservation and return of circulation. Coronary perfusion pressure depends on diastolic blood pressure and right atrial pressure. The spontaneously beating heart receives the majority of its perfusion during diastole with linear correlation between coronary artery blood flow and aortic diastolic pressure. During chest compressions, aortic pressure rises concurrently with right atrial pressure. During chest decompression, the right atrial pressure falls faster and lower than the aortic pressure, generating a pressure gradient that perfuses the heart. Thus, coronary perfusion occurs during diastole or the *release* of chest compression. In a porcine model of asphyxial CA, survival was improved when CPR was targeted to a coronary perfusion pressure of more than 20 mm Hg (hemodynamic goal-directed CPR). Similarly, end-tidal carbon dioxide level (a surrogate for cardiac output) more than 10–15 mm Hg during CPR is associated with improved survival outcomes. Clinical and laboratory studies have shown that the delivered ventilation rate during CPR frequently exceeds AHA guidelines and is associated with poor cardiac output during CPR. Hyperventilation leads to increased intrathoracic pressure, which in turn impedes venous return to the heart and thereby decreases cardiac output. It is, therefore, very important to ventilate at the specified rate especially as the majority of pediatric CA result from respiratory failure. Appropriate identification and management of CA rhythms by health-care providers have also been shown to be deficient in actual practice. For VF and pulseless VT-CA, prompt defibrillation and high-quality CPR are recommended. As the mortality rate increases by 7–10% per minute of delay to defibrillation, such delays in treatment must be avoided. Patient factors (like location at the time of arrest, witnessed/unwitnessed, comorbidities, age, sex, and race) and provider factors (like CPR quality, teamwork, identification and reversal of cause of arrest) determine outcomes from CA. The importance of diagnosing and treating the underlying cause of arrest is fundamental to the management of all CA. PEA is often caused by reversible conditions and can be treated successfully, if

those conditions are identified and corrected. According to AHA guidelines for management of CA, the provider should recall the Hs and Ts to identify factors that may have resulted in the arrest or may be complicating resuscitative efforts.

For all practical purposes, the depth of chest compressions should be at least one-half the anterior-posterior diameter of the chest and delivered at least at a rate of 100 compressions per minute in children. Providers should allow full recoil during chest compressions and avoid learning to improve passive return of blood into the right heart. It is highly recommended to switch the chest compression provider every 2 minutes due to development of provider fatigue and inability to maintain high-quality CPR. One should remember to use a backboard under the patient and a step stool for chest compression provider to improve chest compression quality, monitor and use hemodynamic parameters like arterial blood pressure (whenever an arterial line is in place) and end-tidal carbon dioxide levels (through capnography) to improve the quality of CPR.

Lack of leadership and poor teamwork can result in poor clinical outcomes from CPR, even if high-quality CPR is delivered. CPR is associated with chaos and stress among team members, especially, if there is a lack of clear leadership, communication, teamwork and increased conflicts among team members. Previous studies have established the crucial role of leadership in managing emergency situations—clear leadership is associated with improved cooperation within team, task performance, and transfer of information with decreased team conflicts. A code leader is expected to perform multiple roles while leading a code—role assignment, data analysis, problem-solving, monitor multiple physiologic parameters, monitor parameters of quality of CPR, ensure delivery of high-quality CPR through feedback to the team members and ensure good team communication while orchestrating the AHA algorithm of CPR and working toward identifying and treating reversible causes of CA.

During the post-arrest phase, the patient should be managed in a dedicated PICU with close monitoring of parameters of vital organ perfusion, such as heart rate, respiratory rate, urine output, lactate levels, systemic mixed venous saturation and neurological status, through frequent and regular clinical examination as well as electroencephalography (EEG), when available. Providers should aim for normoxemia and normocarbida through optimum titration of ventilator settings. It is important to monitor and support metabolic parameters to avoid hyponatremia and maintain normoglycemia. Progressively worsening hypoxic-ischemic encephalopathy due to secondary neuronal injury and post-arrest myocardial dysfunction are the major causes of death after initial recovery from CA. Neuroprotective strategies, such as induced mild therapeutic hypothermia and aggressive management of seizures, should be considered in comatose survivors of CA to improve outcomes. Goal-directed hemodynamic support through titrated infusions of inotropes is important to support post-arrest myocardial dysfunction.

### Special Considerations

CPR and post-resuscitation care differ between different age groups and among patients with special health-care needs. For distinct differences in CPR between patients of different ages and in special situations (congenital heart disease, trauma, drowning, toxic ingestions), readers are encouraged to refer to specific PALS and Neonatal Resuscitation Program (NRP) guidelines. In children with congenital heart disease who have undergone palliative or corrective cardiac surgery, the open-chest wound poses unique challenges with effective external cardiac compressions. In such circumstances, inexperienced providers should begin external chest compressions near the edges of the sternal wound or from

the sides until open cardiac massage can be started by a skilled provider such as the surgeon. In patients with severe pulmonary hypertensive crisis leading to CA, pulmonary vasodilators such as inhaled nitric oxide should be continued during CPR. Since the current literature supports use of therapeutic hypothermia for neonatal hypoxic ischemic encephalopathy and comatose adult victims of CA, therapeutic hypothermia should be initiated soon after ROSC in neonates and adolescents. While the results of the therapeutic hypothermia after pediatric CA trial are awaited, one could consider use of induced, mild hypothermia (32–34°C) in comatose children after CA arrest for 24–48 hours followed by slow rewarming over 24 hours.

## OUTCOMES/PROGNOSTIC FACTORS

Though recent studies have shown an overall increase in the number of pediatric CA survivors without severe neurological disability over time, a significant number of children continue to exhibit mild or moderate neurologic disability after CA. The prognosis is invariably poor in comatose patients with absent pupillary or corneal reflexes, or absent or extensor motor responses 3 days after CA. Patients with myoclonic status epilepticus within the first day of arrest have a poor prognosis. Prognosis cannot be based on circumstances surrounding CPR like duration of anoxia or CPR, cause of the arrest and type of cardiac arrhythmia. Bilateral absent cortical somatosensory evoked potential within 1–3 days following arrest predict poor outcome. Burst suppression or generalized epileptiform discharges on EEG predict poor outcomes, but not with high accuracy. High-serum neuron-specific enolase levels at days 1–3 after arrest accurately predict poor outcome, but there are inadequate data to support or refute the prognostic value of other serum and cerebrospinal fluid biomarkers, neuroimaging and intracranial pressure monitoring.

## PREVENTION

Almost every CA in children is preventable. Since the majority of CA in children result from refractory hypoxia and/or circulatory shock, early recognition and aggressive management of respiratory and circulatory failure could potentially prevent CA. Preventive measures need to be applied not only at a micro level (initial and booster training on PALS and NRP, hospital code teams, monitoring systems), but also at a macro level (policymaking, community training, World Health Organization guidelines, financial support for preventive health).

## IN A NUTSHELL

1. The International Liaison Committee on Resuscitation leads international efforts to develop and revise guidelines for CPR every 5 years.
2. Majority of pediatric CA result from respiratory failure leading to hypoxemia and bradycardia with loss of circulation and PEA.
3. Pathophysiology of CA in children differs significantly from adults due to differences in growth and development.
4. The four phases of CA include pre-arrest, no-flow, low-flow and post-CA phases.
5. Development of rapid response teams can identify children at risk for progression to CA and stabilize them.
6. Early recognition of CA and prompt institution and maintenance of high-quality CPR is essential for favorable outcomes.
7. Post-arrest management should be provided in a dedicated PICU.

## MORE ON THIS TOPIC

- Acosta P, Varon J, Sternbach GL, Baskett P. Resuscitation great. Kouwenhoven, Jude and Knickerbocker: The introduction of defibrillation and external chest compressions into modern resuscitation. *Resuscitation*. 2005;64:139-43.
- Berg RA, Nadkarni VM. Pediatric cardiopulmonary resuscitation. In: Ornato JP, Peberdy MA. *Contemporary Cardiology: Cardiopulmonary Resuscitation*. Totowa, NJ: Humana Press Inc; 2005.
- Bhalala US. Cooling after pediatric cardiac arrest: A hot topic. *J Pediatr Crit Care*. 2014;1:75-84.
- International Liaison Committee on Resuscitation. From: <http://www.ilcor.org/home/>. Accessed May 15, 2014.
- Kleinman ME, Srinivasan V. Postresuscitation care. *Pediatr Clin North Am*. 2008;55:943-67.
- Nadkarni VM, Larkin GL, Peberdy MA, et al. First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA*. 2006;295:50-7.
- Sutton RM, Friess SH, Maltese MR, et al. Hemodynamic-directed cardiopulmonary resuscitation during in-hospital cardiac arrest. *Resuscitation*. 2014;85:983-6.
- Sutton RM, Nadkarni VM, Abella BS. "Putting it all together" to improve resuscitation quality. *Emerg Med Clin North Am*. 2012;30:105-22.
- Wijdicks EFM, Hijdra A, Young GB, et al. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;67:203-10.



## Chapter 7.3

### Basic Life Support (BLS)

Shalu Gupta

The term basic life support (BLS) is used to describe maintenance of a clear airway and support of breathing and the circulation in cases of cardiac arrest, without the use of equipment other than a simple airway devices or resuscitating bags. Cardiopulmonary resuscitation (CPR) is the combination of chest compression and rescue breathing, and forms the basis of modern BLS. Rapid and effective bystander CPR is associated with successful return of spontaneous circulation (ROSC) and neurologically intact survival in children.

The chances of survival after cardiac arrest are increased when the event is witnessed and when a bystander institutes CPR prior to the arrival of the emergency services. The major causes of death in infants and children are respiratory failure, sepsis, neurological diseases, injuries and sudden infant death syndrome. The best chance of a successful outcome for the patient is achieved if chest compressions are started as soon as cardiac arrest is diagnosed. The key changes in the current American Heart Association BLS 2010 guidelines are highlighted (**Table 1**). Infants' BLS guidelines apply to infants less than 1 year of age, child guidelines apply for children from 1 year till puberty, and adults are beyond puberty. Puberty is defined as breast development in females and presence of axillary hairs in males.

**Table 1** Key changes in AHA CPR guidelines 2010

S. No.	Recommendations 2010
1.	Change of BLS sequence from A-B-C to C-A-B
2.	Emphasis on high quality CPR
3.	Removal of <i>look, listen, feel</i> from the initial assessment
4.	Use of cricoid pressure is not recommended
5.	For infants a manual defibrillator is preferred. If a manual defibrillator is not available, an AED with pediatric dose attenuator may be used. If neither is available an AED without a dose attenuator may be used
6.	Recovery position is recommended
7.	De-emphasis on pulse check
8.	Emphasis on team resuscitation concept

Abbreviations: AHA, American Heart Association; CPR, cardiopulmonary resuscitation; BLS, basic life support; AED, automated external defibrillator; A-B-C, airway-breathing-compression; C-A-B, compression-airway-breathing.

### THE CHAIN OF SURVIVAL

Most of the arrests in children and infants are secondary to respiratory failure and shock. Therefore, early identification of the illness and early institution of the treatment reduce the likelihood of developing pediatric arrest. A preventive link is added so as to identify at risk children early. The five key components of pediatric chain of survival are listed in **Box 1**.

#### BOX 1 Key components of pediatric chain of survival

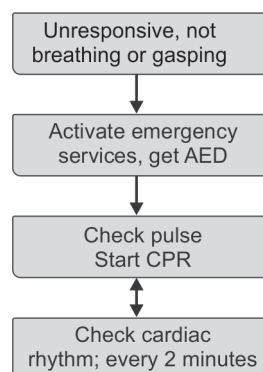
- Prevention of arrest
- Early institution of high quality cardiopulmonary resuscitation
- Rapid activation of the emergency response system
- Effective advanced life support (rapid stabilization, transport, and rehabilitation)
- Integrated postcardiac arrest care.

### CAB or ABC?

As per the revised 2010 guidelines, CAB (chest compression, airway, breathing/ventilation) is recommended (**Flow chart 1**). This despite the fact that most of the cardiac arrest in pediatric age group is asphyxial and therefore, ventilations are extremely important in resuscitating such kids. However, there is not enough evidence to support whether the sequence starting with ventilations [ABC (airway, breathing, compression)] is any different from sequence starting with compressions (CAB). The steps of BLS for a health-care provider are shown in **Table 2**. The C-A-B sequence was preferred because of the following reasons:

- In adults the major cause of cardiac arrest is ventricular fibrillation (VF); here chest compressions, if started early carry a better outcome with minimal interruptions.
- Starting chest compression is easy and quick, as compared to positioning of head, opening the airways and giving rescue breaths. This would improve the likelihood of receiving a bystander CPR in a pediatric arrest victim.
- Starting CPR with compression first with a compression ventilation ratio of 30:2, delays ventilation by only 18 sec for a lone rescuer. This interval further decreases when there are two rescuers.
- It offers harmonization of guidelines across age groups.

**Flow chart 1** Simplified steps in basic life support



Abbreviations: AED, automated external defibrillator; CPR, cardiopulmonary resuscitation.

**Table 2** BLS sequence for healthcare providers

Steps	Action to be taken
Step 1	Assess that the scene is safe
Step 2	Check the responsiveness and breathing. If there is no response, no breathing or only gasping, shout for help
Step 3	If you are alone, for sudden witnessed arrest activate the emergency response system, get an AED and return
Step 4	Check the central pulse (within 10 sec) either carotid, brachial or femoral artery
Step 5	If there is no pulse or despite adequate oxygenation and ventilation the heart rate is <60/min with signs of poor peripheral perfusion, start chest compressions
Step 6	Give 2 rescue breaths
Step 7	After about 2 min, or 5 cycles, if not done, activate the emergency response system and get an AED/defibrillator
Step 8	Apply AED pads and check for the cardiac rhythm
Step 9	If the rhythm is shockable, give shock followed immediately with CPR

Abbreviations: AED, automated external defibrillator; CPR, cardiopulmonary resuscitation.

## Assessment of the Scene

Always make sure that the place where CPR is to be carried is safe both for the rescuer and the victim. Check for the responsiveness and breathing of the victim. If a victim is not responsive and not breathing or not breathing normally (gasping), activate the emergency response system and start CPR.

**Agonal breathing** Agonal breathing or gasps is not a normal breathing. Particular care should be taken to recognize agonal breathing (irregular, often noisy, gasps) as a sign of cardiac arrest and not a sign of life. Gasps may appear forceful or they may be weak, and there may be some time gap in-between gasps. In an unresponsive victim, it is a sign of cardiac arrest.

**Pulse check** Take at least 5 sec and *not more than 10 sec* to feel for a central pulse. If within 10 sec you are not able to feel or are not sure of a pulse, start CPR. Feel for brachial pulse in infants and carotid or femoral pulse in children. Although an absent central pulse in an unconscious patient is a sure sign of cardiac arrest, it has been shown that the accuracy of such a pulse check can be very poor. Unless the rescuer is trained, experienced, and confident in feeling for the carotid pulse, a diagnosis of cardiac arrest should be assumed, if the patient is unresponsive and not breathing normally.

**Inadequate breathing** If the victim has a palpable pulse greater than or equal to 60 beats per minute (bpm), but the breathing is inadequate, give rescue breaths at a rate of 12–20 breaths per minute (1 breath every 3–5 sec) till good spontaneous breathing resumes. Check pulse every 2 min.

*If the victim has a palpable pulse rate less than 60 bpm and signs of poor peripheral perfusion (cyanosis, mottling, pallor), despite providing adequate oxygenation and ventilation, start chest compression.*

**Cricoid pressure** The use of cricoid pressure has not been recommended because it may hamper ventilation and delay the placement of an advanced airway in the victim. Even if the cricoid pressure is applied, some degree of aspiration can still occur.

## Circulatory Support

The emphasis is on high quality chest compressions, so as to generate blood flow to the vital organs and to achieve ROSC. The components of high quality CPR are listed in **Box 2**.

### BOX 2 Components of high quality cardiopulmonary resuscitation

- Chest compression of appropriate rate and depth. *Push fast* at a rate of at least 100 compressions per minute. *Push hard* with sufficient force to compress at least one-third of the anterior-posterior depth of the infant's chest, or approximately 1½ inches (4 cm), and 2 inches (5 cm) in children
- Allow complete chest recoil after each chest compression to allow the heart to refill with blood. Incomplete recoil is harmful as it decreases the blood flow created by chest compressions
- Minimize interruptions of compressions
- Avoid excessive ventilations.

The compressions should preferably be given on a hard surface. The correct place to compress the chest is in the center of the lower half of the sternum. Do not compress over the xiphoid or the ribs. Use the inter-nipple line as a landmark (**Fig. 1**). Chest compression and chest relaxation or recoil time should be approximately equal. In infants, a two finger chest compression technique or a two thumb chest encircling technique can be used. The two thumb chest encircling technique (**Fig. 2**) produces better blood flow, more consistent depth of chest compression, and generates higher blood pressure, than the two finger technique (**Fig. 3**). In adults and children, you can use one or two handheel technique. Place the heel of your hand on the center of the victim's bare chest on the lower half of sternum. The rescuer's arms should be kept straight with the elbows locked.

The compression ventilation ratio for single rescuer is 30:2, i.e., after 30 compressions, open the airways and give 2 breaths. For two rescuers, the ratio is 15:2. In adults the ratio is 30:2 irrespective of the number of rescuers. If an advanced airway is in place, compression and ventilation cycles are not required. Instead, the



**Figure 1** The position of the hands during chest compression in a child



**Figure 2** Two thumb chest encircling hand technique in infants



**Figure 3** Two finger chest compression technique in infants

chest compression should be given at least 100 per minute without pausing for ventilation. The breaths should be given at a rate of 8–10 breaths per minute (breath every 6–8 sec).

### Ventilatory Support

To open the airway, the patient's head should be tilted backwards (without hyperextension of the neck) and the jaw lifted to pull the tongue forward off the posterior pharyngeal wall (head-tilt chin-lift maneuver) (**Fig. 4**). If cervical spine injury is suspected a jaw thrust maneuver without head tilt should be used. If the rescuer is not able to provide ventilation, the lay rescuer should continue with chest compressions only.

To give breaths to an infant, mouth-to-mouth and nose, can be used. In children, mouth-to-mouth technique can be used. To give mouth-to-mouth ventilation, the patient's nose should be pinched closed. The rescuer should then take a breath, make a firm seal with his or her lips around the patient's mouth, and breathe out, watching as the victim's chest rises. This should take about a second, and it is important to avoid overinflation as this will allow air to enter the esophagus and stomach. Subsequent gastric distension causes not only vomiting but also passive regurgitation into the lungs, which often goes undetected. The expired air is then allowed out passively.



**Figure 4** Head-tilt chin-lift maneuver for opening the airways

Because of the potential risk of transmission of infection, some form of barrier device, preferably a ventilation mask (for mouth-to-mask ventilation) or a filter device placed over the mouth and nose can be used. Bag and mask devices can also be used by a health-care worker for giving positive pressure ventilation. The bag and mask ventilation requires competence and expertise and *is therefore not recommended by a lone rescuer during CPR*. Always select the appropriate size mask for the victim.

The quality of chest compressions deteriorate with time as the rescuer gets fatigued. Therefore the rescuer should switch roles, and rotate his position every 2 min or 5 cycles.

### Defibrillation

The two shockable rhythms are VF and pulseless ventricular tachycardia (VT). The interval from collapse to defibrillation is one of the most important factors of survival from sudden cardiac arrest following VF or pulseless VT. Children who suddenly collapse are more likely to have VF or pulseless VT and therefore require immediate defibrillation and CPR. Automated external defibrillators (AEDs) are computerized devices which can identify shockable and non-shockable cardiac rhythms, and can then deliver shock. For infants a manual defibrillator is preferred,

however if it is not available, then a pediatric dose attenuator can be used for delivering shock. If neither is available, an AED without a dose attenuator can be used. An AED with pediatric dose attenuator is also preferred for children less than 8 years of age. Immediately after delivering shock, start CPR. The AED will prompt the rescuer to reanalyze the rhythm after every 2 min.

The AED may not function properly in certain conditions. If the victim has a lot of chest hair, the AED pads will not stick properly. The AED will also not be able to analyze the cardiac rhythm properly if the victim has an implanted pacemaker, or has a transdermal medication patch, and if the victim's chest is covered with water. Removal of chest hair, medication patch and water is warranted before application of the pads. Avoid placing AED pads directly over the pacemaker.

### Basic Life Support Sequence for Lay Rescuers

The BLS steps to be performed in child or infant who is found unresponsive and not breathing or gasping are shown in **Table 3**. It should be noted that the emphasis is again on high quality chest compression. Also, if the lay rescuer is not trained or is not able to provide ventilation, he should continue with chest compression only. *There is no need to check for pulse (Table 3)*.

**Table 3** Steps of basic life support for a lay rescuer

Steps	Action to be taken
Step 1	Ensure that the area is safe for you and the victim
Step 2	Look for responsiveness and breathing. If child/infant is not responsive, and not breathing or gasping, shout for help immediately if alone. Otherwise send the second rescuer to activate the local emergency response system
Step 3	If the victim is breathing with no injury, turn the victim onto left side ( <i>recovery position</i> )
Step 4	If the victim is not responsive, and not breathing or gasping, start CPR
Step 5	Open airways and provide ventilation
Step 6	Coordinate chest compression and ventilation
Step 7	Activate the emergency response system

Abbreviation: CPR, cardiopulmonary resuscitation.

### Choking

Foreign body airway obstruction is an emergency. The common causes of choking are liquids in infants and food items (e.g., nuts, round candies, and grapes), balloons and small objects in children. Early recognition and prompt removal of the airway obstruction are the keys to success. Airway foreign bodies can cause symptoms ranging from mild-to-severe airway compromise. Signs of choking included sudden onset of coughing with or without respiratory distress, gagging, stridor, or wheezing. In mild airway obstruction, the victim has good air exchange, and coughs forcefully with wheeze. However, in severe airway obstruction, the victim will have poor or no air exchange, weak or ineffective cough, weak or no voice, respiratory difficulty and cyanosis. The victim will often be seen clutching his neck with his hands (*universal choking sign*).

If the airway obstruction is mild, do not interfere and allow the victim to have spontaneous coughing and breathing effort. Allow him to expel the foreign body by his own attempt, and monitor for any deterioration. If there is severe airway obstruction, perform a subdiaphragmatic abdominal thrust (*Heimlich maneuver*) until the foreign body is expelled or the victim becomes unconscious. If the child becomes unconscious, activate the emergency response system and start CPR with one exception. Every time you open the



airway to ventilate, look for the foreign body. If you are able to see a foreign body, remove it with your fingers gently. *Do not do blind finger sweep.*

In an infant with severe airway obstruction, hold the infant facedown with the head slightly lower than the chest, deliver up to 5 back slaps forcefully between the infants shoulders blade, using the heel of your hand, then deliver up to 5 downward chest thrusts in the middle of the chest. Repeat this sequence of 5 back slaps and 5 chest thrusts, until the foreign body is expelled or the victim becomes unconscious. If the infant becomes unconscious, activate the emergency response system and start CPR with one exception.

### MORE ON THIS TOPIC

Berg MD, Schexnayder SM, Chameides L, et al. Part 13: Pediatric basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S862-75.

Field JM, Hazinski MF, Sayre MR, et al. Part 1: Executive summary: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 Suppl 3):S640-56.

Gupta S. Pediatric BLS updates 2010. *Indian Pediatr*. 2011;48: 821-3.

Handley AJ. Basic life support. *BMJ*. 2014;348:g1730.

Highlights of the 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Dallas, TX: American Heart Association; 2010.

### IN A NUTSHELL

1. Agonal breathing or gasps is not a normal breathing. It is a sign of cardiac arrest and not a sign of life.
2. Do not take more than 10 sec to feel for a pulse.
3. Provide high quality cardiopulmonary resuscitation.
4. Use head-tilt, chin-lift maneuver for opening the airways after ruling out cervical spine injury.
5. Give two slow breaths.
6. The compression ventilation ratio for single rescuer is 30:2, and for two rescuers the ratio is 15:2.
7. Use automated external defibrillator as soon as possible for shockable rhythms. For infants, a manual defibrillator is preferred.
8. Recognize early signs of choking (universal choking sign).



## Chapter 7.4

# Pediatric Advanced Life Support (PALS)

Banani Poddar

The vast majority of children who deteriorate to cardiac arrest do so as a result of respiratory failure or shock. Cardiac arrhythmias or primary cardiac conditions leading to so called *sudden cardiac arrest* is rare in children and constitutes only 10–15% of all cardiac arrest. While it is feasible to recognize and treat children with respiratory and cardiac illnesses with good outcomes, the outcome of cardiac arrest in children (in-hospital and especially out of hospital) is generally dismal. Survival is around 27% for in-hospital cardiac arrests and 6% for out-of-hospital cardiac arrests. Hence, it is of utmost importance to prevent cardiac arrest.

In a patient who has progressed to cardiac arrest, the important determinant of a good outcome is the early institution of basic life support. Often, pediatric cardiac arrest takes place at home or at school; hence, the importance of basic life support, which is known as *bystander cardiopulmonary resuscitation (CPR)*, cannot be overstated. Advanced life support is successful only when good quality BLS has been instituted in a timely fashion.

## Recapitulation of Rapid Cardiopulmonary Assessment of a Sick Child

The systematic and stepwise assessment of the seriously ill or injured child has been described earlier and is shown in **Table 1**. To recapitulate, this consists of:

**Initial impression** A rapid visual and auditory assessment and includes a quick overview of consciousness, breathing and color. This quick *from the door* assessment helps in deciding whether the patient has a life-threatening condition, in which case immediate therapy is instituted.

**Primary assessment** This is a rapid hands-on approach of airway, breathing, circulation, disability and exposure (ABCDE). Each aspect is evaluated systematically and helps in assessing the type and severity of physiologic derangements.

**Secondary assessment** A focused history and focused systemic examination further adds to the primary assessment.

**Tertiary assessment** This consists of the important laboratory tests and radiology which help in assessing the child's physiology.

If at any time during above evaluation, a life-threatening problem is identified, immediate therapy is instituted. Further, the cycle of evaluate, identify and intervene is used sequentially so as to be able to identify problems, intervene appropriately and re-evaluate for any change in the patient's status. During the resuscitation process, repeated reassessments are required to assess the effects of therapy and further improvement or deterioration.

With the above assessment, the child could be identified to be one of the following:

- Stable
- In respiratory failure and/or shock
- In cardiopulmonary failure.

The management of respiratory failure and shock are dealt with in other chapters. The child in cardiopulmonary failure needs immediate attention as the child may deteriorate to cardiac arrest in a few minutes. Call for help immediately and proceed to manage the child according to the cardiac arrest algorithm. Check for a

pulse, if that is absent, start CPR with chest compressions first. If a pulse is present, check for breathing. If the patient is not breathing, start rescue breathing. If in spite of adequate ventilation and oxygenation, the child's heart rate is less than 60/min, start chest compressions. If the patient's breathing is adequate, proceed for a complete evaluation.

## BRADYARRHYTHMIAS

### Definition

A heart rate which is less than normal for the age and level of activity of the child is referred to as bradycardia. Since the heart rate of a child is different in different age groups (*refer to* chapter 7.1, Table 2), a fixed heart rate cannot be defined; however, a heart rate less than 60/min is ominous. When bradycardia is associated with an abnormal rhythm, a bradyarrhythmia is said to exist.

### Causes

Bradycardia can be either due to cardiac conditions (primary) or noncardiac conditions (secondary). While the former is due to a disease process of the cardiac conduction system due to congenital or acquired heart conditions, the latter is due to other conditions. Secondary bradycardia is much more common in critically ill children and is seen with hypoxemia, hypothermia, metabolic acidosis, hypotension, raised intracranial pressure (ICP) and as a result of drugs. When associated with signs of shock and/or respiratory distress or failure, this is referred to as symptomatic bradycardia. Hypoxemia is the most common cause of bradycardia in children.

### Signs and Symptoms

It is usually seen terminally before a cardiac arrest. Hence, the child is usually unresponsive and has gasping respiration. Cardiac output is a product of stroke volume and heart rate. The child has a limited capacity to increase the stroke volume and hence a fall in heart rate is associated with a fall in cardiac output. The patient develops features of hypotensive shock with altered sensorium and finally cardiopulmonary failure and cardiac arrest.

### ECG Changes

Electrocardiogram (ECG) changes seen with bradycardia include: (1) Sinus bradycardia; and (2) atrioventricular block (AV block). **Figures 1A to D** show various bradycardia rhythms. The management of AV block requires expert opinion and further details are not elaborated here. However, symptomatic bradycardia is managed irrespective of the ECG rhythm.

### Management

The priorities of management include: (a) adequate oxygenation and ventilation; (b) good quality CPR, if there is no response to the above; and (c) attachment to a monitor to identify the rhythm. Drugs have a limited role. The steps in the management of symptomatic bradycardia are summarized in **Flow chart 1**. Open the airway and ensure a patent airway. In case of a patient with an advanced airway, tube blockage by secretions could cause bradycardia; clear the airway by suctioning. Assist breathing, if necessary. Administer 100% oxygen. Attach the patient to a monitor to ascertain the rhythm. Establish intravenous (IV)/intraosseous (IO) access. Following the above actions, reassess cardiopulmonary status.

- If heart rate continues to be less than 60/min with poor perfusion, start chest compressions
- If bradycardia persists, administer the following drugs:
  - Epinephrine IV/IO or endotracheal (ET); repeat every 3–5 min. Adrenaline or epinephrine is available as 1:1000

**Table 1** Recapitulation of pediatric assessment

Initial impression					
Consciousness		Breathing		Color	
Primary assessment					
Airway					
Clear		Maintainable		Not maintainable	
Breathing assessment					
Respiratory rate and pattern		Respiratory effort	Chest expansion and air movement	Abnormal lung/airway sounds	Pulse oximetry
Normal	Normal	Normal	Gurgling	Normal oxygen saturation (> 94%) Hypoxemia	
Irregular	Increased	Decreased	Stridor		
Fast	Nasal flaring	Unequal	Snoring		
Slow	Retractions	Prolonged expiration	Barking cough		
Absent (apnea)	Head bobbing		Hoarseness		
	See-saw pattern		Grunting		
	Inadequate		Wheezing		
	Weak efforts		Crackles		
			Unequal		
Circulatory asesment					
Heart rate and rhythm		Pulses	Capillary refill time	Skin color and temperature	Blood pressure
Normal	Central and Peripheral	Normal: ~2s	Pallor	Normal Hypotensive	
Fast	Normal	Prolonged: > 2s	Mottling		
Slow	Weak		Cyanosis		
	Absent		Warm skin		
			Cool skin		
Disability assessment					
Neurological response (AVPU scale)					Pupil size and light reaction
Alert	Responds to voice	Responds to pain	Unresponsive	Normal	Abnormal
Exposure					
Temperature			Skin		
Normal/high/low			Rash/evidence of trauma		
Secondary assessment			Tertiary assessment		
Focused medical history and examination			Laboratory tests/imaging		
Physiological status					
System involved		Type of problem		Severity	
Respiratory	Upper airway obstruction Lower airway obstruction Parenchymal lung disease Disordered control of breathing		Respiratory distress Respiratory failure		
Circulatory	Hypovolemic Cardiogenic Distributive Obstructive		Compensated shock Hypotensive shock		
Cardiopulmonary failure					

Abbreviation: AVPU, alert, voice, pain, unresponsive.

solution; it is diluted 10 times to a concentration of 1:10000. The dose is 0.1 mL/kg of 1:10000 solution IV/IO and 0.1 mL/kg of 1:1000 solution for ET administration.

- **Atropine:** Atropine is indicated only when increased vagal tone is suspected or in primary AV block; can repeat after 5 min. The dose is 0.02 mg/kg (a minimum dose of 0.1 mg must be used).
- In case of persistent bradycardia, consider pacing.
- Look for and correct the correctable causes of bradycardia; e.g., metabolic acidosis, hypothermia, raised ICP, drug intoxication

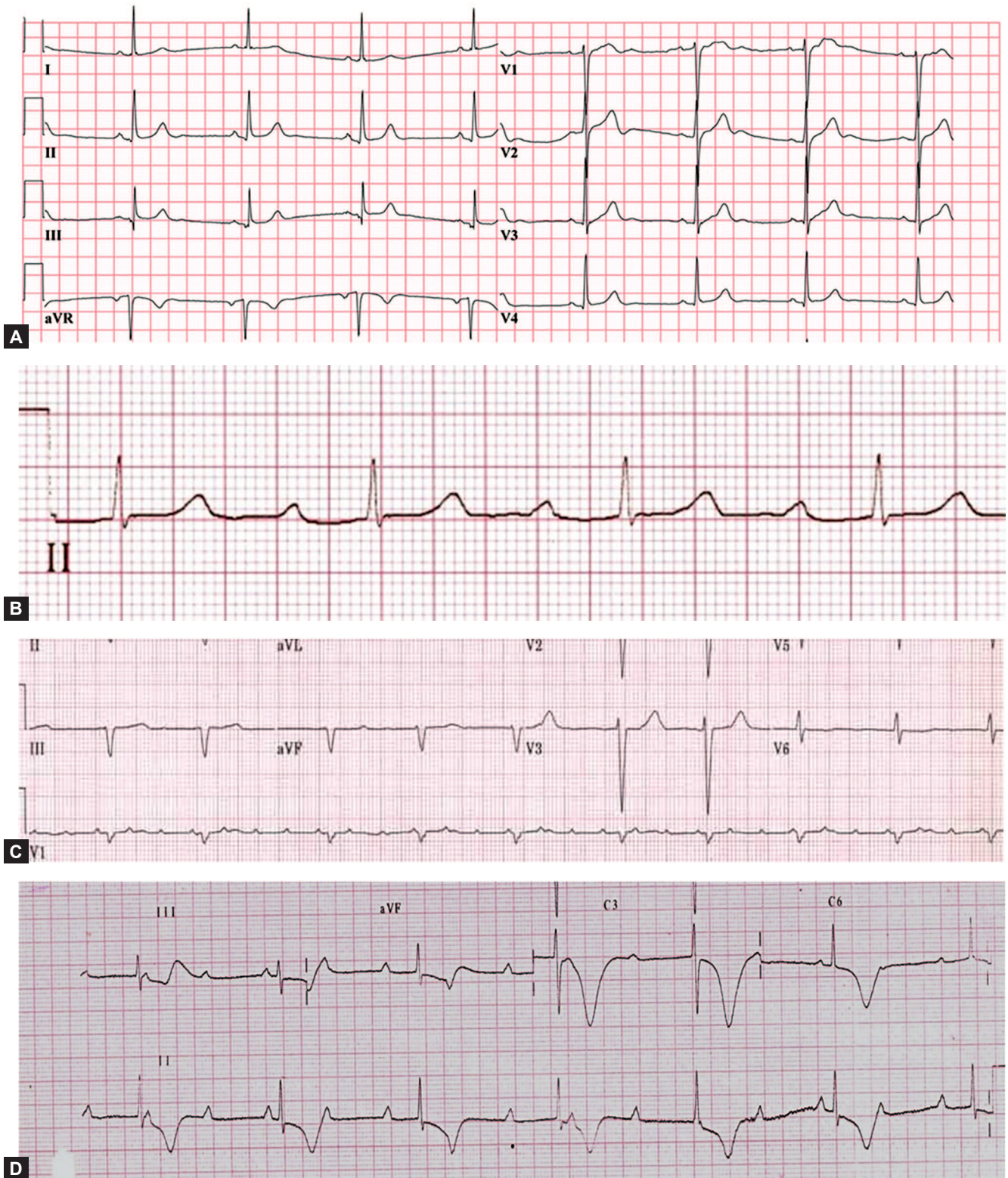
- If there is no cardiopulmonary compromise, continue to support airway, breathing, and circulation (ABC) with oxygen. Evaluate the rhythm and consult a pediatric cardiologist.

At any time, if the child develops pulseless arrest, manage according to the cardiac arrest algorithm.

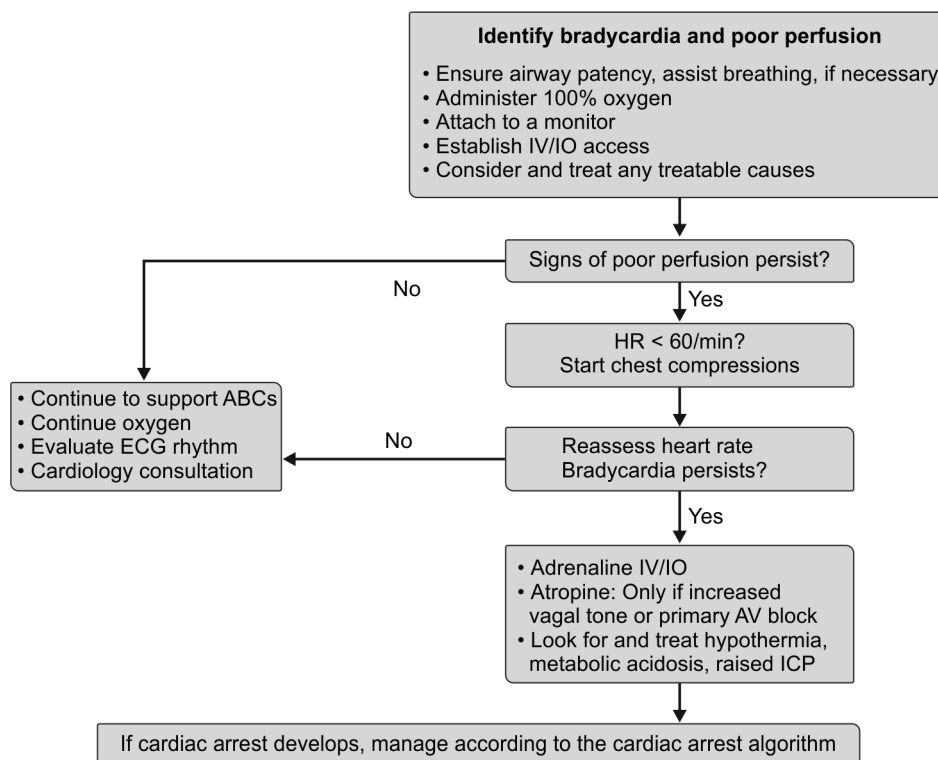
## TACHYARRHYTHMIAS

Tachycardia is a heart rate greater than normal for the age of the child. Tachycardia is common and often, a nonspecific response to any stress, anxiety or illness. When associated with an abnormal rhythm, it is referred to as tachyarrhythmia.





**Figures 1A to D** Bradycardia: (A) Sinus bradycardia; (B) First degree AV block; (C) 2:1 AV block; and (D) Complete AV block

**Flow chart 1** Management of pediatric bradycardia with cardiopulmonary compromise

Abbreviation: ICP, intracranial pressure.

## Causes

*Sinus tachycardia* is seen as a result of any underlying condition such as fever, dehydration, pain, anxiety or any other stress. However, in a critically ill child, tachycardia is a marker of an underlying problem and a search for the cause is warranted.

*Supraventricular tachycardia (SVT)* An abnormal tachyarrhythmia where the origin is in the atria or AV node. AV reentrant tachycardia, atrial ectopic tachycardia and AV junctional tachycardia are the different types of supraventricular tachycardia. **Table 2** highlights the key differences between sinus tachycardia and SVT.

*Ventricular tachycardia (VT)* Here, the abnormal tachyarrhythmia originates in the ventricles.

## Diagnosis and Management

A rise in the heart rate initially causes an increase in the cardiac output. However, beyond a certain stage, the time for filling of the ventricles decreases and the cardiac output falls. Children, especially infants, with SVT can remain asymptomatic for a variable period of time. After a certain time, the compensatory mechanisms fail and hemodynamic compromise ensues. Older children, on the other hand, become conscious of the fast heart rate and complain of palpitations. Infants can have nonspecific complaints of excessive fussiness and refusal of feeds. In children with pre-existing heart diseases, SVT can cause significant hemodynamic compromise. VT, on the other hand, compromises ventricular filling and contraction; hence hemodynamic compromise is seen early. Moreover, it is an unstable rhythm and often changes to ventricular fibrillation (VF) or pulseless VT. Thus, a child with VT should be managed urgently. The two important points to note for the emergent management of tachycardia are:

1. Presence of hemodynamic compromise (signs of poor perfusion including weak pulses, prolonged capillary refill,

signs of shock, hypotension, respiratory distress and altered sensorium)

2. Duration of the QRS complex on the ECG.

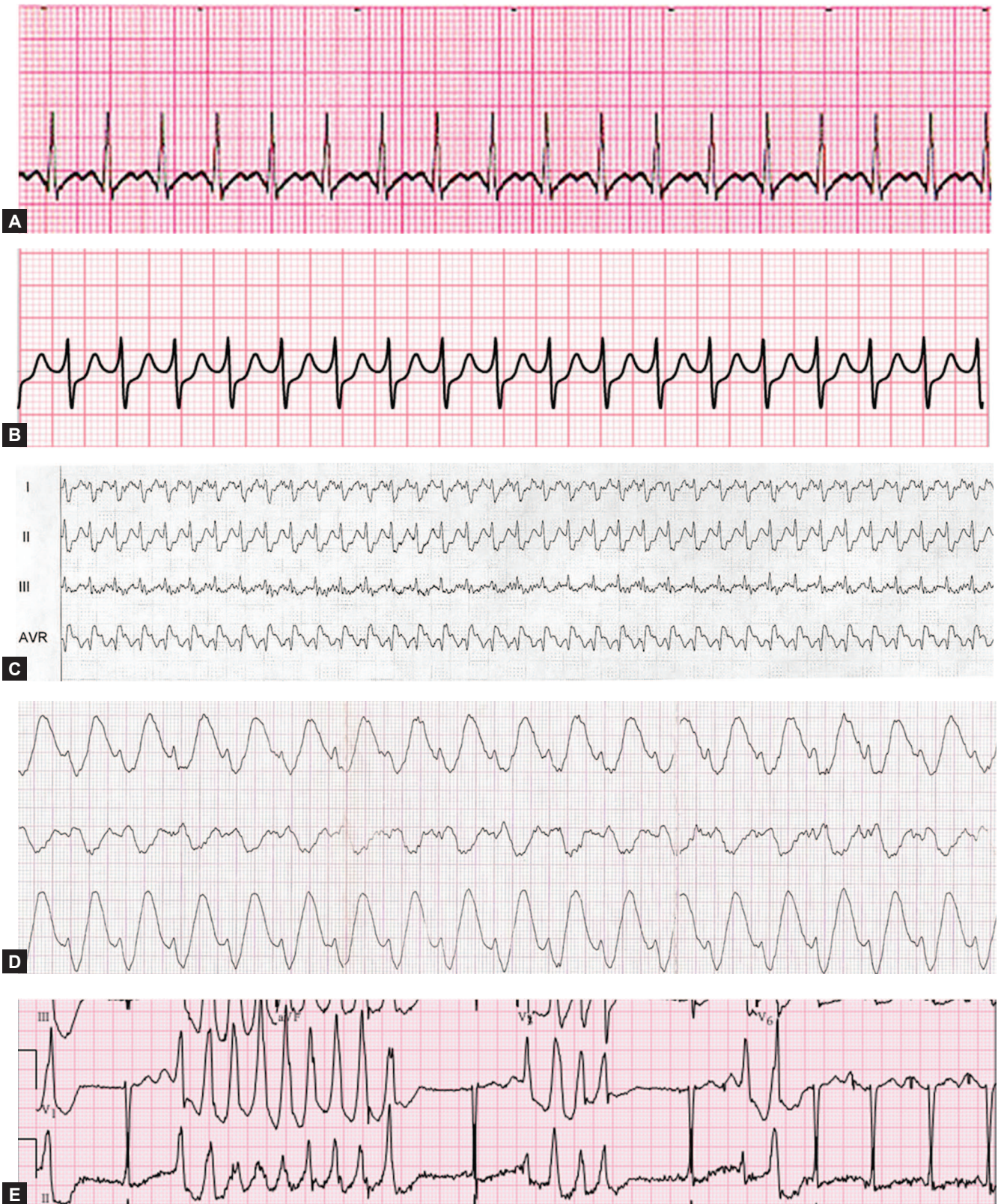
Narrow complex tachycardia (QRS duration < 0.09 sec) is a sinus tachycardia or SVT. Wide complex tachycardia (QRS duration ≥ 0.09 sec) are ventricular tachycardia (VT) or rarely, SVT with aberrant conduction. **Figures 2A to E** show various tachycardia rhythms. In the presence of signs of poor perfusion, the rhythm is said to be unstable and this should be treated urgently.

*Sinus tachycardia* The heart rate is increased in response to some condition such as fever, dehydration, etc. (**Table 2**). A history compatible with a reason for tachycardia, presence of P waves on ECG and change in heart rate with activity are the cardinal features to differentiate sinus tachycardia from SVT. A search for the cause of tachycardia and treatment of the underlying cause are all that is required.

*Supraventricular tachycardia* The management depends on the presence of hemodynamic compromise. In a hemodynamically stable child (stable SVT), there is no urgency of management and the patient can be evaluated thoroughly, while monitoring the patient for signs of shock. Steps of management of SVT are outlined in **Box 1**.

*Ventricular tachycardia* The presence or absence of signs of poor perfusion would dictate the steps in management. The initial steps in the management (ABC, oxygen, ECG monitoring, vascular access) remain the same. Further management differs in the two situations: *In a patient with adequate perfusion*, pharmacologic conversion of the rhythm with amiodarone or procainamide is preferred. Lidocaine may also be used, if these drugs are not available. Adenosine may be administered, if the child is stable and there is any doubt about the rhythm. Adenosine would not affect the rhythm in a VT but an SVT would revert. *In a patient with poor perfusion*, synchronized cardioversion is preferred.





**Figures 2A to E** Tachycardia: (A) Sinus tachycardia; (B) Supraventricular tachycardia; (C) SVT with aberrant conduction; (D) Ventricular tachycardia; and (E) Torsades de pointes



**Table 2** Differentiation between sinus tachycardia and SVT

Factors	Sinus tachycardia	Supraventricular tachycardia
History	Gradual or insidious onset Reason for tachycardia obvious (fever, dehydration, hemorrhage, pain)	Abrupt onset Nonspecific history, especially in infants; symptoms s/o CHF +/-
Heart rate	Infant: Usually $\leq 220$ /min Child: Usually $\leq 180$ /min	Infant: Usually $> 220$ /min Child: Usually $> 180$ /min
ECG	P waves: Normally present (upright in leads I/aVF) R-R interval: Variable with activity	P waves: Absent/inverted/abnormal (inverted in leads II/III/aVF) R-R interval: No variation
Chest X-ray	Normal, unless pneumonia is the cause of ST	Cardiomegaly, pulmonary edema may be present

**BOX 1 Steps of management in a supraventricular tachycardia**

- In stable SVT, the steps of management are:
  - Support ABCs and oxygenation as required
  - Attach to a monitor
  - Obtain a 12 lead ECG and identify the rhythm
  - Identify and treat reversible causes, if any (e.g., electrolyte disturbance)
  - Try vagal maneuvers
  - Establish vascular access
  - Administer adenosine intravenously. Adenosine 0.1–0.2 mg/kg is given as a rapid IV push followed immediately by a saline flush as the half-life of the drug is only a few seconds
  - Amiodarone 5 mg/kg IV over 20 min may be used in case of recurrence after initial response to adenosine.
- In an unstable SVT, the steps of management are:
  - Support ABCs and start oxygen
  - Attach to a monitor
  - Obtain a 12 lead ECG, if possible
  - Synchronized cardioversion 0.5–1 joules/kg for the first dose, followed by 2 joules/kg
  - If vascular access is present, administer adenosine
  - In case of response followed by reverting to SVT, administer IV amiodarone.

Abbreviations: ABC, airway, breathing, circulation; SVT, supraventricular tachycardia.

**Torsades de pointes** This is a polymorphic VT wherein the amplitude and the polarity of the QRS complexes change and gives an appearance of rotating around the isoelectric line of the ECG. This is associated with hypomagnesemia and long QT syndrome, congenital or acquired due to drug toxicity with class IA antiarrhythmics (e.g., quinidine, procainamide) or class III antiarrhythmics (e.g., sotalolol, amiodarone). This arrhythmia is treated with IV magnesium sulfate 25–50 mg/kg slow IV over 10–20 min.

**Reversible causes** Several reversible causes can also lead to tachycardia and tachyarrhythmias. These include the Hs and the Ts; i.e., Hs—hypovolemia, hypoxia, hypokalemia or hyperkalemia, acidosis ( $H^+$  ion), hypoglycemia, hypothermia and the Ts—toxins, tension pneumothorax, tamponade (cardiac), thrombosis (coronary/pulmonary) and trauma (hypovolemia). Look for these and manage accordingly.

### Vagal Maneuvers

Normally, heart rate decreases on vagal stimulation and this is more pronounced in infants and young children. In children

with SVT, vagal stimulation and its attendant effect on heart rate may terminate the arrhythmia. Hence, this can be tried in stable children with SVT. The following maneuvers increase vagal tone:

- Ice can be placed in a small plastic bag or a glove and held against the upper half of the face for an infant or a young child. Take care not to occlude the nose or mouth as that would interfere with breathing. Do not press hard on the eyes as this can cause retinal injury.
- An older child can be asked to perform a Valsalva maneuver by blowing through a narrow straw.
- Carotid sinus massage can be performed safely in older children.

### Synchronized Cardioversion

Synchronized shocks are delivered using a defibrillator to coincide with the R wave of the patient's QRS complex. This prevents delivery of the shock during the T wave which could otherwise result in progression to ventricular fibrillation. The energy dose required is 0.5–1 joule/kg for the first dose; if there is no response, repeat with a dose of 2 joules/kg. Electrical cardioversion is painful. Whenever possible, obtain vascular access and administer procedural sedation and analgesia before cardioversion. However, in a hemodynamically unstable patient, this should not delay cardioversion.

The algorithm for management of tachycardia is provided in **Flow chart 2**.

## CARDIAC ARREST

Cardiac arrest is the cessation of blood circulation as a result of absent or ineffective mechanical activity of the heart. As blood circulation stops, the perfusion of all the organs stops and these organs abruptly stop functioning. The patient quickly becomes unconscious and stops breathing. If not rapidly reversed, cardiac arrest leads to the death of the patient. The child is unresponsive, with apnea or gasping respiration and no detectable pulse.

### Causes

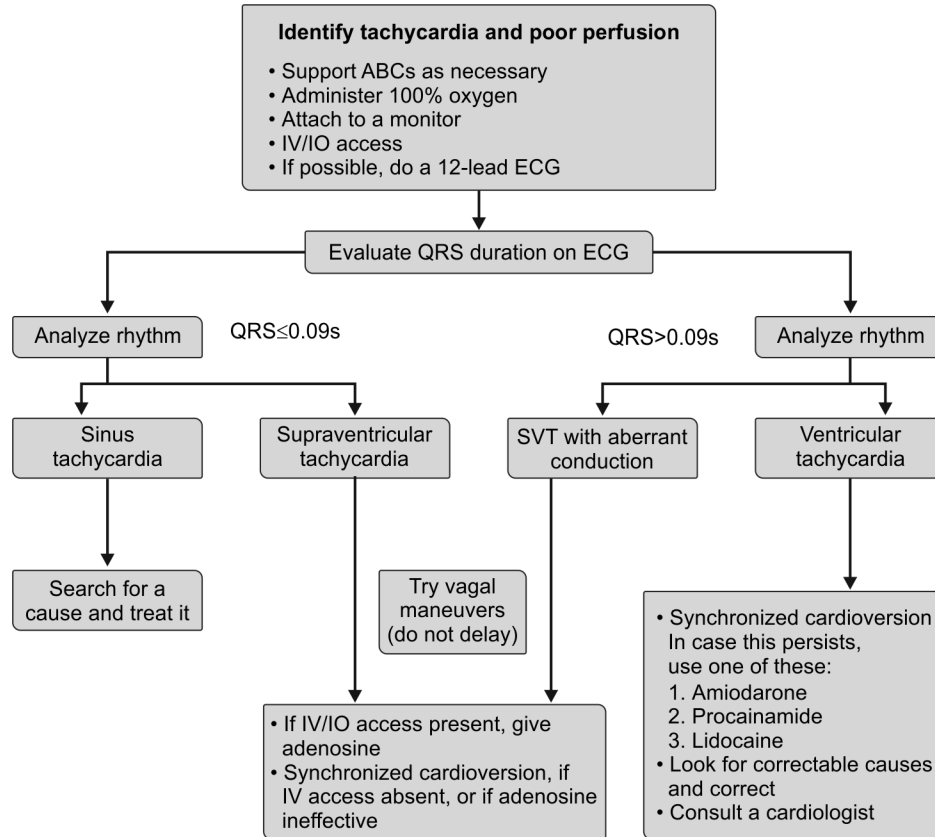
When shock or respiratory failure is untreated, it progresses to cardiopulmonary failure leading to cardiac arrest. Most cardiac arrests in children are due to this final common pathway, which is referred to as hypoxic or asphyxial cardiac arrest. A small proportion of cardiac arrests (10–15%) occur primarily due to cardiac rhythm disorders (ventricular fibrillation or pulseless VT) as a result of underlying predisposing conditions such as congenital long QT syndrome, hypertrophic cardiomyopathy or anomalous coronary artery. Several reversible causes have been identified which could lead to cardiac arrest and also prevent response to resuscitative measures. These include the Hs and the Ts, as mentioned above.

### Cardiac Rhythms During Cardiac Arrest (Figs 3A to C)

When a patient with cardiac arrest is attached to a monitor, one of the following arrest rhythms is found: (i) asystole; (ii) pulseless electrical activity (PEA); (iii) ventricular fibrillation; and (iv) pulseless VT.

**Asystole** Absence of all cardiac electrical activity, characterized on ECG by a flat line.

**Pulseless electrical activity** Organized electrical activity is seen on the ECG, but there is absence of a pulse; this is also referred to as electromechanical dissociation. The ECG often shows a slow rate with wide QRS complexes. If left untreated, then rhythm

**Flow chart 2** Management of pediatric tachycardia with cardiopulmonary compromise

deteriorates to asystole. PEA is often caused by the reversible causes, the Hs and the Ts.

**Ventricular fibrillation** Disorganized and chaotic electrical activity in the form of undulations of the baseline is seen. Since there is no organized contraction, the heart is unable to pump blood and pulses are not palpable.

**Pulseless ventricular tachycardia** VT without a pulse is managed differently and is one of the arrest rhythms.

Asystole and PEA are the most common initial rhythms seen in pediatric cardiac arrest. VF or pulseless VT require defibrillation in the management and are referred to as *shockable rhythms*. Survival and outcome in children with *shockable rhythms* is better than for children with asystole or PEA.

## Management

The aim of management is to restore a spontaneous and perfusing cardiac rhythm. The steps of management are outlined in **Box 2**. The management algorithm for cardiac arrest is shown in **Flow chart 3**.

**High quality CPR** The first and most important aspect of management of cardiac arrest is to start high quality CPR. To recapitulate, high quality CPR includes chest compressions of adequate depth ( $\geq 1/3$ rd of the anteroposterior diameter of the chest), a rate of approximately 100/min, allowing complete chest recoil, minimal interruptions of chest compressions, compression: ventilation ratio of 15:2 with two rescuer CPR till such time as an advanced airway is in place and subsequently without interruptions for ventilations. Every 2 min, CPR is interrupted for rhythm check. Chest compressions are tiring

and hence the compressor should be rotated after every 2 min or 5 cycles. Excessive ventilations interfere with venous return and are detrimental; hence this should be avoided. Interruptions of chest compressions for rhythm check and/or rotation of compressor should not take longer than 10 sec.

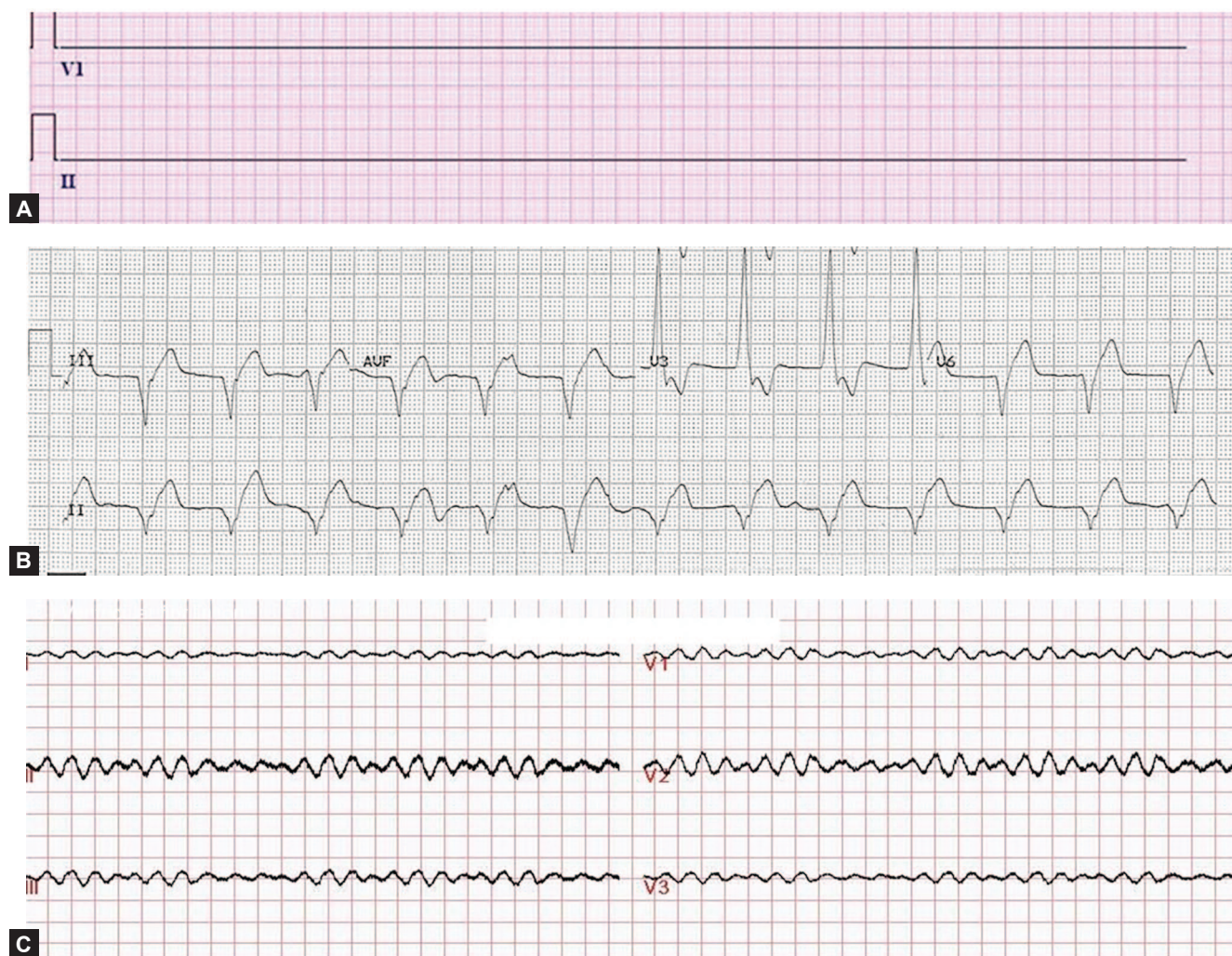
**Defibrillation** Since there is no organized cardiac activity, synchronization while delivering the shock is not required. An unsynchronized shock is defibrillation. The first dose is 2 joules/kg body weight; subsequent doses are 4 joules/kg. Higher doses of up to 10 joules/kg (maximum being the adult dose) may be given. When defibrillation is ineffective, administer adrenaline and repeat defibrillation. The second drug which may be given is amiodarone; this may be repeated up to 2 times for refractory VF/VT.

**Drug delivery during CPR** Drugs should be administered during compressions, preferably either just before or after delivering the shock. The compressions circulate the drug before the next rhythm check. **Table 3** provides the dosage of various drugs used during CPR.

**Advanced airway** While it is not essential to use an advanced airway during resuscitation, it is always preferred. The rate of ventilation should be around 8–10 breaths/min. Excessive inflation should not be used. It is preferable to confirm ET tube placement with capnography; this would help in monitoring the quality of compressions too.

**Hs and Ts** The importance of these reversible causes cannot be overstated. Each of these conditions should be ruled out. Often, nonresponse to adequate resuscitation efforts is due to one of the Hs or Ts. A careful evaluation for each of these is essential.





**Figures 3A to C** Arrest rhythms: (A) Asystole; (B) Pulseless electrical activity; and (C) Ventricular fibrillation

#### BOX 2 Management of cardiac arrest

- High quality CPR
- Provide oxygen
- Assess rhythm
- Establish vascular access
- In case of a non-shockable rhythm, administer adrenaline IV/IO and repeat every 3–5 min. Look for the Hs and Ts and treat any reversible cause
- In case of a shockable rhythm, obtain a defibrillator and deliver shock at a dose of 2 joules/kg. Resume CPR soon after delivering the shock. In case of persistent shockable rhythm, repeat defibrillation with a higher dose of 4 joules/kg. If there is no response to defibrillation and the rhythm continues to be shockable, administer epinephrine and then amiodarone and repeat defibrillation
- Consider advanced airway whenever feasible and as soon as an experienced person is available.

Abbreviation: CPR, cardiopulmonary resuscitation.

#### Determinants of Outcome and Decision to Terminate Resuscitation

The following factors portend a favorable outcome after cardiac arrest: witnessed arrest, bystander CPR and a short interval from arrest to resuscitation by professionals. There are no definite guidelines

as to when to stop resuscitation efforts. The reason for the cardiac arrest, the presence of any underlying chronic disease, time taken to start resuscitation and the circumstances where the resuscitation is being done would all influence when the resuscitation efforts are stopped. In certain circumstances, resuscitation efforts should be continued for a prolonged period, such as hypothermic patients, drug intoxication and refractory VF or VT.

#### Team Concept

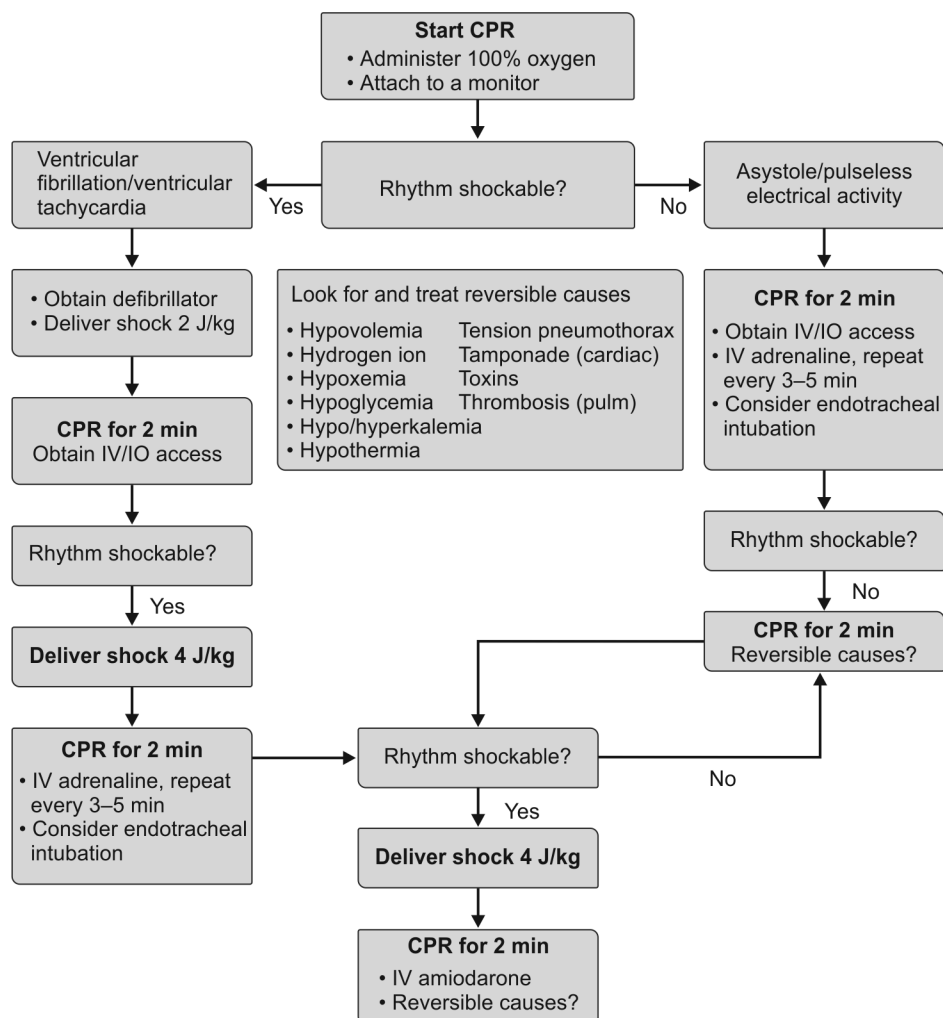
During the resuscitation of a sick child, many tasks have to be performed in a time-bound and systematic manner; also, health-care providers tend to get anxious and the situation often becomes chaotic. It is desirable to perform all actions in a coordinated manner and having trained team members designated for the necessary actions greatly enhances the quality of resuscitation. A team of at least five members is desirable with the roles of airway management and providing ventilation, chest compression, venous access and drug delivery, placing the patient on the monitor and monitoring and providing defibrillation; all supervised by a team leader.

#### Post-resuscitation Care

In the event of a successful resuscitation from cardiac arrest and return of spontaneous circulation, the child is vulnerable to suffer cardiac arrest again and several factors influence long-term



**Flow chart 3** Management of pediatric cardiac arrest  
(Call for help and ask for emergency resuscitation drugs)



outcome, i.e., survival and quality of life. Post-resuscitation care is one of the most important aspects which determine the long-term outcome. Hence, it is equally important to provide optimal care at this time. A systemwise evaluation, monitoring and support of all organ systems form the basis of post-resuscitation care. The most important aspects are listed here:

- Maintain normothermia; avoid hyperthermia at all costs. The role of inducing moderate hypothermia in children is not yet well established.
- Maintain normoglycemia; hyperglycemia is deleterious.
- Ensure adequate ventilation. Maintain normal levels of  $\text{PaCO}_2$  and  $\text{PaO}_2$ . Hyperoxemia is harmful; hence after the resuscitation phase, oxygen should be titrated to maintain a pulse oximeter  $\text{SO}_2$  around 94–95%. Hyperventilation compromises cerebral blood flow and is deleterious;  $\text{PaCO}_2$  levels should be maintained around 35 mm Hg.

- Shock is often present in this phase. Treat and correct shock aggressively with volume resuscitation and vasopressor infusions as required. Adrenaline infusion is the drug of choice in the post-resuscitation phase. An adequate mean arterial pressure is required to maintain adequate cerebral perfusion. Myocardial depression is common and should be addressed appropriately.
- Optimize electrolytes, especially sodium. Maintain sodium levels around 140 mEq/L.
- Look for and treat seizures aggressively.
- Administer prophylaxis for gastric stress ulcer bleeding.
- Monitor and maintain urine output.
- The child should be managed at a center where meticulous attention to all these details is given. A pediatric intensive care unit equipped to provide this level of care is preferred.

**Table 3** Drugs used during resuscitation

Drug	Dose (IV/IO)	Concentration available	Comments
Adenosine	0.1–0.2 mg/kg	3 mg/mL	Use rapid bolus using two syringe technique
Adrenaline/Epinephrine	0.01 mg/kg/dose or 0.1 mL/kg of 1:10,000	1 mg/mL (1:1000)	For IV/IO, 1:10,000 conc. is used; for ET dose, 1:1000 conc. is used
Amiodarone	5 mg/kg over 20 min	50 mg/mL	May need to be continued as an infusion
Atropine	0.02 mg/kg, minimum dose is 0.1 mg	0.6 mg/mL	Maximum dose 0.5 mg for a child
Calcium chloride	20 mg/kg/dose slow IV (0.2 mL/kg)	100 mg/mL	Administer with ECG monitoring. (In case of calcium gluconate, the dose is 0.6 mL/kg)
Glucose	0.5–1 g/kg/dose	D10W (0.1 g/mL) D25W (0.25 g/mL) D50W (0.5 g/mL)	In case of hypoglycemia, after bolus, ensure adequate glucose infusion rate
Lidocaine	1 mg/kg slow IV	20 mg/mL	Needs to be followed up with infusion
Magnesium	25–50 mg/kg slow IV over 10–20 min	500 mg/mL	Drug of choice for <i>torsades de pointes</i>
Procainamide	3–6 mg/kg over 5 min	100 mg/mL	May repeat every 5–10 min to a maximum of 15 mg/kg
<b>Vasoactive drug infusions*</b>			
Drug	Preferred dose range	Differential actions at different infusion doses (mcg/kg/min)	Comments
Adrenaline	0.05–1.0 mcg/kg/min	0.05–0.3: Inotropic action predominates 0.3–2.0: Vasopressor action + inotropy > 2.0: Vasopressor alone	Drug of choice for cold shock Increases myocardial oxygen demand and causes lactic acidosis
Dopamine	2–20 mcg/kg/min	2–10: Inotropic action predominates > 10: Vasopressor action	Usually the first vasoactive started for shock.
Dobutamine	2–20 mcg/kg/min		First choice among the inotropes Volume optimization required before starting infusion
Noradrenaline	0.02–2 mcg/kg/min		Drug of choice for warm shock
Milrinone	0.25–0.75 mcg/kg/min	50 mcg/kg over 60 min can be used as a bolus	Is an inodilator Lusitropic action predominant May need volume bolus before starting infusion
Vasopressin	0.2–2 milliunits/kg/min		Useful for warm shock Limited pediatric literature

\*All vasoactive infusions are preferably given through a central venous line. Adrenaline, dopamine, noradrenaline and vasopressin infusions can all cause skin necrosis, if extravasation occurs. Action of the drugs is also faster, if infused through a central vein.

### IN A NUTSHELL

1. Cardiac arrest in the pediatric patient is a culmination of progressive respiratory failure or shock, or rarely, a combination of the two.
2. Early, aggressive, high quality CPR improves the outcome from cardiac arrest.
3. Prevention of cardiac arrest is important and forms the first and most important link in the pediatric *chain of survival*.
4. Cardiac arrhythmia as a cause of cardiac arrest occurs in only 8–10% of pediatric cardiac arrests; however, in such patients, early defibrillation is required.
5. The most common cause of bradycardia is hypoxemia; hence the management of bradycardia is to ensure adequate ventilation and oxygenation.
6. Tachycardia is classified into *narrow complex* and *wide complex* based on the duration of the QRS complex.
7. Sinus tachycardia is the most common tachycardia and this occurs in response to a wide variety of stimuli including fever, pain, anxiety, dehydration, etc.
8. Ventricular tachycardia is inherently an unstable rhythm and needs immediate attention.
9. In a patient with cardiac arrest, the rhythms that can be found include asystole, PEA (organized rhythm in the absence of mechanical contractions), ventricular fibrillation and ventricular tachycardia.
10. There are a number of *reversible causes* of cardiac arrest and the response to resuscitation is suboptimal unless these are attended to. These include several metabolic and electrolyte disturbances, toxins and tamponade from pneumothorax or pericardial effusion.

### MORE ON THIS TOPIC

- American Heart Association. Pediatric Advanced Life Support: Provider Manual 2011.
- Deasy C, Bernard SA, Cameron P, et al. Epidemiology of paediatric out-of-hospital cardiac arrest in Melbourne, Australia. *Resuscitation*. 2010;81:1095-100.
- Foltin GL, Richmond N, Treiber M, et al. Pediatric prehospital evaluation of NYC cardiac arrest survival (PHENYCS). *Pediatr Emerg Care*. 2012;28:864-8.
- Haque A, Rizvi A, Bano S. Outcome of in-hospital pediatric cardiopulmonary arrest from a single center in Pakistan. *Indian J Pediatr*. 2011;78:1356-60.
- Kleinman ME, Chameides L, Schexnayder SM, et al. Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S876-908.
- Tham LP, Chan I. Paediatric out-of-hospital cardiac arrests. epidemiology and outcome. *Singapore Med J*. 2005;46:289-96.
- Topjian AA, Berg RA. Pediatric out-of-hospital cardiac arrest. *Circulation*. 2012;125:2374-8.
- Yang WC, Lin YR, Zhao LL, et al. Epidemiology of pediatric critically-ill patients presenting to the pediatric emergency department. *Klin Padiatr*. 2013;225:18-23.

# Section 8 INTENSIVE CARE

**Section Editor** Rakesh Lodha

## Chapter 8.1

### Pediatric Intensive Care Unit

*Dhiren Gupta, Neeraj Gupta, Manpreet Sethi*

Pediatric critical care has come a long way over the past several years, not only in the developed Western countries but also in the developing world. This in turn has led to the establishment of various state-of-the-art pediatric critical care units in all parts of the world. Better understanding of the pathophysiology of life-threatening conditions combined with great technological advances has made it possible to monitor and treat critically sick children in the present time. Needs for pediatric critical care are very different from that of adult critical care and, thus, critically ill children are best managed by personnel specially trained to manage such children. This has resulted in the demand for separate pediatric critical care specialists. American Board of Pediatrics recognized the fact in 1985 by setting up a separate speciality of pediatric critical care.

Level 3 pediatric intensive care unit (PICU) must be adept in handling various complicated medical, surgical and traumatic emergencies encountered in children of all ages other than newborns, though a multidisciplinary approach is required. Level 2 PICUs were defined as units capable of providing interim care and transport of critically ill children who require transfer to higher centers and to efficiently manage children with disorders of moderate complexity, thus avoiding their long-distance transfers. However, whatever the level of PICU, the same standards of quality care should be applicable to both, and a good communication system must exist between the two for timely referral of sick patients.

#### ORGANIZATION AND ADMINISTRATION

Pediatric intensive care unit should be a separate acute care unit that provides specialized tertiary level pediatric critical care. It may serve as a regional referral center for critically ill children. Intensive care in a PICU should be provided only by providers who are capable of managing complex pediatric medical and surgical emergencies. The key team should include pediatric medical and surgical specialists, nurses, physiotherapists, pharmacists, medical social workers, dieticians, etc.

#### PHYSICAL DESIGN AND FACILITIES

There are certain mandatory requirements while designing a PICU:

1. For the sake of patient and staff safety, the access to the PICU should be strictly monitored and there should be no thoroughfare to other departments through PICU.
2. The PICU should be closely located to the lift area for easier patient transport and also to the duty doctor's room for the

prompt clinical response and also be close to the family waiting areas.

3. Although the manned (physically or electronically) entry and exit points should be there, emergency exit points should also be provided.
4. Future adaptability and expansion and utilization of space, equipment should be taken into consideration.

#### AMBIENT AND ATMOSPHERIC FEATURES

Specific guidelines as regards to noise and lighting in PICU have been developed for smooth functioning of unit. The permissible noise level as laid down by WHO is less than 45 decibels (dB) in the day and less than 20 dB at night. Sound proofing of walls and ceilings by using materials of high-sound absorption capabilities should be provided for. Overhead lighting should be 20 foot candles whereas spot lighting when required for certain procedures should be of 150 foot candles strength. Wherever possible, access to outside natural light is preferred. Appropriate color schemes and good interiors lend an additional friendliness to the environment of PICU. Every PICU should have a controlled airflow to prevent and minimize airborne infections.

#### FLOOR PLAN

While designing PICU, provision for several distinct rooms should be made. Apart from the patient area, a separate area is required for drug and parenteral nutrition preparation that should meet strict sterility codes. A family counseling room separate from the patient area is necessary to update and discuss the patient status with the family. Also wherever possible, a satellite pharmacy within the PICU is desirable for providing emergency medications.

#### BEDSIDE FACILITIES

It is recommended that a PICU should have 8–12 rooms. Having less than 6 beds is not cost-effective and when beds are more than 14, the quality of care may suffer. A minimum of 250 square feet area for individual rooms in PICU and 225 square feet area per patient forward type bed is mandatory. Also, the distance between two beds must be at least 5–8 feet. Provision for 1 or 2 isolation rooms for care of immunocompromised children or children with infectious disease must be kept. The head of each bed should be readily accessible for emergency airway management. In a view of better workspace organization, equipment columns that are suspended from the ceiling are most useful (**Fig. 1**). To ensure proper patient privacy, walls or curtains should be provided in between the beds. There should be enough space between the beds to perform required procedures like central line insertion, chest tube placement or to perform portable X-ray, ultrasound, echocardiography, etc. Two suction outlets, two oxygen outlets and two air outlets must be provided on the walls along with two electrical outlets. Bed design should ensure railings on both the sides to prevent the child from falling. Apart from the above, there should be a provision for an emergency alarm button in case of





**Figure 1** Equipment stands suspended from ceiling

any emergency needing prompt action. Finally, emergency power backup and gas supply at each bedside are also essential.

## HAND HYGIENE AND PREVENTION OF INFECTION

Strict measures for prevention of transmission of infections in PICU need to be instituted. Those include providing alcohol-based antimicrobial hand rub solution at every bed for use in between the patient examination. An operation theater type sink using elbow or foot operated water supply and antiseptic soap solution source at a conveniently and unavoidable location in the PICU where the usual handwash should take place. Apart from this, masks, caps and gowns should be worn by all people entering the PICU at any time.

## PERSONNEL

### Medical Director

A medical director should be amongst the personnel involved in the patient care in PICU. His responsibilities would include patient triage, implementation of policies and procedures, coordination of multiple consultants, duty roster management so that some qualified pediatrician (resident/fellow/attending staff) is always available round the clock. Apart from clinical services, he must be in charge of in-service education and also function as arbiter and patient advocate.

### Physician Staff

Although it is desirable to have full-time pediatric intensivist in the PICU, due to scarcity of resources in countries like ours, the minimum qualification of an in-house physician should be that of senior postgraduate in pediatrics or anesthesia for a Level 1 PICU.

### Nursing Staff

The nurse in charge of PICU should have substantial expertise and experience in pediatric care. Her duties include ensuring a safe practice environment, adequate and appropriate staffing and taking care of supplies and equipment in the PICU. Nurses on duty should be well versed with pediatric critical care nursing through regular teaching and orientation programs and should undergo complementary reviews at regular intervals.

## Ancillary Support Personnel

Other personnel required at various levels of pediatric critical care are the backbone and include orderlies, nursing attendants, technicians, storekeepers, sweepers, etc.

## LEVELS OF CARE

### Level 3 (Highest)

All patients with multiple organ failure of an immediate life-threatening nature who require complete assistance, such as hemodynamic support, ventilatory support, renal replacement therapy as well as other drug or device-related organ support fall in this category. Provision for one nurse per patient is required in Level-3 care.

### Level 2 (Intermediate)

Patients with single organ failure who need monitoring and drug or device-related support fall in this category. The acceptable nurse-patient ratio is 1:2.

### Level 1 (Lowest)

Patients with some signs of organ dysfunction requiring continuous monitoring and some drug- or device-related support fall in this category. They are considered to be at risk for developing an acute organ failure. Even patients who are recovering from one or two organ dysfunction are included in this category. Here, three patients may be attended by one nurse.

## HOSPITAL FACILITIES AND SERVICES

No PICU can run efficiently without an excellent support from emergency department. In all hospitals with PICUs, the emergency department should be staffed with physicians who are experienced in pediatric resuscitation. Support from other services like pediatric surgery, blood bank, radiology, laboratories, pharmacies and diagnostic services should be readily available.

## Drugs and Equipment

There should be prompt availability of all drugs and equipment required for resuscitation and advanced life support and monitoring for any patient in the PICU. Along with the life support equipment, devices for diversion and entertainment should be available for children who are conscious.

## Crash Cart

A crash cart containing emergency drugs, defibrillation and portable monitors should be readily available and accessible. All emergency drugs and equipment should be systematically arranged in the cart and an easy-to-understand checklist should be available.

## Prehospital Care

Since quite often patients in the PICU are retrieved and transported from the site of injury or from another hospital, an effective and integrated global system of mobile communication within the PICU is desirable. Moreover, the PICU should be provided with multiple telephone lines to ensure that no outside calls are missed even at busy times. It is imperative to have rapid access to poison control cell.

## Quality Improvement

Strict multidisciplinary quality control must be employed by the PICU for quality assessment purposes. Observed and predicted morbidity and mortality rates for a particular level of severity of illness must be assessed by objective methods and outcomes between similar units must be compared.

## COMMUNICATION WITH THE FAMILY

The family of patient in PICU should form an important part of patient care. The family should be updated about the patient's status regularly. Information regarding current patient status, nature of illness, possible complications, and course in the next 24 hours, a detailed patient care plan, planned investigations and procedures, the anticipated duration of PICU stay and expenses must be discussed not only at admission to PICU but also daily and recorded appropriately in the case sheet.

## TRAINING AND CONTINUING EDUCATION

There should be a written plan for training all health-care professionals about the basics of pediatric critical care. Apart from this, there should be a well-designed teaching program for all residents, postgraduates, etc., working in the PICU covering most aspects of pediatric critical care. This can be achieved through bedside teaching, formal lectures, presentations and journal clubs. All health-care workers looking after critically ill children should be encouraged to attend regional and national level meetings concerning pediatric critical care. Fellowship programs should be started in sufficiently busy tertiary level PICUs. Research forms an essential and integral part to understand disease and its management. It must be undertaken within the PICU in an attempt to improve techniques and treatments that may in turn improve the overall mortality and morbidity.

## SPECIAL CHALLENGES

### Role of Leader in PICU

The administrative hierarchy should be clearly outlined while setting up the organizational structure of the PICU. The leader of the team should be one who is well-accepted and respected not only by people in pediatric critical care but also other specialties and who possesses good skills in patient management apart from being good at organization and mentorship. His/her main role is to streamline the multidisciplinary teamwork and maintain effective communication to ensure smooth functioning of the PICU. Concrete policies and principles need to be laid down while setting up a PICU for effective functioning and best patient care. This includes a written set of protocols and policies toward patient care to minimize errors. A common goal in the best interests of the patient care is concise and clear communication between all members of the team.

### Dealing with Complications

It is not uncommon to encounter complications and adverse events among the critically sick children during their stay in PICU. These may occur by chance, or due to the underlying disease itself, technical failures or human errors. Such events, when they occur, should not result in blame games among the health-care providers. Instead, they should be addressed with constructive criticism and discussed and analyzed in detail through audits and meets so that appropriate changes and actions can be made to prevent such events in the future.

## DECISION-MAKING IN PEDIATRIC INTENSIVE CARE UNIT

Ideally all major decisions regarding patient care are made after multidisciplinary clinical rounds. These must be documented legibly and then communicated to the primary caregivers who execute the orders or plan. However, in cases of emergency, the caregiver on duty should be given full authority to take his/her own decisions that he or she feels is most appropriate at the time. Also such good decisions that have improved patient outcome should be appreciated by the seniors.

## COST CONTAINMENT

Good quality care at the most effective cost should be the goal of any successful intensive care team and, therefore, all cost containment strategies should be employed.

## INDIAN SCENARIO

The difference in pediatric intensive care between developed and developing worlds are still significant (**Figs 2 and 3**). Poor space allocation, limited electricity supply, lack of effective oxygen supply and even of clean water coupled with infection, poor nutrition and sanitation along with poor primary health care including immunization account for the differences in outcomes of critically sick children between the developed



**Figure 2** Bedside facility of a pediatric intensive care unit in western world



**Figure 3** Bedside facilities in an Indian pediatric intensive care unit

and developing world. Moreover, financial and budget issues challenge the sustainability of PICUs. Additional challenges are nonavailability of pediatric subspecialists and lack of adequate diagnostic facility and equipment, etc. Also, poor retrieval and transportation of critically ill patient add to higher mortality rates. Despite all these constraints, India has seen a rapid growth in the field of pediatric intensive care over the past few years. PICUs' bedside facilities have improved remarkably over the last decades with better performance and enhanced family satisfaction.

### IN A NUTSHELL

1. Needs for pediatric critical care are very different from that of adults and, thus, critically ill children are best managed in a separate PICU by personnel specially trained to manage such children.
2. Though the setting up and running of pediatric intensive care facilities in developing countries is a difficult and challenging task, the very exigencies of developing countries necessitate such establishment.
3. There are certain mandatory requirements while designing a PICU. Based on facilities available, a PICU is labeled as Level 1 to Level 3 (highest).
4. High incidence of infections, malnutrition, chronic diseases, etc. necessitates a robust pediatric intensive care infrastructure.

### MORE ON THIS TOPIC

- Balachandran R, Nair SG, Kumar RK. Establishing a pediatric cardiac intensive care unit—Special consideration in a limited resources environment. *Ann Pediatr Card.* 2010;3:40-9.
- Basnet S, Adhikari N, Koirala J. Challenges in setting up pediatric and neonatal intensive care units in a resource limited country. *Pediatrics.* 2011;128:e986-92.
- Khilnani P. Consensus guidelines for pediatric intensive care units in India. *Indian Pediatr.* 2002;39:43-50.
- Rosenberg DI, Moss MM, et al. Guidelines and levels of care for pediatric intensive care units. *Crit Care Med.* 2004;32:2117-27.
- Rungta N. ICU planning and designing in India—Guidelines 2010. From: <http://www.isccm.org/PDFfiles/Section1.pdf>. Accessed July 1, 2014.
- Valentin A, Ferdinande P. Recommendations on basic requirements for intensive care units: structural and organizational aspects. *Intensive Care Med.* 2011;37:1575-87.



## Chapter 8.2

# Shock

Srinivas Murthy, Niranjana Kissoon

Shock is inadequate oxygen delivery or impaired oxygen utilization to meet the metabolic needs of the body. It has a variety of inciting causes and is the common final pathway for death and disability in children. This chapter will discuss aspects of the physiology and the classification of shock, as well as provide an overview of clinical assessment tools to differentiate etiologies and dictate initial management strategies.

## PHYSIOLOGY

Shock is an exceedingly complex syndrome that, if uninterrupted, leads to irreversible cellular and tissue damage and death. An insufficient oxygen supply to tissues results in cellular anaerobic metabolism and inefficient energy generation, leading to cellular acidosis and organ dysfunction. It is this vital organ dysfunction that will ultimately lead to death.

Adequate tissue oxygenation is dependent on a variety of factors that affect both the supply and demand of oxygen. Total blood volume, cardiac output or blood pressure contribute to oxygen supply, while impaired cellular function, such as seen in severe sepsis, disrupts oxygen utilization. Any combination of factors resulting in oxygen demand exceeding oxygen supply will lead to shock. While the presence of shock is sometimes obvious, a measure of the relative contributions of the contributing variables relating to delivery and consumption are important to determine an approach to treatment.

## Determination of Tissue Oxygen Delivery

Oxygen delivery ( $DO_2$ ) to tissues is dependent upon two main components—the arterial oxygen content and the cardiac output. Oxygen delivery is the amount of oxygen delivered to tissues of the body per minute, and is typically in the range of 600 mL/min/m<sup>2</sup> in times of rest. As oxygen content consists primarily of oxygen carried by hemoglobin molecules, blood oxygen content can often be predicted by examining the saturation through pulse oximetry, assuming a normal hemoglobin concentration.

The amount of blood flow, and hence cardiac output, can be calculated by determining the amount of oxygen delivered and consumed through a tissue bed as described using the Fick principle (see Equation 4, **Table 1**). However, this approach is impractical for clinicians because measurements of oxygen consumption are labor and equipment intensive. However, a very rough estimate of cardiac output trends can be determined through oxygen saturations from the arterial and mixed venous circulations and assumed constant oxygen consumption (see Equation 5, **Table 1**).

## Determination of Tissue Oxygen Consumption

Tissue oxygen consumption ( $VO_2$ ) is typically independent of tissue oxygen delivery at rest, with oxygen delivery vastly exceeding oxygen consumption (**Fig. 1**). In times of health, there are numerous compensatory mechanisms to ensure that this situation is maintained. For instance, cardiac output is easily augmented through catecholamines and other stress responses; blood flow is redistributed to vital organ systems, namely the brain, heart, and kidneys; and microcirculatory alterations enhance tissue extraction through recruitment of small capillary networks and locally-released inflammatory mediators. In shock, these compensatory mechanisms are overwhelmed, and oxygen consumption becomes dependent upon oxygen delivery. This leads to anaerobic metabolism as discussed above.

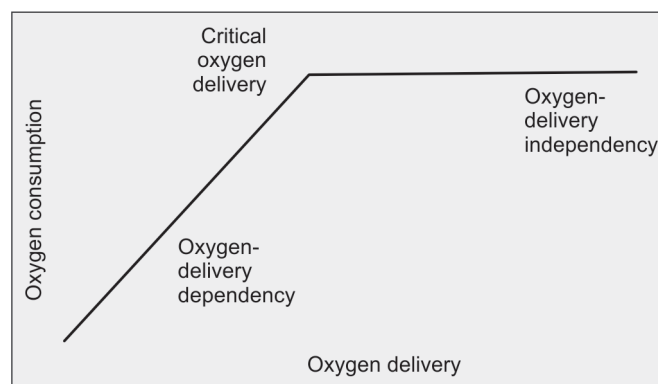
As evidenced by equations 4 and 5 (**Table 1**), the use of mixed venous saturations can be useful in clarifying these complex relationships. In normal situations, the ratio of oxygen consumption to oxygen delivery is approximately 0.2–0.3, producing a mixed venous saturation of 70–80%, assuming a normal arterial saturation. In shock states, when oxygen consumption is dependent upon oxygen delivery, this oxygen extraction ratio may increase, producing a mixed venous saturation below 50%, which indicates severe circulatory compromise and impending anaerobic metabolism. Alternatively, if oxygen extraction is limited by a cellular inability to extract oxygen, such as during sepsis, the mixed venous saturation may be abnormally high, with an oxygen extraction ratio of 0.1 (**Table 2**).

## CLASSIFICATION

Given the above, oxygen delivery can be inadequate when any one of three conditions is met: (1) inadequate tissue blood flow; (2) inadequate oxygen or substrate delivery; or (3) inadequate oxygen extraction. However, in most instances, an isolated condition rarely exists and there is a considerable overlap of contributors.

**Table 1** Important hemodynamic formulas for the child in shock

1. Oxygen delivery = (Cardiac output) × (Oxygen content) $DO_2 = CO \times CaO_2$
2. Cardiac output = Heart rate × Stroke volume $CO = HR \times SV$
3. Oxygen content = (Hemoglobin × oxygen saturation × 1.34) + (0.003 × arterial oxygen tension) $CaO_2 = Hb \times SaO_2 \times 1.34 + 0.003 \times PaO_2$
4. Oxygen consumption = Oxygen delivery × Oxygen extraction (Modified Fick equation) $VO_2 = DO_2 \times O_2ER$
5. Oxygen consumption = Cardiac output × (Arterial – Venous oxygen content) $VO_2 = CO \times (Ca - Cv)$



**Figure 1** Oxygen delivery as it relates to oxygen consumption. At the inflection point, oxygen consumption is dependent upon oxygen delivery, and tissue dysoxia occurs

**Table 2** Causes of a low mixed venous saturation

1. Low arterial saturation
2. High oxygen consumption
3. Low cardiac output
4. Low hemoglobin concentration



Inadequate tissue flow consists of inadequate cardiac output or inadequate circulating volume. When there is inadequate cardiac output due to myocardial failure, cardiogenic shock ensues due to insufficient blood flow to tissues. When there is insufficient circulating blood volume because of dehydration or blood loss, hypovolemic or hemorrhagic shock results. Similarly, shock results with a loss of *effective* vascular volume, such as in anaphylaxis or after acute spinal cord resection, where systemic flow is inadequate.

Recalling the formula for arterial oxygen content, it is clear that acute respiratory failure will lead to shock, if hemoglobin molecules have been desaturated for enough time to lead to tissue hypoxia. Additionally, acute hemolysis leading to a rapid loss of oxygen carrying capacity will lead to a shock state. Finally, conditions such as carbon monoxide poisoning or methemoglobinemia may lead to a shock state, as oxygen delivery will be substantially impaired.

When oxygen delivery is adequate, extraction is crucial for maintaining tissue homeostasis. In septic shock, an inability of tissues to extract the needed oxygen due to microvascular changes and mitochondrial dysfunction is often a contributing factor.

In addition to classification based upon physiologic derangements as outlined above, shock can be classified by its stage. Compensated shock refers to early disease, where blood pressure is maintained, tissue perfusion is mostly adequate, and there are subtle signs of shock, such as tachycardia, tachypnea, altered capillary refill and mild lactic acidosis. This can progress to decompensated shock, where compensatory mechanisms are overwhelmed and clear signs of organ dysfunction exist due to dysoxia and progressive acidosis. Blood pressure will often suffer in this stage of shock, further compromising tissue perfusion, with progressive multiple organ failure. Irreversible shock occurs when there is widespread cellular and organ dysfunction, leading to death, in spite of intensive medical therapies.

## MAJOR ETIOLOGIES

Shock in children can be due to a variety of causes, with frequent overlapping of the major categories of cardiogenic, hypovolemic, and distributive shock, which can sometimes be differentiated by hemodynamic parameters (**Tables 3 and 4**). Myocarditis, rheumatic heart disease and unrepaired congenital heart disease are the major causes of childhood cardiogenic shock in Asia. Additionally, septic shock often presents with features of cardiogenic shock, and a serious bacterial infection must always be considered in the differential diagnosis.

**Table 3** Physiologic characterization of types of shock

	Cardiac output	Systemic vascular resistance	Mixed venous saturations
Cardiogenic	Low	High	Low
Hypovolemic	Normal	High	Low-Normal
Distributive	High	Low	Low-High

**Table 4** Major etiologies of shock

Cardiogenic	Direct myocardial injury—Ischemia, infection, inflammation High afterload—Pulmonary hypertension, severe aortic coarctation Inadequate diastolic filling—Cardiac tamponade, tension pneumothorax Inadequate heart rate—Sinus node dysfunction
Hypovolemic	Trauma, dehydration, burns
Distributive	Anaphylaxis, spinal shock, sepsis, adrenal insufficiency

*Hypovolemic shock* is secondary to either dehydration, where a total body fluid volume is depleted, without a significant decrease in oxygen carrying capacity, such as in diarrhea; or hemorrhage, where there is a loss in oxygen carrying capacity due to a major loss in red blood cell volume, in addition to the depletion in total body fluid volume. Signs of shock typically occur when more than 20–30% of blood volume has been lost.

Similarly, *spinal shock* is due to an inability to maintain sympathetic tone and systemic vascular resistance, leading to inadequate tissue blood flow, secondary to spinal cord injury and trauma. Anaphylactic shock also leads to an inability to maintain vascular tone, but due to the uncontrolled release of endogenous vasodilators.

*Septic shock* is often a combination of all classes of shock. There is often poor cardiac function due to septic cardiomyopathy, with poor tissue perfusion due to the massive inflammation and vasodilation caused by the severe infection. Finally, an inability to use delivered oxygen makes septic shock especially challenging to treat. The etiologies of septic shock are broad and dependent upon local epidemiology, with bacterial infections, dengue, malaria and fungal diseases all prominent (**Table 5**).

**Table 5** Major microbiologic etiologies of pediatric septic shock in Asia

Bacterial	Viral	Other
<ul style="list-style-type: none"> <li>Enterobacteriaceae, such as <i>E. coli</i> and <i>Klebsiella spp.</i></li> <li><i>Neisseria meningitidis</i></li> <li><i>Staphylococcus aureus</i></li> <li><i>Streptococcus pneumoniae</i></li> <li><i>Streptococcus pyogenes</i></li> <li><i>Salmonella typhi</i></li> <li><i>Enterococcus spp.</i></li> <li><i>Haemophilus influenzae</i></li> </ul>	<ul style="list-style-type: none"> <li>Dengue</li> <li>Influenza</li> <li>Herpes family viruses</li> </ul>	<ul style="list-style-type: none"> <li>Malaria</li> <li>Typhus</li> <li>Fungal diseases, such as <i>Candida</i></li> </ul>

## CLINICAL FEATURES

The diagnosis of the child with shock is made clinically, through a rapid assessment of history, physical exam findings and ancillary tests. There is no one test that will differentiate shock from non-shock, but rather its diagnosis relies on astute clinical expertise to recognize a combination of signs and symptoms indicative of circulatory compromise.

## History

Despite the time-sensitive nature of management of the child with shock, documenting a focused history is crucial to better dictate management. Eliciting this history can occur concurrently with the initial evaluation and resuscitation and should focus on differentiating the potential causes of shock, as these may be difficult to determine just through a physical exam. Any history of prior illnesses or congenital anomalies, signs and symptoms of infections, or traumatic events must be inquired about. For neonates and infants, a maternal and birth history is helpful, as well as pre-existing symptoms of congenital heart disease.

## Physical Examination

The diagnosis and classification of shock can be tremendously clarified by a focused and efficient clinical exam. The practitioner must examine for signs of decreased organ or peripheral perfusion in a systematic way. As mentioned above, only vital sign abnormalities, such as tachycardia and tachypnea, are present in early, compensated shock, and these are major components of the criteria for the systemic inflammatory response syndrome (SIRS) (**Table 6**).

**Table 6** Systemic Inflammatory Response Syndrome Criteria

- Core temperature (measured by rectal, bladder, oral or central probe) of  $>38.5^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ .
- Tachycardia, defined as a mean heart rate more than two standard deviations above normal for age, or for children younger than one year of age, bradycardia defined as a mean heart rate  $<10$ th percentile for age.
- Mean respiratory rate more than two standard deviations above normal for age or mechanical ventilation for an acute pulmonary process.
- Leukocyte count elevated or depressed for age, or  $>10\%$  immature neutrophils.

As tissue perfusion becomes compromised, documenting neurologic status, capillary refill, and the presence of a central to peripheral temperature gradient are helpful. These can be simply determined by laying hands on the patient and obtaining a rough assessment of overall perfusion. Skin mottling, decreased peripheral temperatures and altered capillary refill are often the first signs of impending shock, and should be taken seriously as the first stages in screening for level of acuity. The physical exam can help differentiate the shock between *warm shock*, where there is vasodilation, and *cold shock*, where extremities are cold with widespread vasoconstriction as a result of sympathetic responses to maintain perfusion to vital organs. This differentiation can help with staging the severity of shock, as well as in determining an etiology and dictating management strategies.

Volume status can be determined through skin turgor and fontanel status, depending upon the age. Cardiac function is assessed through auscultation for third heart sounds and examination for signs of acute heart failure, such as rales and hepatomegaly. Hypotension is a very late stage finding in pediatric shock; one should not wait for development of hypotension to diagnose shock. In children, hypotension is defined as a systolic blood pressure less than the fifth percentile of normal for age (**Table 7**). Finally, any focal symptoms, such as signs of infection, neurologic abnormalities, or cutaneous findings that point to an inciting etiology must be quickly determined to better dictate therapy.

**Table 7** Low systolic blood pressures for age in children

Age	Normal
$<28$ days	$<60$ mm Hg
1–12 months	$<70$ mm Hg
1–10 years	$<70 + (2 \times \text{age in years})$ mm Hg
$>10$ years	$<90$ mm Hg

## LABORATORY INVESTIGATIONS

The arterial blood gas, including a lactic acid and base deficit, will help quantify the degree of tissue dysfunction, and can guide response to therapy. As mentioned above, mixed venous saturations, when taken from an appropriate site, can be extraordinarily useful, both in guiding therapy and determining an etiology. Individual markers of organ function, such as liver enzymes, renal markers, such as creatinine, and markers of endothelial dysfunction, such as coagulation profiles, are also useful for both the diagnosis and prognosis of shock. Documentation of the presence, or absence, of the SIRS is useful (**Table 6**). An echocardiogram should be obtained to document cardiac function and volume status, if readily available, and cultures and other diagnostic tests should be performed to help guide specific therapies, depending upon the clinical scenario.

## INITIAL MANAGEMENT

The initial management of the child with shock requires focused attention and constant re-evaluation of chosen strategies. Upon recognition of the child with shock, supportive measures should be immediately instituted.

### Supportive Care

Supportive care includes ensuring that the patient is monitored with continuous electrocardiography and pulse oximetry. Intravenous access should be urgently obtained, with intraosseous access as an option in the child with difficulty in cannulating peripheral veins. Urine output should be carefully documented with placement of a urine catheter and invasive blood pressure monitoring with arterial catheterization is recommended, where available. Along these lines, the patient should be transferred to the highest level of care readily available, in a safe and timely fashion. The overall goal of therapy for shock is to restore the oxygen deficit that has occurred. Respiratory support should be provided, including oxygen delivery via face-mask or nasal cannula as needed, to maintain adequate gas exchange and saturations. There is no role for providing supranormal quantities of oxygen in shock—this has been disproven, and is associated with an increased risk of oxygen toxicity.

In children with signs or symptoms of infection, appropriate antibiotics should be promptly administered, given strong data illustrating that delays in delivery of antibiotics associated with worsened outcomes in the adult patient with septic shock. The choice of antibiotics is dependent upon the individual patient and local epidemiology, and should be integrated into institutional protocols to ensure timeliness.

### Fluid Resuscitation

The traditional mainstay of shock management is in the restoration of circulating blood volume through the administration of intravenous fluids. Infusing fluids has the theoretically beneficial effects of augmenting cardiac output, and hence, oxygen delivery, through improving the preload, assuming that cardiac function is appropriate. Predicting which child should receive fluids, however, and how much to infuse, is difficult.

Children with distributive, septic shock are traditionally responsive to fluid, and can tolerate up to 60 mL/kg before noticeable pulmonary edema, while children in cardiogenic shock will likely tolerate very little fluid infusion. However, most children do not fall neatly into one of these categories, making decision-making regarding fluid administration very complex. The simple rule is that every child in shock should be considered for a fluid challenge, with constant re-assessment for signs of improvement. In regions where there is no accessibility to modern intensive care supports such as mechanical ventilators, fluid administration has been associated with harm in the child with acute febrile illness. The mechanism of this worsening is likely due to underlying cardiac dysfunction leading to cardiovascular collapse and chronic anemia leading to hemodilution. Hence, if there is rapid development of signs of cardiac failure or worsening shock, such as hepatomegaly, rales, or jugular venous distension, then fluid administration should be immediately ceased. Additionally, if one is in a setting where there is a high burden of malaria, chronic anemia, malnutrition or there is a lack of accessibility to mechanical ventilation, fluid administration should be used very cautiously in the child with shock.

Markers of improvement with fluid resuscitation should be constantly re-evaluated, such as heart rate, level of alertness, blood pressure and urine output. Peripheral perfusion can be used as a surrogate marker of adequacy of resuscitation, in the absence of quantitative markers. If there is minimal improvement on these

markers, then central venous cannulation should be performed, if available, for rapid infusions, central venous pressure monitoring and mixed venous saturation sampling.

### Crystalloids or Colloids

The type of fluid to be administered has been studied extensively, without any specific conclusions. Isotonic crystalloid solutions are the standard of care in most regions of the world, with normal saline being the most used fluid for the acute resuscitation of children with shock. Colloid solutions, such as 5% albumin or starch solutions, are less widely used, primarily due to their costs. Colloid solutions have the theoretical benefit of maintaining intravascular volume; numerous studies, however, have not proven a substantial benefit to colloid solutions for a variety of types of shock, when compared with crystalloid, with further studies ongoing. The current recommendations are to use isotonic crystalloid as the first-line fluid for the resuscitation of shock, regardless of setting or etiology, given its ease of access and safety data. Newer data on the use of chloride-poor solutions, such as Plasmalyte or Ringer lactate, are emerging, with some promise, although further study is needed. In children with shock and severe anemia (Hb < 5g/dL), acute blood transfusions will augment oxygen carrying capacity and should be the first line fluid for resuscitation.

### Ventilation

Additionally, intubation should be considered at this juncture, depending upon the clinical status and gas exchange parameters. Administering the sedation required for intubation, however, should be done cautiously, given the fragile hemodynamic state of children in shock. The use of noninvasive ventilation, such as with continuous positive airway pressure (CPAP) or BiPAP, for maintaining gas exchange has great promise, and has been used more and more frequently over recent years. This avoids the need for sedation, as well as decreases costs and the risks of nosocomial infections. There is also the benefit of augmenting cardiac output through positive pressure ventilation, given the frequent cardiac dysfunction present in children with shock. Hence, in the child in shock with ventilatory requirements, a trial of noninvasive ventilation is often warranted.

The mixed venous saturations and lactic acid levels have been used to help guide resuscitation during shock, with a target-mixed venous saturation of more than 70% and lactic acid level of less than 2 mmol/L. These numbers can be closely monitored during resuscitation, if available, to decide upon whether further fluid administration is indicated, as well as in monitoring cardiac output. The rate of rise of lactic acid in children with shock has been shown to be one of the most accurate predictors of a bad outcome. Interventions that result in a decline in mixed venous saturations should be modified so as to target a normal oxygen extraction ratio.

Regardless of institutional capabilities, a protocolized approach to the resuscitation of the child in shock has been shown to be effective in reducing mortality. This protocol should be tailored to each institution, depending on personnel and equipment available, and should include rapid deployment of the appropriate people, obtaining a diagnosis, monitoring of hemodynamic parameters, determining fluid responsiveness, and transferring the patient to the appropriate level of care (**Flow chart 1**).

### Vasoactive Agents

In patients who are fluid-unresponsive but remain with signs of shock, vasoactive agents are recommended. Vasoactive agents are those that assist in maintaining systemic perfusion through either vasopressor activity and maintaining blood pressure in the hypotensive patient; inotropic activity to augment cardiac output and oxygen delivery; or vasodilation to assist with cardiac output in the patient with

cardiogenic shock and adequate blood pressure. Many drugs used in current practice exert a combination of these effects, depending on the dose used (**Table 8**) and the resultant receptor activity.

The choice of first-line agents depends upon the physiology, and frequent titration of dose is required to optimize clinical response. The physiologic effect of different agents is dose-dependent, and practitioners must be aware of changes in drug activity with altered dosing. Additionally, the physiologic response to these agents is attenuated over time, and will often require progressive escalation or cycling of vasoactive agents to maintain optimal effects.

Dopamine exerts a variety of effects: at low doses, it acts predominantly at dopaminergic receptors located on the renal, coronary and cerebral vascular beds, causing vasodilation and increased perfusion. At increasing doses, it progressively stimulates beta-1, and then alpha-1 receptors, causing increased cardiac output and then vasoconstriction. Epinephrine initially acts at beta-1 receptors at lower doses, but then becomes a potent alpha-1 agonist at higher doses, potentially limiting the hoped-for inotropic effects.

It is important to remember that titration should not be targeted towards normalization of blood pressure, but rather to optimize oxygen delivery to major organs. Hence, following quantitative markers, such as mixed venous oxygen saturations and lactic acid levels are very useful. Additionally, neurologic status, capillary refill and urine output are all markers of response to vasoactive agents.

### The Malnourished Child

The malnourished child with shock is an especially challenging situation, and carries an especially high level of mortality. The rapid infusion of volume often precipitates cardiovascular collapse in these children, given the baseline poor cardiac function and co-morbid anemia. World Health Organization guidelines recommend very small fluid boluses, followed by early consideration of blood transfusion, although the administration of any fluid to the malnourished child is not without controversy. The very early use of vasoactive agents in the malnourished child with shock has been proposed by some authors, although this has not been adequately studied.

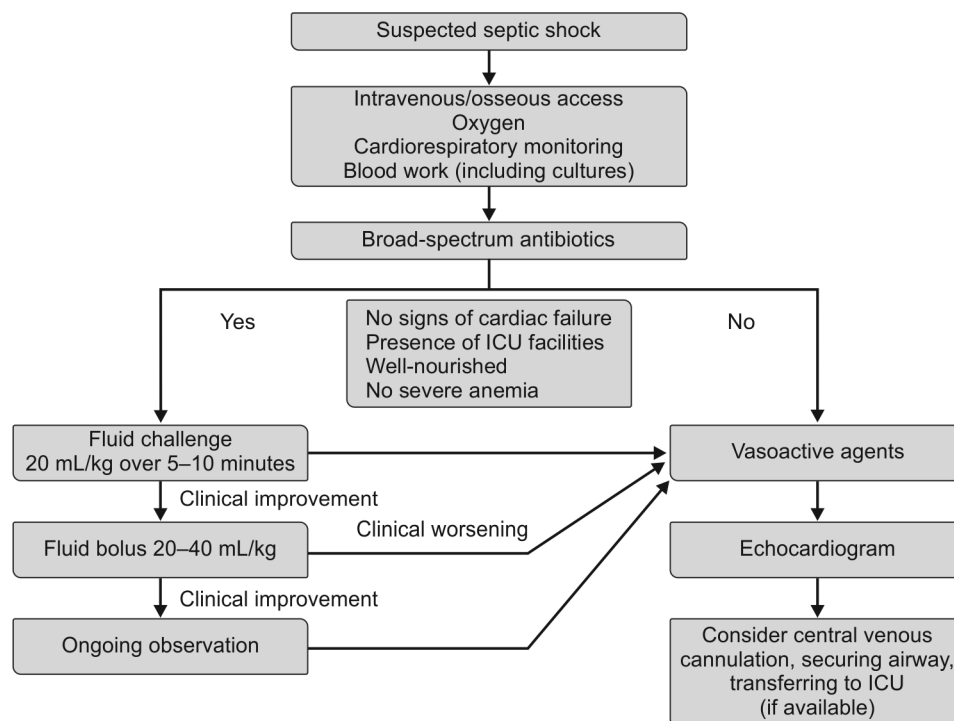
### Other Therapeutic Options

Other therapeutic options for shock are entirely dependent on the underlying etiology. In patients with hypovolemic shock, replacement of intravascular volume is the mainstay of therapy. This is the same for hemorrhagic shock, with volume replacement performed with blood. Transfusing children with shock, either sepsis or cardiogenic, and a hemoglobin less than 9 g/dL may be indicated to optimize blood oxygen content, although the data on this approach is limited and must be weighed against their individual fluid tolerance. As mentioned above, severe anemia (hemoglobin less than 5 g/dL) should be urgently transfused with packed red blood cells or whole blood, depending upon availability.

Corticosteroids for shock are controversial, with varying protocols as to the timing, dose and type of steroids to be administered. In shock that is resistant to catecholamine administration, it is recommended that 2 mg/kg of hydrocortisone are given in a timely fashion, followed by q 6h dosing of 1 mg/kg to supplement adrenal activity. Further study on the role of steroids is ongoing.

### Postresuscitation Care

Upon achieving some degree of stability, a variety of hospital-based therapies are important to ensure ongoing recovery. If there is a documented source of infection, this needs to be appropriately targeted with antibiotics, depending on microbiologic results, and removed, if possible, in the case of abscesses or empyema.

**Flow chart 1** Suggested algorithm for the initial management of suspected septic shock in children**Table 8** Vasoactive agents useful for children in shock

Agent	Receptor		Standard doses	Major clinical activity
	Alpha	Beta		
Norepinephrine	+++	+	0.02–0.2 mcg/kg/min	Vasoconstriction
Dopamine	++	++	5–20 mcg/kg/min	Vasoconstriction Inotropy
Epinephrine	+	+++	0.02–1 mcg/kg/min	Inotropy
Dobutamine	-	+++	5–20 mcg/kg/min	Inotropy Vasodilation
Milrinone	PDE-3 inhibition		0.25–1 mcg/kg/min	Vasodilation
Vasopressin	V1 agonist		0.0005–0.002 U/kg/min	Vasoconstriction

Feeding should be instituted with an age-appropriate nutritional formula as early as possible via nasogastric tube if on stable doses of vasoactive agents. If available, consultation with other clinicians can help guide further therapy, such as infectious diseases, cardiology and surgery, depending on the specific clinical scenario. If intubated, the use of low-tidal volume ventilation strategies, with permissive hypercapnia, will minimize barotrauma and lead to earlier extubation. Above all, frequent monitoring for signs of further deterioration in this postacute resuscitation period are vital to ensure optimal recovery.

## OUTCOMES

Mortality rates for pediatric shock are entirely contingent on the inciting etiology and the location of care. Pediatric septic shock in India has a mortality rate of upwards of 50%. Hypovolemic shock, often the result of dehydration due to diarrhea, has a much lower mortality rate of between 5 and 10%. The outcome for hemorrhagic shock as a result of trauma is dependent upon whether the child can

rapidly get resuscitated with transfused blood. Cardiogenic shock due to congenital heart disease has a very poor prognosis, given the poor accessibility to urgent cardiac surgery in most regions.

Markers for a bad prognosis include signs of decompensated shock such as an initial blood pH of less than 7.1, a rapid rise of lactic acid levels, and a severely abnormal mixed venous oxygen saturation that does not respond to initial resuscitation. Children with co-morbid chronic disease or malnutrition typically do worse than previously healthy children. Younger children appear to have similar survival rates as older children. Survivors of shock often have significant complications of their disease, with neurologic alterations being the major concern due to a period of hypoperfusion during the shock state.

## PREVENTION

Shock in children is almost entirely preventable. However, this requires a multi-faceted, multi-disciplinary approach across sectors, including, but not exclusive to, ensuring full vaccination compliance, early screening and diagnosis of congenital heart disease, and ensuring accessibility to primary health-care during times of mild illness and trauma prevention strategies. In the primary health-care setting, ensuring that children with acute illness are recognized and treated before signs of decompensated shock ensue will significantly reduce the burden of pediatric shock. Treating children during these 'golden hours' will result in significant improvement, and missing out on this opportunity to improve their outcomes will invariably result in more frequent and severe cases of shock. This may include referring children to higher levels of care early in their course if there is a suspicion that shock may soon develop, for further monitoring, hydration, and supportive care as needed, in as safe and expeditious a manner as possible. The greatest challenge in this regard is in recognizing the child who is soon to develop shock, a skill that is difficult to learn, and in ensuring that resources are available for an efficient transport. The use of early warning scores may assist clinicians in this regard, although further study is required before implementation.



### IN A NUTSHELL

- Shock is a syndrome where oxygen supply is inadequate for oxygen needs.
- Shock can be classified in a variety of ways:
  - Physiologically: (1) Inadequate tissue flow; (2) Inadequate blood substrate delivery; (3) Inadequate oxygen extraction.
  - Mechanistically: (1) Distributive; (2) Cardiogenic; (3) Hypovolemic.
  - By stage: (1) Compensated; (2) Decompensated; (3) Irreversible.
  - By clinical exam: (1) Warm shock; (2) Cold shock.
- Septic shock is the most common cause of pediatric shock globally, and can fall within any of the above classifications.
- Treatment is primarily geared at restoring oxygen balance by enhancing oxygen delivery primarily through supportive care, fluids and vasoactive agents.
  - Treatment can be monitored through serial clinical exams and blood gas measurements.
- For septic shock, early antibiotics are the mainstay of therapy.
- The outcomes for children with shock are variable and dependent upon the inciting cause and the access to higher levels of care.
- Shock can be prevented, or minimized, if it is recognized early in its course and appropriately acted upon.

### MORE ON THIS TOPIC

- de Oliveira CF, de Oliveira DS, Gottschald AF, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcome comparison with and without monitoring central venous oxygen saturation. *Intensive Care Med.* 2008;34:1065-75.
- Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med.* 2013;39:165-228.
- Khilnani P, Singhi S, Lodha R, et al. Pediatric Sepsis Guidelines: Summary for resource-limited countries. *Indian J Crit Care Med.* 2010;14:41-52.
- Lodha R, Oleti UP, Kabra SK. Management of septic shock. *Indian J Pediatr.* 2011;78:726-33.
- Maitland K, Kiguli S, Opoka RO, et al. FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. *N Engl J Med.* 2011;364:2483-95.
- Ranjit S, Aram G, Kissoon N, et al. Multimodal monitoring for hemodynamic categorization and management of pediatric septic shock: a pilot observational study. *Pediatr Crit Care Med.* 2014;15:e17-26.
- Ranjit S, Kissoon N. Bedside echocardiography is useful in assessing children with fluid and inotrope resistant septic shock. *Indian J Crit Care Med.* 2013;17:224-30.
- Singh D, Chopra A, Pooni PA, Bhatia RC. A clinical profile of shock in children in Punjab, India. *Indian Pediatr.* 2006;43:619-23.
- Wills BA, Nguyen MD, Ha TL, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med.* 2005;353:877-89.

## Chapter 8.3

# Acute Respiratory Distress Syndrome

Venkat Shankar

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are common causes of acute hypoxemic respiratory failure in adults and children. It was recognized as a clinical syndrome by Laennec as early as 1821 and elegantly described by Sir William Osler in 1925. Nevertheless, the term ARDS was coined by Ashbaugh in 1967 who also provided a comprehensive and definitive description of the clinical and pathological picture. The initial name adult respiratory distress syndrome was changed to acute respiratory distress syndrome in 1994 to include the children with this disorder as well. In 1994, a consensus conference [American-European Consensus Conference (AECC)] established the clinical criteria for encouraging a consistent identification and definition of this syndrome (**Table 1**). Over the past 20 years, the AECC definition has been widely used for studying ARDS across the world. Recently, a new revised definition (Berlin definition) has

been proposed to address some of the shortcomings of the original AECC definition (**Table 2**).

## EPIDEMIOLOGY

Early estimates from the National Institutes of Health suggested an annual incidence of 75 per 100,000 people in the US. The recent US and European reports of incidence of ARDS have been much lower, around 5–33 new cases/100,000 adults per year. There have been only a small number of population-based studies in children published in the past decade from around the world and they report a much lower incidence of 2.9–9.5 cases/100,000 children per year. However, the incidence is still significant when viewed from the perspective of a pediatric critical care provider and the resultant resource utilization for children with ARDS in pediatric intensive care unit (ICU) is substantial. The reported incidence of ARDS in children admitted to pediatric ICU ranges from 8.5 to 16 per 1,000 ICU admissions. The earlier reported adult mortality associated with ARDS was 40–60%. However, the more recent mortality attributable to ARDS in adults is 34–36%. The death associated with ARDS is often multifactorial and associated with multiple organ system dysfunction and is difficult to assign it to just the hypoxemic respiratory failure. In children, there is a paucity of outcome data, with the reported mortality being slightly lower than adults, in the range of 27–35%.

## ETIOLOGY

A variety of clinical conditions that can cause lung injury either directly or by a systemic inflammatory response can lead to ARDS. The common disorders causing direct lung injury are pneumonia, aspiration, inhalation, trauma and near-drowning whereas the systemic ones include sepsis, shock, pancreatitis, burns, cardiopulmonary bypass, transfusion of blood products and drug toxicity. These disorders are listed in **Table 3**. In the tropical countries, a variety of infections can cause ARDS by causing systemic inflammatory response that subsequently leads to ALI. The common ones include malaria, dengue, scrub typhus, leptospirosis and influenza.

## PATHOGENESIS AND PATHOPHYSIOLOGY

During the early phases of ARDS, there is intense inflammatory response that leads to endothelial injury and increased permeability of the alveolar-capillary interface resulting in exudation of protein-rich edema fluid in the alveolar air space.

**Table 1** American-European Consensus Conference definition of acute respiratory distress syndrome (1994)

Clinical feature	Criteria
Timing	Acute onset
Chest radiograph	Bilateral infiltrates
Oxygenation	Severe hypoxemia on oxygen therapy
Acute lung injury	$\text{PaO}_2/\text{FiO}_2$ ratio < 300
Acute respiratory distress syndrome	$\text{PaO}_2/\text{FiO}_2$ ratio < 200
Noncardiogenic origin of pulmonary edema	Pulmonary artery occlusion pressure less than 18 mm Hg or other clinical assessment of lack of elevated left atrial filling pressure

Abbreviations:  $\text{PaO}_2$ , arterial partial pressure of oxygen;  $\text{FiO}_2$ , fraction of inspired oxygen.

**Table 2** The Berlin definition of acute respiratory distress syndrome (2012)

Clinical feature	Criteria
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging*	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation**	
Mild	$200 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$ with PEEP or CPAP $\geq 5 \text{ cm H}_2\text{O}$ ***
Moderate	$100 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm H}_2\text{O}$
Severe	$\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm H}_2\text{O}$

\*Chest radiograph or computed tomography scan.

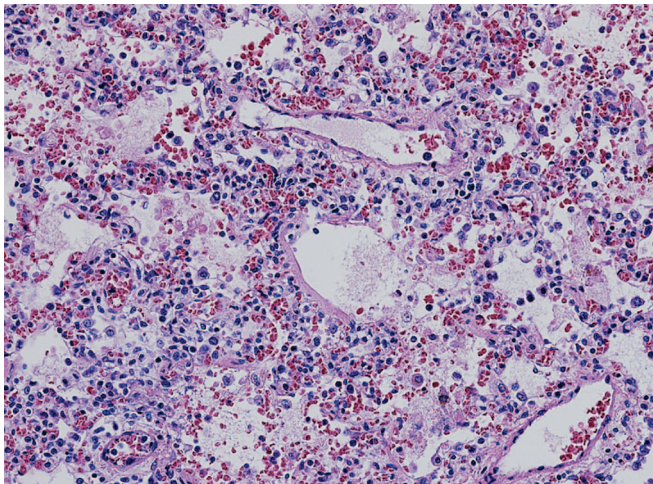
\*\*If altitude is higher than 1000 m, the correction factor should be calculated as follows:  $[\text{PaO}_2/\text{FiO}_2 \times (\text{barometric pressure}/760 \text{ mm Hg})]$ .

\*\*\*This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Abbreviations: CPAP, continuous positive airway pressure;  $\text{FiO}_2$ , fraction of inspired oxygen;  $\text{PaO}_2$ , partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

**Table 3** Common clinical conditions leading to acute respiratory distress syndrome in children

Systemic cause	Direct pulmonary injury
Sepsis	Viral/bacterial pneumonia
Septic shock	Aspiration pneumonia
Hypovolemic shock	Gastric content aspiration
Pancreatitis	Hydrocarbon inhalation
Burns	Smoke inhalation
Cardiopulmonary bypass	Noxious gas inhalation
Fat embolism	Thoracic radiation
Multiple organ major trauma	Near drowning
Malaria	Fungal pneumonia
Transfusion related acute lung injury	Bronchoalveolar lavage/ surfactant washout
Multiple organ system dysfunction/ failure	Ventilator-induced lung injury
Drug toxicity	Traumatic lung contusion
Ischemia-reperfusion injury	

**Figure 1** Microscopic appearance of lung in acute respiratory distress syndrome showing extensive alveolar injury, exudation, inflammatory cells and proliferative changes  
Source: Photomicrograph by Dr Elena Puscasu.

There is an accompanying alveolar epithelial injury that results in dysfunction and loss of Type I cells as well as the cuboid type II alveolar epithelial cells. This leads to alveolar epithelial disruption, alveolar flooding, loss of gas exchange capability, loss of surfactant, potential for secondary bacterial infection and ultimately fibrosis (**Fig. 1**). The presence of fluid in the air space leads to activation of cytokines and other proinflammatory mediators, neutrophil and macrophage activation causing further inflammatory response.

Due to the alveolar air space fluid exudation and increased lung water, the pulmonary compliance is significantly reduced and it leads to poor gas exchange, mismatch between ventilation-perfusion ratio (V/Q) and hypoxemia. There are many areas of the lung that have nonexistent gas exchange leading to significant intrapulmonary shunt and severe pulmonary venous desaturation.

The desaturated pulmonary venous admixture leads to severe arterial hypoxemia, a hallmark of ARDS.

The lung is not uniformly affected, and has areas of relatively preserved alveolar units interspersed with severely atelectatic lung segments. Consequently, ARDS lung is not overall a poorly compliant lung but has differential compliance in different parts of the lung. This has led to the hypothesis that ARDS lungs are not stiff lungs but more of a *baby lung* with an overall reduced area of gas exchange available, akin to the lungs of a small baby. The resultant compliance will correlate with the degree of the normally ventilated tissue. Along with the severe arterial hypoxemia, hypercapnea is often present in ARDS due to decreased effective area for alveolar ventilation secondary to the alveolar injury and increased physiological dead space.

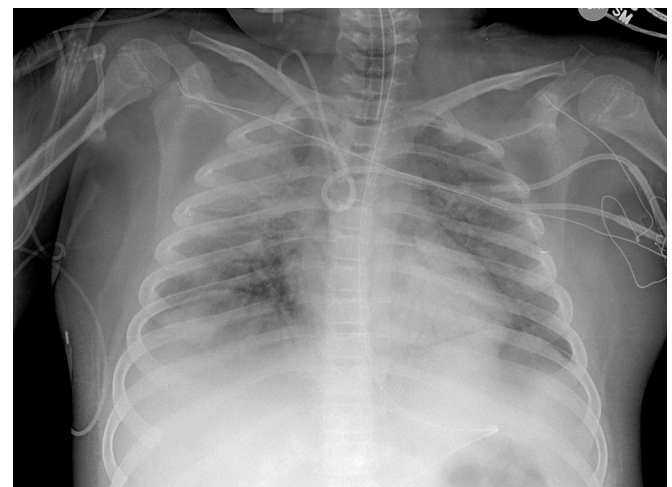
Secondary pulmonary hypertension is often seen in cases of ARDS. This is a result of parenchymal destruction, microvascular thrombosis, vascular spasm and compression and hypoxic pulmonary vasoconstriction.

The initial exudative phase of ARDS is often followed by a proliferative phase when new type II alveolar cells proliferate, along with fibroblasts, myofibroblasts and new matrix is deposited as there is a slow resolution of the pulmonary edema. This proliferative phase can start as early as 72 hours after the onset of ARDS and can last for 7–10 days. This phase could resolve and lead to reconstitution and repair or sometimes it could lead to progressive fibrosis phase that often leads to progressive hypoxemia, increased dead space and hypercapnea, and inability to wean from respirator and can lead to mortality.

There is an observed association between ARDS and multiple organ system failure (MOSF) that is poorly understood. The presence of MOSF is a major predictor of poor outcome.

## CLINICAL FEATURES

The syndrome is characterized by an acute severe progressive hypoxemia after an inciting event or clinical condition as listed in **Table 3**. There is dyspnea and increased work of breathing due to poor compliance and increased dead space. The auscultation could reveal diminished breath sounds and crackles, although these are not necessarily present. The chest radiographs often will reveal bilateral patchy radiodensities/infiltrates (**Fig. 2**). The CT scan reveals patchy distribution of the disease with areas of atelectasis and other areas of relatively preserved lungs (**Fig. 3**).

**Figure 2** Chest radiograph in acute respiratory distress syndrome showing bilateral infiltrates





**Figure 3** Chest CT showing uneven distribution of alveolar derecruitment with more severely affected dependent lung segments

The AECC definition for diagnosing ARDS is listed in **Table 1**. This definition has been widely used, however was not specific about the timing of an *acute onset* and was subject to unreliability due to variable application of positive end-expiratory pressure (PEEP), which was not defined. The Berlin definition (**Table 2**) defines acute onset as less than 7 days after a known clinical insult or new respiratory symptoms. It specifies a minimum amount of PEEP ( $>5$  cm H<sub>2</sub>O) as a prerequisite and further categorizes the ARDS into mild, moderate and severe based on the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ). It also improves the inter-rater reliability of radiologic findings by more specific description of the radiologic criteria. These revised definitions also removed the criterion used in AECC definition for establishing a pulmonary capillary wedge pressure below 18 cm H<sub>2</sub>O and added more clarity to improve ability to exclude cardiac causes of bilateral infiltrates. Although both compliance and physiological dead space are significantly altered in ARDS, there is no easy method of measuring these parameters in many clinical settings. Consequently, the revised definition has not included these as part of the criteria.

The pediatric cases of ARDS have similar presentation and definition as the adults. However, it is occasionally difficult in children to place an invasive arterial line for monitoring arterial  $\text{PaO}_2$ . Consequently, in children with acute hypoxemic respiratory failure that are managed without arterial lines, traditional criteria cannot be used to diagnose ARDS. Consequently, noninvasive correlates of hypoxemia have been recently established with a proposal to modify definition of ARDS for children to include noninvasive parameters as well. Peripheral capillary oxygen saturation to  $\text{FiO}_2$  ratio ( $\text{SpO}_2/\text{FiO}_2$ , substituting  $\text{SpO}_2$  for  $\text{PaO}_2$ ) and the oxygen saturation index [ $(\text{FiO}_2 \times \text{mean airway pressure})/\text{SpO}_2$ ] are being currently validated as surrogates for measuring the degree of hypoxemia and establishing their validity.

## Complications

The complications associated with ARDS can be related to the underlying clinical disorder that led to ARDS or due to the progressive hypoxemia and impaired lung mechanics. As mentioned earlier, there is a very high incidence of MOSF associated with ARDS. Acute kidney injury and renal failure are common in children with ARDS. Due to the cardiopulmonary interaction, both the pathophysiology of lung disease as well as the treatment used

(positive pressure mechanical ventilation leading to increased mean airway pressure) can cause significant cardiovascular dysfunction. The preload (decreased venous return), the afterload (increased due to pulmonary hypertension) as well as contractility (hypoxemia, coronary ischemia) are affected, often necessitating vasoactive agents to support cardiac output. The lungs can have evidence of barotrauma—air leaks like pneumothorax or pneumomediastinum or subcutaneous emphysema. There could be ventilator-induced lung injury secondary to high settings of the ventilator required. Secondary infections are often a risk due to presence of endotracheal tube, invasive vascular lines and urinary catheter. Prolonged mechanical ventilation, need for tracheostomy and chronic ventilation, muscular weakness due to disuse, critical illness myopathy or malnutrition are complications that are often seen.

## APPROACH TO DIAGNOSIS

The diagnosis of ARDS is often established based on the presence of an underlying clinical disorder and an acute progressive hypoxemic respiratory failure with radiological findings as defined in the two definitions. The essential laboratory test is the  $\text{PaO}_2$  in an arterial blood sample. This is required to calculate the  $\text{PaO}_2/\text{FiO}_2$  ratio. A plain anterior-posterior view chest radiograph is usually sufficient to establish the radiological findings. In occasional cases, a high-resolution chest CT is helpful in better delineating the extent and distribution of the parenchymal pathology. An echocardiogram may be useful in ruling out any primary cardiac disorder as the primary cause of pulmonary edema. Additional laboratory values that help with establishing diagnosis or help with management include arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ), pH, lactate and complete blood count and serum electrolytes, renal and hepatic function tests. Blood culture, tracheal secretion culture, bronchoalveolar lavage, pleural fluid analysis and lung biopsy are other possible tests that can help with the management. Measurement of physiological dead space and pulmonary compliance can be helpful in evaluating the extent of disease and its progress. A valuable test during severe hypoxemia is the measurement of systemic central venous oxygen saturation ( $\text{ScvO}_2$ ) obtained from a central venous line placed near right atrium that can help with optimizing oxygen delivery and tailoring the therapies. Measuring tissue oxygenation in cerebral and splanchnic tissues using near infrared spectroscopy is increasingly being used to monitor adequacy of tissue oxygenation during extremely hypoxic states in ARDS to prevent organ dysfunction and permanent injury. All children with ARDS should have continuous noninvasive monitoring of systemic oxygenation ( $\text{SpO}_2$  by pulse oximeters) and ventilation (end-tidal  $\text{CO}_2$  by capnography).

## MANAGEMENT

The broad goals of management of ARDS are:

- Treatment of the underlying disorder
- Provide adequate oxygenation and ventilation without causing iatrogenic harm
- Support the multiple organs systems showing dysfunction.

Although there has been a lot of research in attempting to attenuate or modify the lung injury and its course, no specific therapy has been found till date that alters the course of the injury. The initial supportive measures include ensuring patency of the airway, clearance of secretions, and providing supplemental oxygen via nasal cannula or facemask. There has been an increasing early use of humidified high flow nasal cannula systems that can provide higher flows of 8–32 L/min in a safe manner.



## Noninvasive Ventilation

Noninvasive positive-pressure ventilation (NPPV) has been suggested for early ARDS either with a nasal prong or facemask providing continuous positive airway pressure or bilevel positive airway pressure. This is especially desirable in children who are immunosuppressed where endotracheal intubation and mechanical ventilation may pose additional risk. The NPPV can help with recruitment of alveoli, improving functional residual capacity (FRC), stabilizing the chest wall, unloading the inspiratory muscles and improving respiratory mechanics. However, NPPV often requires sedation to reduce anxiety and to maintain proper seal, which may pose a risk of respiratory depression. In addition, there is risk of aspiration of oropharyngeal secretions as well as gastric distention and emesis.

## Endotracheal Intubation and Mechanical Ventilation

This is the most effective way of optimizing oxygenation and ventilation in patients with ARDS. Over the last 15 years, the emphasis has shifted from achieving near normal blood gas values of  $\text{PaO}_2$  and  $\text{PaCO}_2$  to providing sufficient oxygenation and ventilation while ensuring lung protection and avoiding ventilator-induced lung injury. This has led to use so-called *lung protective* settings of lower  $\text{FiO}_2$ , limiting plateau pressures to less than 30 cm  $\text{H}_2\text{O}$ , low tidal volume (6–8 mL/kg). Consequently, the accepted targets often include  $\text{PaCO}_2$  in 60–80 mm Hg range, pH of 7.25 or higher and a  $\text{SpO}_2$  of 88% or greater (**Tables 4 and 5**). There is wide variation amongst various centers about the preferred mode of mechanical ventilation for ARDS, with no evidence to suggest superior outcomes of one mode over another (**Flow chart 1**).

## Open Lung Strategy

Preventing repeated opening and closing of alveolar segments is believed to be more protective for the lungs. Similarly, preventing overstretching or overdistention of the alveoli is considered to be desirable. These are often achieved by using adequate PEEP often in the range of 5–18 cm of  $\text{H}_2\text{O}$ . Some practitioners advocate for early application of high frequency oscillatory ventilation (HFOV) as an ideal lung protective ventilation by providing optimal recruitment of lungs without cyclic shear trauma due to tidal ventilation. However, there is paucity of recent pediatric literature supporting this approach. Additionally, two recent large randomized studies in adults have failed to show HFOV to improve outcomes.

## Extracorporeal Membrane Oxygenation

It has been used as a rescue therapy for supporting oxygenation and ventilation when conventional treatment has failed. Despite lack of large RCT showing clear outcome benefits, extracorporeal membrane oxygenation (ECMO) is useful for reducing the potential for ventilator-induced lung injury by minimizing the settings on conventional ventilator. Both venovenous as well as venoarterial ECMO can be utilized. Many cases of severe ARDS during the recent pandemic of H1N1 influenza were successfully managed using venovenous ECMO in adults. A modification of ECMO with lower flow rates and simpler technology called extracorporeal  $\text{CO}_2$  removal is able to effectively remove  $\text{CO}_2$ , thereby helping reduce the barotrauma or lung injury in patients with ARDS and extremely noncompliant lungs.

In many instances, despite optimizing the mechanical ventilation settings or using venovenous ECMO, one has to accept lower oxygenation (permissive hypoxemia) and higher  $\text{CO}_2$  (permissive hypercapnea) to prevent any further ventilator-

**Table 4** Permissive hypercapnea

Benefit	Risk
Right shift of oxygen dissociation curve	Increased intracranial pressure
Increased cardiac output	Pulmonary hypertension
Reduced ventilator-induced lung injury	Right ventricular dysfunction
Better lung healing potential	Arrhythmias

**Table 5** Lung protective ventilation strategy

Parameter	Recommendation
Tidal volume	6–8 mL/kg of ideal body weight
Plateau pressure	< 30 cm of $\text{H}_2\text{O}$ (water)
$\text{FiO}_2$	< 0.6
PEEP	Greater than lower inflection point, or a value that optimizes dynamic compliance
Arterial pH	> 7.20, may use sodium bicarbonate to buffer
Arterial $\text{PaO}_2$	> 50 mm Hg (with concurrent monitoring tissue oxygenation/venous saturation and lactate to ensure adequate oxygen delivery)

Abbreviations:  $\text{PaO}_2$ , arterial partial pressure of oxygen;  $\text{FiO}_2$ , fraction of inspired oxygen, PEEP, positive end-expiratory pressure.

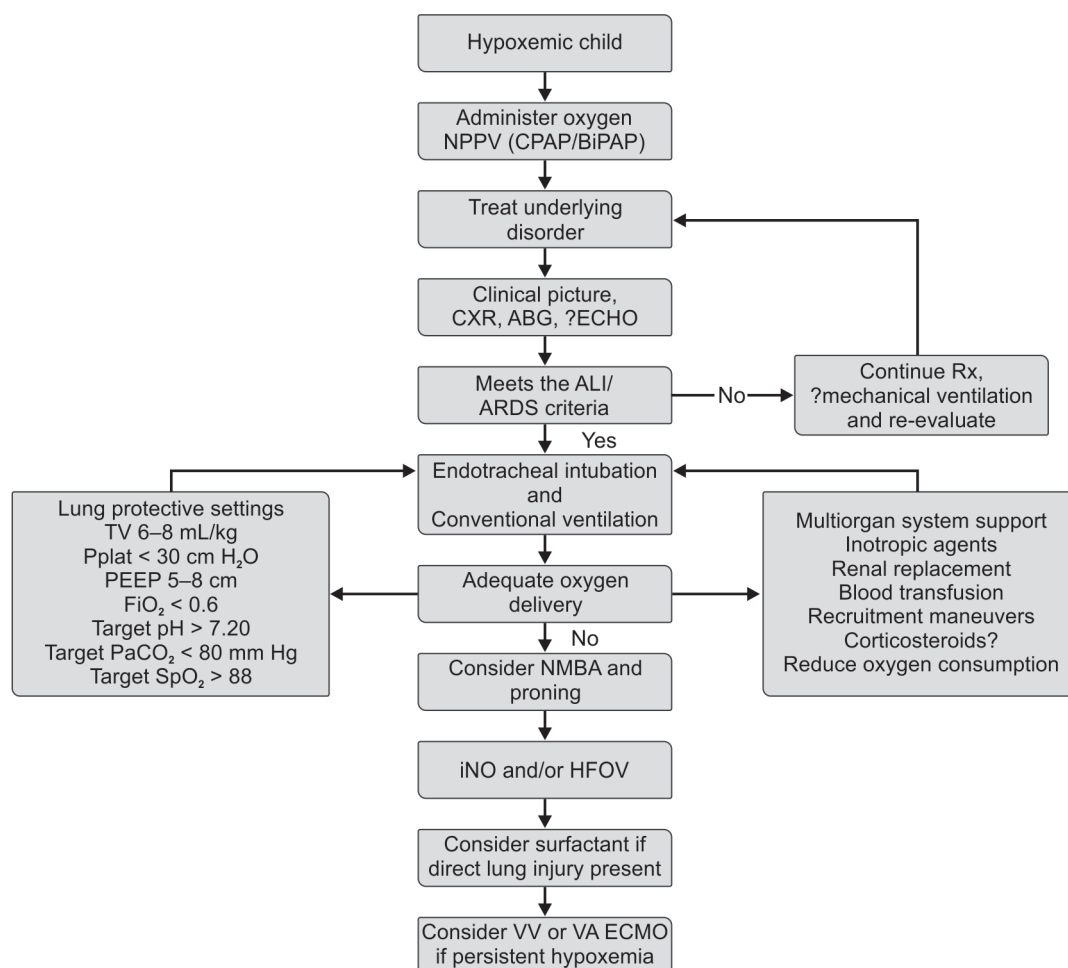
induced injury to the relatively healthy alveolar units. In these situations, it is helpful to focus on monitoring and improving oxygen delivery and reducing consumption rather than just trying to improve oxygen saturation. The oxygen delivery  $\text{DO}_2$  is determined by cardiac output as well as hemoglobin concentration in addition to oxygen saturation by the following formula:

$$\text{DO}_2 = \text{CO} \times (\text{Hb} \times 1.39 \times \text{SaO}_2 + \text{PaO}_2 \times 0.003)$$

Where CO = cardiac output, Hb = hemoglobin concentration of blood,  $\text{SaO}_2$  = oxygen saturation of arterial blood,  $\text{PaO}_2$  = partial pressure of oxygen in arterial blood. As is evident, one can help the oxygen delivery by improving cardiac output (fluid bolus, inotropic support) or hemoglobin (red cell transfusion) even in the presence of a lower  $\text{SaO}_2$ .

## Prone Positioning

It has been used as an adjunctive therapy to the ventilator management. The child is prone for at least 18 hours or more everyday. From a physiological standpoint, prone position improves the V/Q matching, and improves aeration to the dorsal portion of the lungs and helps recruit the dependent alveoli. Although prone positioning has been shown to improve oxygenation, it has not shown any improvement in outcomes of ventilator-free days or survival except in a small subgroup of adults with severe hypoxemia with  $\text{PaO}_2/\text{FiO}_2$  ratio of 100 or less. On the other hand, proning is also associated with accidental dislodgement of endotracheal tube or vascular access and pressure-related ulcers (**Table 6**). Other methods of recruitment maneuvers have been described to augment alveolar recruitment and FRC. Often they can produce immediate and dramatic improvement in oxygenation. However, routine use of these techniques has not been recommended, as there has not been any demonstrable improvement in outcomes.

**Flow chart 1** A suggested algorithm for management of acute respiratory distress syndrome in children

**Abbreviations:** NPPV, noninvasive positive-pressure ventilation; CPAP, continuous positive airway pressure; BiPAP, bilevel positive air pressure; CXR, chest X-ray; ABG, arterial blood gases; ECHO, echocardiography; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure;  $\text{PaCO}_2$ , arterial partial pressure of oxygen;  $\text{FiO}_2$ , fraction of inspired oxygen; iNO, inhaled nitric oxide;  $\text{SpO}_2$ , peripheral capillary oxygen saturation; VV, venovenous; VA, venoarterial; TV, tidal volume; Pplat, plateau pressure; NMBA, neuromuscular blocking agent; ECMO, extracorporeal membrane oxygenation.

### Inhaled Nitric Oxide

Inhaled nitric oxide or other inhaled pulmonary vasodilators like aerosolized prostacyclin have been used to improve oxygenation in children with ARDS. Unfortunately, despite showing a transient improvement in oxygenation, these therapies have not conferred any survival benefits in large-scale studies.

### Corticosteroids

They have been studied extensively in the setting of adult patients with ARDS to attenuate the inflammatory and fibroproliferative response. There have been variable results between various studies and no consistent survival benefit has been observed. Consequently, the use of corticosteroids in ARDS remains controversial.

### Surfactant

Acute respiratory distress syndrome often leads to a secondary deficiency of surfactant due to destruction of type II cells and the inflammatory exudates. However, the role of exogenous

administration of surfactant in ARDS remains controversial. There has been a single small study in children that showed improved outcomes in ARDS associated with direct lung injury.

### Muscle Relaxants

Prolonged use of neuromuscular blocking agents can lead to muscular atrophy, myopathy and inability to wean of the ventilator. However, recent experience indicates that judicious use of muscle relaxants in early phase of ARDS in adults improves survival outcomes and ventilator-free days. No pediatric experience is available currently, but use of muscle relaxants to promote improved ventilator-patient synchrony, optimize oxygen consumption and delivery has been an acceptable therapy.

### Fluids

Total body fluid overload seems to be associated with worsening pulmonary compliance, hypoxemia and unfavorable outcomes in adults and children. Consequently, fluid restriction or early

**Table 6** Adjunctive therapy for acute respiratory distress syndrome

Therapy	Rationale	Current evidence/comments
Inhaled nitric oxide, aerosolized prostacyclin	Pulmonary vasodilator, improved V/Q matching and oxygenation	Despite significant improvement in oxygenation, failed to show improved clinical outcomes
Prone positioning	Improved aeration of dorsal lung segments, improved V/Q matching, better recruitment of alveoli	Definite improvement in oxygenation seen. Survival benefits seen only in severe ( $\text{PaO}_2/\text{FiO}_2 < 100$ ) hypoxemia group. Risk of endotracheal tube dislodgment, pressure ulcers
Recruitment maneuvers (RM)	Alveolar derecruitment is common with low tidal volume ventilation, RM can improve V/Q mismatch	Transient increase in oxygenation seen. No change in barotrauma or mortality. Use of concomitant high PEEP to maintain recruitment
Surfactant administration	Loss of surfactant due to alveolar cell injury, inflammatory exudate causes atelectasis	Suggestion of modestly improved outcomes in ARDS secondary to direct lung injury. Expensive and impractical
Neuromuscular blocking agents	Patient-ventilator dyssynchrony can cause worse oxygenation, lung injury	Recent evidence showing survival benefits if used early in adults. Risks of prolonged muscle weakness and ventilator dependency
Corticosteroids	ARDS is due to inflammatory process and steroids can modulate inflammatory response	Variable results from various adult ARDS studies. No consistent outcome benefits observed. Remains controversial
Fluid restriction	Total body fluid overload associated with poor compliance, oxygenation and poor outcomes	Fluid restriction after initial shock resuscitation or diuresis often shows improved oxygenation. No consistent survival benefits shown
Continuous venovenous hemofiltration (CVVH)	Total body fluid overload associated with poor compliance, oxygenation and poor outcomes. Possible clearing of cytokines	Early aggressive CVVH shown in children with stem cell transplant to improve outcome in a small case series. No conclusive evidence about outcome benefits despite improved oxygenation
Early enteral nutrition, fatty acid supplements, antioxidants	Decreased muscle loss, better diaphragm strength, attenuated inflammatory response	Conflicting results about benefits of early enteral feedings on outcomes, supplementing fatty acids not conclusively shown to change outcomes

*Abbreviations:* PEEP, positive end-expiratory pressure; ARDS, acute respiratory distress syndrome; V/Q, ventilation-perfusion ratio;  $\text{PaO}_2$ , arterial partial pressure of oxygen;  $\text{FiO}_2$ , fraction of inspired oxygen.

aggressive diuresis/continuous hemofiltration in cases of renal failure is desirable.

### Nutrition

Ensuring adequate nutrition despite fluid restriction is essential for healing of lungs and ability to wean of the mechanical ventilator. Enteral nutrition is possible in most children, and chances of the success of enteral feeds are higher with transpyloric feeding.

### Organ Support

As mentioned earlier, most children with ARDS do not die due to severe hypoxemia but rather due to MOSF. Providing cardiac, renal, hepatic, hematologic and neurologic organ system support is an essential component of the management strategy and these specific organ support therapies are discussed elsewhere in this book.

### PROGNOSTIC FACTORS

Unlike adults, severity of hypoxemia (lower  $\text{PaO}_2/\text{FiO}_2$  ratios) at presentation has been shown to be a predictor of poor outcome and mortality in children. Presence of multiple organ system failure, pre-existing immunocompromised state and a history of stem cell transplantation are also predictors of poor outcome. Overall, the reported mortality of children with ARDS is lower than those of adults as described earlier.

### IN A NUTSHELL

1. ARDS and ALI are a significant cause of morbidity and mortality in children.
2. The diagnosis is established using an internationally accepted standard clinical, laboratory and radiologic criteria.
3. A large number of common systemic or lung-related clinical conditions could lead to ARDS.
4. The cornerstone of management is mechanical ventilation to provide adequate oxygenation and ventilation without causing iatrogenic lung injury.
5. The mechanical ventilation should be lung protective, using low tidal volume (6–8 mL/kg), limited plateau pressure (< 30 cm of  $\text{H}_2\text{O}$ ) and sufficient PEEP to avoid atelectasis and optimal recruitment to keep the lungs open.
6. Permissive hypercapnea is usually required, and lower oxygenation saturations are acceptable if there is evidence of adequate oxygen delivery.
7. Multiple organ failure is commonly associated with ARDS and is a major determinant of the outcome. Multiple organ system support is often needed in the ICU.
8. Multiple therapies including inhaled nitric oxide, prone position, corticosteroids, surfactant, fluid restriction and ECMO are still being evaluated for their beneficial effects on clinical outcomes in ARDS.

**MORE ON THIS TOPIC**

- ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307:2526-33.
- Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet*. 1967;2:319-23.
- Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European Consensus Conference on acute respiratory distress syndrome: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Consensus Committee. *J Crit Care*. 1994;9:72-81.
- Curley MA, Hibberd PL, Fineman LD, et al. Effect of prone positioning on clinical outcomes in children with acute lung injury: a randomized controlled trial. *JAMA*. 2005;294:229-37.
- Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med*. 2013;368:795-805.
- Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. *J Clin Invest*. 2012;122:2731-40.
- National Heart, Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Rice TW, Wheeler AP, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA*. 2012;307:795-803.
- The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301-8.
- Willson DF, Thomas NJ, Markovitz BP, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. *JAMA*. 2005;293:470-6.
- Zimmerman JJ, Akhtar SR, Caldwell E, Rubenfeld GD. Incidence and outcomes of pediatric acute lung injury. *Pediatrics*. 2009;124:87-95.



## Chapter 8.4

# Respiratory Failure

Lokesh Guglani

Respiratory failure is the inability of the respiratory system to maintain adequate oxygenation of the blood and body tissues, or the loss of its ability to ventilate adequately. In this condition, the respiratory system is unable to meet the metabolic demands of the body for the purpose of oxygenation and/or elimination of carbon dioxide. It can occur as an acute process due to several respiratory and nonrespiratory disorders, or become chronic in those with underlying chronic lung, heart or neuromuscular disorders. Severe acute respiratory failure is associated with an imminent risk of cardiac arrest, while those with chronic respiratory failure can develop complications such as pulmonary hypertension and cor pulmonale, or remain at risk for the development of acute-on-chronic respiratory failure due to an intercurrent illness. It is important for pediatricians to recognize early signs and symptoms of respiratory failure in infants and children to provide timely and appropriate treatment for their patients.

## EPIDEMIOLOGY

Acute respiratory infection (ARI) remains the leading cause of acute respiratory failure in children. Bacterial pneumonias account for the majority of cases, and are associated with 1.1 million deaths per year in children less than 5 years of age, accounting for one-fifth of the mortality in this age group. Children with severe malnutrition, pre-existing illnesses (HIV infection or measles), and other environmental risk factors (parental smoking, exposure to biomass fuels) have the greatest risk. Chronic lung infections such as tuberculosis and circulatory shock (due to various causes) also account for significant morbidity in the pediatric age group. The spectrum of disorders associated with respiratory failure in the neonatal age group is different from that seen in older children and has been covered in Section 17.

## ETIOLOGY

The etiology of respiratory failure in children can be conceptually divided into broad categories involving the lungs, the muscles involved in respiration (the so-called *pump* that drives respiration), the neural networks involved in regulation of breathing, cardiac disorders and systemic illnesses that affect the respiratory system as well. **Box 1** highlights these categories and the specific conditions that cause respiratory failure in children.

## PATHOGENESIS

Acute respiratory failure has been traditionally categorized based on the presence of hypoxemia and/or hypercapnia into two broad categories. *Type I respiratory failure* occurs due to any condition that leads to hypoxemia ( $\text{PaO}_2 < 50$  mm Hg on room air). *Type II respiratory failure* is characterized by elevated  $\text{pCO}_2$  levels more than 50 mm Hg (unless there is chronic respiratory failure when the level could be higher) that develops in response to hypoventilation due to a number of etiologies listed under *pump failure*. It is important to remember that as alveolar  $\text{pCO}_2$  and thus arterial  $\text{pCO}_2$  rise, the  $\text{PaO}_2$  will also fall. Hence, Type II respiratory failure will have both hypercarbia and hypoxemia.

The lung can be imagined in a simplified model of gas exchange to contain alveoli that show matching of ventilation with perfusion to maintain oxygenation and facilitate removal of carbon dioxide

(**Fig. 1**). Any disease process that affects this balance is likely to lead to hypoxemia and this is highlighted in the scenarios presented in **Figure 1**. The middle segment in **Figure 1** is the normal state of gas exchange where alveolar blood flow is perfectly matched with alveolar ventilation leading to a V/Q ratio of 1. However, in situations where airflow obstruction limits the alveolar ventilation (left panel in **Figure 1**), the lung tries to overcome imbalances in ventilation to different alveolar units by reducing the perfusion of under-ventilated alveolar units (through hypoxic pulmonary vasoconstriction) to maintain the overall V/Q ratio of the lung. With increasing degree of airways obstruction (such as in severe acute exacerbation of asthma), these compensatory mechanisms can be overcome and overt hypoxemia can develop due to decline in alveolar ventilation that is out of proportion to the changes in perfusion (low V/Q ratio). The other extreme can be seen in situations where pulmonary perfusion alone is affected while ventilation remains intact. In this case, the relatively well ventilated but poorly perfused alveolar units constitute an alveolar dead space where no effective ventilation is occurring and the V/Q in these units is more than 1. With complete obstruction of pulmonary blood flow in a large vessel (for example, due to pulmonary embolism), the V/Q ratio can approach infinity and lead to significant hypoxemia and decompensation. At any given time, the V/Q ratio of all the alveolar units put together in the normal lung is maintained as close to 1 as possible. Depending on the severity of the disease processes, number of alveolar units involved, and presence of pre-existing lung disease, the functional impact on oxygenation and ventilation can vary from no obvious symptoms to severely symptomatic hypoxemia and/or hypercarbia.

It is, therefore, very useful to understand the basic pathophysiology of hypoxemia in patients with respiratory failure. All of the conditions listed in **Box 1**, from a mechanistic standpoint, can be categorized under one of the following four main causes of hypoxemia (ignoring high altitude, which also causes hypoxemia, for the sake of simplicity). Measurement of alveolar-arterial  $\text{PaO}_2$  difference (also called A-a gradient) can help to diagnose the likely cause of hypoxemia (**Table 1**). Normally the arterial  $\text{pO}_2$  is slightly lower than alveolar  $\text{pO}_2$  due to normal anatomic shunt (bronchial and thebesian veins), and some degree of V/Q mismatch and diffusion limitation in the normal lung. The normal value for the A-a (Alveolar-arterial) gradient ranges between 5 and 10 mm Hg and it increases with age. It is calculated with the following equation:

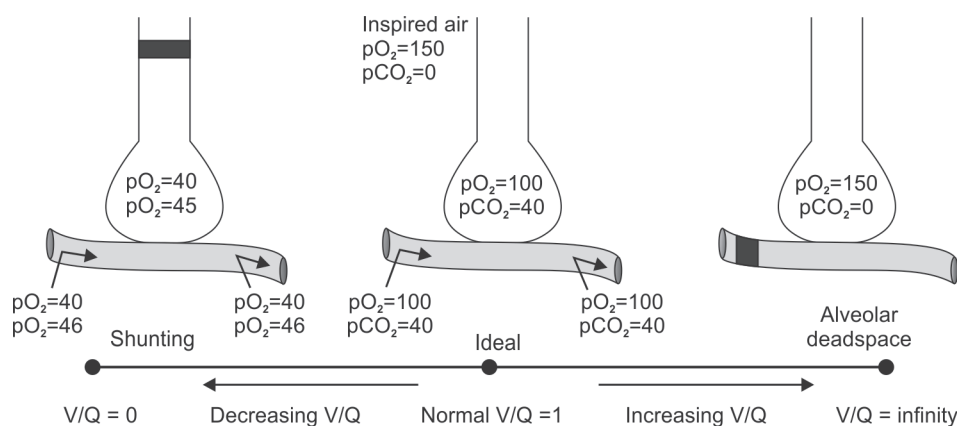
$$\text{A-a gradient} = [\text{FiO}_2 \times (\text{P}_B - 47) - \text{PaCO}_2/\text{R}] - \text{PaO}_2$$

An increase in the A-a gradient can occur due to increased right to left shunt, increased V/Q mismatch, impaired diffusion, higher inspired partial pressure of oxygen, decreased mixed venous pressure of oxygen or due to a shift of the oxyhemoglobin dissociation curve.

Ventilation perfusion mismatch remains the most common cause of hypoxemia in the pediatric age group. Diffusion block refers to processes that impair gas exchange at the alveolar membrane due to presence of fluid (pulmonary edema), inflammatory infiltrate (pneumonia), surfactant dysfunction [neonatal respiratory distress syndrome (RDS)], etc. Hypoventilation encompasses all the conditions listed under pump failure (or neuromuscular weakness) causing respiratory muscle dysfunction. In specific congenital heart defects or pulmonary arteriovenous malformations, significant right to left shunting can cause hypoxemia and respiratory failure as well.

## CLINICAL FEATURES

The evaluation of the child with respiratory distress involves determination of the severity and its underlying cause. The presence of tachypnea and retractions suggests respiratory



**Figure 1** Ventilation-perfusion relationships in the lung

### BOX 1 Etiology of respiratory failure in children

#### Related to the Lungs or Airways

##### Infections

- Bacterial pneumonia
- Viral bronchiolitis
- Pulmonary tuberculosis
- Croup
- Bacterial tracheitis

##### Inflammatory disorders

- Involving the airways: Severe acute asthma
- Bronchiolitis obliterans (postinfectious)
- Involving the lung parenchyma: Acute respiratory distress syndrome
- Pulmonary edema
- Meconium aspiration syndrome

##### Airway disorders

- Subglottic or tracheal stenosis
- Extrinsic airway compression (vascular ring, enlarged lymph nodes, peritonsillar/retropharyngeal abscess)
- Vocal cord paralysis (bilateral)
- Airway foreign body

##### Air leak syndromes

- Tension pneumothorax
- Pneumomediastinum

##### Vascular disorders

- Primary pulmonary hypertension
- Persistent pulmonary hypertension (PPHN)
- Pulmonary embolism

##### Disorders of surfactant secretion and metabolism

- Neonatal respiratory distress syndrome
- Congenital disorders of surfactant protein metabolism

##### Disorders of lung development

- Chronic lung disease of prematurity (bronchopulmonary dysplasia)
- Pulmonary agenesis or hypoplasia
- Other rare lung malformations: Alveolar capillary dysplasia

##### Other lung disorders

- Pulmonary contusion
- Smoke inhalation injury

- Carbon monoxide poisoning
- Submersion injury and drowning

#### Related to Pump Failure

##### Muscular weakness

- Duchenne muscular dystrophy
- Spinal muscular atrophy

##### Demyelinating disorders

Guillain Barré Syndrome

##### Chest wall disorders

- Severe scoliosis
- Asphyxiating thoracic dystrophy (Jeune's syndrome)
- Flail chest

##### Disorders of neuromuscular junction

Myasthenia gravis

#### Related to Central Nervous System

##### Infections

- Bacterial meningitis, viral encephalitis
- Neurotuberculosis

##### Trauma

- Closed head injury
- Intracranial hemorrhage

##### Pharmacologic agents

Benzodiazepines, barbiturates, narcotics

##### Brainstem disorders

- Extrinsic compression from hemorrhage, tumors, or any other space occupying lesions
- Malformations involving the brainstem

##### Congenital central hypoventilation syndrome (Ondine's curse)

#### Cardiac disorders

- Congestive heart failure
- Congenital heart disease

#### Secondary to Systemic Disorders

##### Sepsis and shock

- Dengue shock syndrome
- Gram-negative sepsis
- Hemorrhagic shock

##### Anaphylaxis and angioedema

Hematologic disorders Acute chest syndrome in sickle cell disease.

distress, and respiratory rate cut-offs for different age groups (as shown in **Box 2**) can objectively identify distress. The appearance of the child including their muscle tone and posture; interaction with the environment (consolability in young infants); nature of their speech or cry; and the use of accessory muscles of respiration (sternocleidomastoid, scalene muscles), with or without head

bobbing or nasal flaring, can help assess the severity by inspection alone. Listening for audible stridor, wheezing, grunting, snoring or muffled speech can further help assess the underlying cause. Auscultation to assess for air entry and presence of adventitious breath sounds (crackles or rales, wheezes, bronchial breath sounds, etc.) can help narrow the differential diagnoses. For children who

**Table 1** Main causes of hypoxemia and the associated changes in  $p\text{CO}_2$ ,  $p\text{O}_2$  and alveolar arterial  $p\text{O}_2$  gradient

Causes of hypoxemia	Arterial $p\text{CO}_2$	Arterial $p\text{O}_2$	Alveolar-arterial $p\text{O}_2$ difference	
			In Room Air	With 100% $\text{O}_2$
Ventilation-perfusion mismatch	Normal, increased or decreased	Decreased	Increased	Normal
Diffusion block	Normal or decreased	Normal at rest, decreased with activity	Normal at rest, Increased during activity	Normal
Hypoventilation	Increased	Decreased	Normal	Normal
Right to left shunting	Normal or decreased	Decreased	Increased	Increased

**BOX 2 Clinical signs of respiratory distress in children**

- Tachypnea: Age-specific cut-offs for respiratory rates in children (breaths/min)
  - Age 0–2 months: > 60 per min
  - Age 2–12 months: > 50 per min
  - Age 1–5 years: > 40 per min
  - Age > 5 years: > 20 per min
- Grunting
- Nasal flaring
- Dyspnea
- Retractions (suprasternal, intercostal or subcostal)
- Cyanosis
- Altered mental status
- Apnea.

may be tiring from the effort of breathing, the slowing of their respiratory rate or the presence of gasping or agonal breaths may signify overt respiratory failure that requires emergent intervention to protect the airway and maintain ventilation.

Monitoring of vital signs (temperature, heart rate, respiratory rate and blood pressure), oxyhemoglobin saturation by pulse oximetry and perfusion (capillary refill time) should be repeated at frequent intervals while the assessment is being continued. Further investigations for assessment of the cause of respiratory failure can be done on the basis of the clinical syndrome at presentation and presence of any underlying chronic (lung or heart) disorders.

**Scoring system** Several clinical scoring systems have been devised for the objective assessment of respiratory distress in infants and children. These scoring systems are especially helpful in serial assessment of the same patient over time as the score can yield data for determining the trends and overall response to therapy for each patient. Some scoring systems have been developed for specific age groups (such as Silverman-Anderson score or Downe's scoring system for neonates) or for specific disorders (such as Westley croup score). These have been used as outcome measures in randomized controlled clinical trials for assessing response to specific therapies, but their usefulness may be limited by interobserver variability in scoring.

Additional findings related to chronic respiratory disorders, such as digital clubbing, presence of polycythemia or poor nutritional status can provide additional clues.

## DIFFERENTIAL DIAGNOSES

Because tachypnea and respiratory distress may occur from several nonrespiratory conditions as well, it is important to consider them in the differential diagnosis of respiratory failure. In some situations, such as cardiac failure or circulatory shock, respiratory failure can develop secondarily due to inadequate tissue perfusion causing metabolic acidosis, which can lead to tachypnea and hyperventilation. Other conditions that cause significant metabolic acidosis, such as diabetic ketoacidosis or

inborn errors of metabolism (organic acidemias), may present with severe tachypnea as well and can be easily mistaken for a primary respiratory process. On the basis of specific investigations, such as radiographs, arterial blood gases, laboratory studies, etc., the underlying diagnosis can be fully established.

## APPROACH TO DIAGNOSIS

Rapid assessment of infants and children presenting with respiratory distress is very important for timely initiation of therapy and to promptly detect those that are critically ill and need immediate intervention. The Pediatric Assessment Triangle (PAT) (refer to chapter 7.1) is a model of assessment that can be applied in all settings (rural or urban, in-hospital or out-of-hospital) and is useful for children of all ages with all levels of illness severity. It also helps to identify the key physiologic impairments that need to be addressed. This provides a rapid assessment of the child's cardiopulmonary status without disturbing the child or needing any sophisticated equipment. In the hospital setting, the PAT assessment can be followed by primary and secondary surveys to further refine the information collected initially.

For children with acute respiratory compromise, the following clinical syndromes should be recognized in the emergency room:

- Acute upper airway obstruction—Foreign body, croup, epiglottitis
- Impending respiratory arrest—tension pneumothorax, cardiac tamponade, flail chest, hemorrhage, CNS injury
- Trauma—pneumothorax, hemothorax, pulmonary contusion, CNS injury
- Nontraumatic lower respiratory tract illnesses
  - Wheezing and/or crackles with fever—pneumonia, bronchiolitis, asthma with viral illness, myocarditis
  - Wheezing and/or crackles without fever—Atypical pneumonia, bronchiolitis, asthma, anaphylaxis, atelectasis, pulmonary edema, heart failure, foreign body, intrathoracic mass, exacerbation of chronic lung disease.
  - Tachypnea with fever—Pneumonia, sepsis, pulmonary embolism, encephalitis
  - Tachypnea without fever—Atypical pneumonia, inhalation of toxins, pulmonary masses, pneumothorax, pulmonary embolism, cardiac or metabolic disorders.
- Other systemic illnesses—Malaria, dengue fever/shock syndrome, neuromuscular disorders, etc.

Besides history, examination and pulse oximetry data, further information can be obtained from chest radiograph, laboratory tests to assess for infections, and blood gases (capillary or arterial, if feasible). For those with trauma, further primary and secondary assessments should be performed to evaluate for other sites of injuries. For patients with impending or overt signs of respiratory failure, the first priority should be to secure their airway and then continue to evaluate them for underlying cause on an ongoing basis.

## BLOOD GASES FOR ASSESSMENT OF GAS EXCHANGE

Measurement of partial pressures of gases such as oxygen and carbon dioxide, as well as estimation of pH and bicarbonate levels can be an essential step in the assessment of respiratory failure (**Table 2**). The respiratory centers in the brainstem regulate breathing by a negative feedback system via the partial pressures of CO<sub>2</sub> in the blood and cerebrospinal fluid. This allows for breath-to-breath changes in tidal volume and breathing frequency to maintain PaCO<sub>2</sub> within the normal range. Any short-term changes in alveolar ventilation that increase partial pressures of CO<sub>2</sub> in the alveolar space has an effect on the PaCO<sub>2</sub> and the pH, causing acute respiratory acidosis. There are buffers (bicarbonate, phosphate and proteins) that try to maintain the pH as close to normal as possible. In children with chronic lung disorders, the build up of carbon dioxide can occur slowly as their lung disease progresses, resulting in chronic respiratory acidosis.

### Blood Gas Classification and Interpretation (Also see Chapters 5.3 and 5.4)

The use of a systematic approach for blood gas classification ensures reproducible results and can help avoid mislabeling of the underlying primary acid base disturbances. The main components include assessment of acid-base status by evaluating the pH as the first step to define acidosis or alkalosis. This is followed by identification of the primary problem with the help of PaCO<sub>2</sub> (for the respiratory component); and then the [HCO<sub>3</sub>]<sup>-</sup> and base excess (for the metabolic component). Finally, assessing the degree of compensation for the primary disturbance acid-base disturbance completes the interpretation.

Once the pH has been classified (normal, acidosis or alkalosis), the next step is to assess for respiratory abnormality by evaluating the PaCO<sub>2</sub>, which generally has an inverse relationship with the pH. All the conditions that alter the PaCO<sub>2</sub> levels in blood are considered to be respiratory disturbances. Metabolic disturbances on the other hand, are defined by exclusion of any respiratory related acid-base disturbances. So when the PaCO<sub>2</sub> is high, the pH will be low due to accumulation of carbonic acid and this constitutes respiratory acidosis. If extent of drop in pH is greater than what would be expected for the elevation of pCO<sub>2</sub> above 40 mm Hg, then there is a mixed acid-base disturbance. However, this may be different in the setting of chronic respiratory acidosis where the extent of drop in pH may be much lower than seen in conditions associated with acute respiratory acidosis.

The third step involves the assessment of the compensatory response, which can be either complete or incomplete. This is based on the extent of change in the opposing (respiratory/metabolic) parameter for each primary acid-base disturbance. If there is respiratory acidosis, then besides a high PaCO<sub>2</sub> and low pH, there will be an accompanying increase in [HCO<sub>3</sub>]<sup>-</sup> level to compensate for this drop in pH and adjust it towards normal. If the pH is restored to the normal range, then full compensation exists but for cases where pH remains below normal, then the

compensation is partial. A stepwise approach for interpreting the arterial blood gas results is shown in **Flow chart 1**.

The renal compensatory mechanisms are generally slower than respiratory compensation for metabolic problems and may take up to 3–6 days. The kidneys compensate for respiratory acidosis and metabolic acidosis of nonrenal origin by excreting fixed acids and retaining the filtered bicarbonate. For respiratory alkalosis or metabolic alkalosis of nonrenal origin, the kidneys compensate by decreasing the hydrogen ion excretion and reducing the retention of filtered bicarbonate.

In patients with chronic respiratory failure, the control of ventilation tends to shift from the respiratory center in the brainstem to the peripheral chemoreceptors located in the carotid and aortic bodies. As the arterial pCO<sub>2</sub> rises, the central respiratory center becomes less sensitive to the rising PaCO<sub>2</sub> level acting as a stimulus for inducing hyperventilation. In fact, ventilation is driven in this situation by the hypoxemia that stimulates the peripheral chemoreceptors. The initiation of supplemental oxygen in someone with hypoxemia and hypercarbia (for example, a patient with Duchenne muscular dystrophy who presents with respiratory distress) will abolish the hypoxic drive for maintaining ventilation and may lead to worsening CO<sub>2</sub> narcosis. This is because supplemental oxygen will correct this patient's hypoxemia, but will not address the hypoventilation that caused the raised PaCO<sub>2</sub> levels in this patient in the first place.

The compensatory changes that take place in the setting of chronic respiratory acidosis and alkalosis are different from those occurring in the setting of acute respiratory acidosis or alkalosis (as shown in **Table 3**). Besides the increase in plasma bicarbonate, the renal response also includes an increase in chloride excretion, causing hyponatremia. This loss of chloride balances the increase in plasma bicarbonate levels, thereby maintaining a normal plasma anion gap.

### Other Tests

Besides changes in blood gas values, patients with chronic respiratory failure can also develop polycythemia (due to chronic hypoxic stimulus) and in extreme cases, right ventricular hypertrophy with pulmonary hypertension (cor pulmonale). This can significantly affect their effort tolerance, which can be objectively measured and tracked with a six-minute walk test. These cases may also be further evaluated by electrocardiogram and echocardiography for the assessment of cardiac function. Assessment of pulmonary function by spirometry can be performed in children older than 6 years of age to monitor progression of chronic lung disease and to assess for improvement in response to therapies.

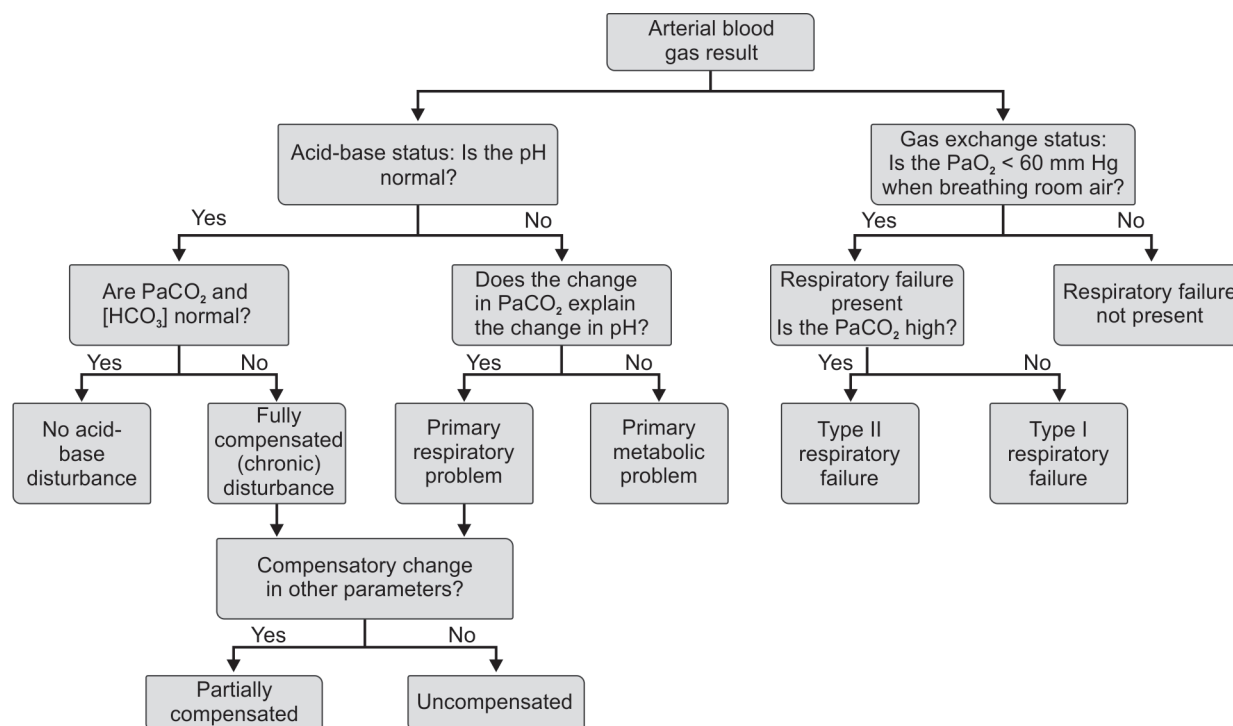
## MANAGEMENT

Management of acute respiratory failure in children generally requires treatment of the underlying cause and support of ventilatory function to maintain adequate oxygenation and tissue perfusion. Please refer to Chapter 7 regarding airway management, rapid sequence intubation and resuscitation. The correction of hypoxemia with supplemental oxygen can be the

**Table 2** Arterial blood gas values: Normal ranges and values from patients with respiratory failure

Arterial blood gas parameters	Normal values	Acute respiratory failure	Chronic respiratory failure	Acute on chronic respiratory failure
pH	7.35–7.45	7.26	7.32	7.28
PaCO <sub>2</sub>	35–45 mm Hg	60 mm Hg	60 mm Hg	70 mm Hg
PaO <sub>2</sub>	80–100 mm Hg	50 mm Hg	50 mm Hg	50 mm Hg
[HCO <sub>3</sub> ] <sup>-</sup>	24 ± 2 mEq/L	26 mEq/L	30 mEq/L	35 mEq/L
[Base excess]	0 ± 2 mEq/L	+2 mEq/L	+6 mEq/L	+10 mEq/L



**Flow chart 1** Blood gas classification and interpretation**Table 3** Changes in blood gas parameters in acute and chronic respiratory failure

	pH Change	HCO <sub>3</sub> Change
Acute respiratory acidosis	Each 10 mm pCO <sub>2</sub> Δ → pH Δ by 0.08	↑ HCO <sub>3</sub> by 1 mEq/L → each 10 mm ↑ in pCO <sub>2</sub>
Chronic respiratory acidosis	Each 10 mm pCO <sub>2</sub> Δ → pH Δ by 0.03	↑ HCO <sub>3</sub> by 3.5 mEq/L → each 10 mm ↑ in pCO <sub>2</sub>
Acute respiratory alkalosis	Each 10 mm pCO <sub>2</sub> Δ → pH Δ by 0.08	↑ HCO <sub>3</sub> by 2 mEq/L → each 10 mm ↓ in pCO <sub>2</sub>
Chronic respiratory alkalosis	Each 10 mm pCO <sub>2</sub> Δ → pH Δ by 0.17	↓ HCO <sub>3</sub> by 5 mEq/L → each 10 mm ↓ in pCO <sub>2</sub>

first step in most patients, but those with significant hypercarbia or respiratory acidosis may also require assisted ventilation. Continuous monitoring of oxyhemoglobin saturations with a pulse oximeter and/or periodic assessment of gas exchange with blood gases (when available) can help in determining the level of support needed for each individual patient according to their needs.

## Oxygen Therapy

**Nasal prongs** These deliver low-flow (1–2 L/min), low-concentration (30–35%) oxygen with two prongs that are inserted in the anterior nares and held by adhesive tape. These can be used with oxygen tanks in a clinic or walled supply in the hospital setting for patients that need lower level of support for maintaining adequate oxygenation.

**Face mask** Simple re-breathing type of face masks deliver about 30–60% concentration at flow rates of 6–10 L/min, since they have holes for the exit of exhaled air that also allow mixing with room air. They should be of adequate size, extending from the bridge of the nose to the tip of the chin, with a snug fit and put no pressure on the eyes. The nonbreathing types of facemasks have an oxygen reservoir attached to them, which allows patients to get pure oxygen held in the reservoir and minimizes mixing with room air. This helps to deliver a higher concentration of oxygen, up to 95–100% with flow rates of 10–12 L/min.

**Others** Other modalities for oxygen administration include oxygen hoods, which are used for neonates and young infants and can deliver up to 30% oxygen concentration without need for humidification; blow by oxygen for those who do not tolerate facemasks or nasal prongs, by holding the tubing close to the nose to deliver free-flow oxygen with variable concentration that cannot be regulated; oxygen tents in patients with croup (to minimize agitation); or via nasopharyngeal catheters.

## Noninvasive Positive Pressure Ventilation (NIPPV)

For patients that have significant hypercarbia and/or hypoxemia that may not respond to oxygen therapy alone, positive pressure support can be provided with less invasive modalities such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). This may be considered prior to the use of traditional invasive ventilatory support and can help avoid intubation and its related complications in several acute reversible as well as chronic conditions with acute decompensation. In general, noninvasive ventilation devices have evolved from use of negative pressure ventilators in patients with poliomyelitis in early 20th century to its current use for both short-term and long-term support in hospital as well as home settings. The decision to initiate NIPPV in patients with impending respiratory failure, those with an acute reversible illness or those with a chronic underlying disorder with acute decompensation, can be made

when certain criteria (**Box 3**) are met and no contraindications for NIPPV (**Box 4**) exist. The lack of skilled personnel/resources to intubate and provide ICU level care or use during transport to a higher level medical facility may be additional indications for the use of NIPPV. For patients with *pump failure* (neuromuscular weakness causing hypoventilation and chronic respiratory failure), the use of NIPPV at night time allows them to rest their fatigued respiratory muscles, improves their lung and chest wall mechanics by reducing microatelectasis and increasing chest wall excursion, and also helps to reset their central chemoreceptor sensitivity to the chronically elevated  $p\text{CO}_2$ s.

#### BOX 3 Indications for initiation of noninvasive positive pressure ventilation

Symptoms of hypoventilation and impending respiratory failure  
Underlying disorders  
Reversible acute conditions—pneumonia, acute asthma exacerbation, etc.  
Chronic respiratory disorders (associated with chronic respiratory failure)  
Neuromuscular disorders  
Upper airway obstruction  
Severe tracheobronchomalacia  
Patients with progressive physiologic impairment  
Nocturnal hypercapnia  
Vital capacity < 15 mL/kg  
Inspiratory force < 20 cm  $\text{H}_2\text{O}$   
Poor cough or secretion clearance with/without atelectasis.

A wide variety of oronasal interfaces (nasal prongs, nasal masks, oronasal masks, total face mask), circuits (single limb or double limb for inhalation and exhalation) and devices with a variety of modes are now available. CPAP is the preferred modality in patients with upper airway obstruction or tracheobronchomalacia or significant atelectasis as it helps to stent open their airways with the continuous positive pressure and maintains adequate airflow. However, BiPAP may be preferable in patients with significant hypoventilation where the higher inspiratory positive airway pressure (IPAP) ensures adequate lung expansion and air entry, and the subsequent lower expiratory positive airway pressure (EPAP) ensures adequate exhalation at a lower pressure. There are 3 different modes that are commonly used with BiPAP, which include:

**Spontaneous (S)** Where the patient's own inspiratory effort triggers the device and cycles it to EPAP.

**Timed (T)** The cycling between IPAP and EPAP is timed by the machine based on the rate of breaths/min set up on the machine.

**Spontaneous/Timed (S/T)** Similar to the spontaneous mode, the device is triggered by the patient's inspiratory effort. However, there is a back-up rate that is set to ensure that if the patient does not take enough spontaneous breaths/min, then the machine provides the minimum back up rate that has been set.

#### BOX 4 Contraindications for use of noninvasive positive pressure ventilation

Unstable airway/unable to protect airway  
Hemodynamically unstable patient  
Uncooperative, agitated patient  
Respiratory arrest, coma or obtundation due to  $\text{CO}_2$  narcosis  
Need for controlled ventilation  
Acute abdominal pathology or recent esophageal surgery  
Facial injury/trauma/burns/anomalies interfering with mask fitting.

**Complications** from NIPPV include facial skin breakdown or necrosis due to repeated pressure (especially on bridge of nose), gastric insufflation (especially in patients with esophageal reflux),

sinus problems, drying and thickening of oral secretions, and eye irritation from airflow leaks from mask. Barotrauma from NIPPV is less likely as the peak pressures usually never go beyond 25 cm  $\text{H}_2\text{O}$  and over distension generally activates the Hering-Breuer inflation reflex. Aspiration from vomiting while wearing a pressurized facemask can be avoided with careful selection of patients for NIPPV (avoiding use in patients with abdominal disorders and those who are obtunded or unable to protect their airways).

### Positive Pressure Ventilation

A majority of patients with respiratory failure will require positive pressure ventilation, especially if they are not suitable candidates for or have failed noninvasive ventilatory support. For delivery of positive pressure support, most patients require endotracheal intubation but in those with chronic respiratory failure, placement of a tracheostomy tube may be necessary to provide a secure, longer-term access to the airway. There are numerous ventilator devices, modes and approaches and these are discussed in detail in Chapter 8.5.

### Prone Positioning

In addition to the use of positive pressure ventilation, several adjunctive strategies, such as prone positioning have been used in patients with acute respiratory distress syndrome (ARDS) in the ICU setting. Because ARDS can have a nonhomogenous distribution and there is a gravity-dependent gradient of opacities evident on imaging, prone positioning allows for better aeration and perfusion of the larger, more posterior portions of the lungs, thereby maintaining ventilation/perfusion matching.

### Inhaled Nitric Oxide

Use of inhaled nitric oxide (iNO) is another adjunctive therapy that is helpful in patients with ARDS who have pulmonary hypertension, as it helps to reduce pulmonary artery pressures. It has also been used in neonates with persistent pulmonary hypertension of the newborn with improved oxygenation and reduced need for extracorporeal membrane oxygenation (ECMO).

### High Frequency Oscillatory Ventilation

High frequency oscillatory ventilation allows recruitment of lung units with higher mean airway pressures while limiting ventilator-induced lung injury by using extremely small tidal volumes and lower peak inspiratory pressures. This allows lungs to be ventilated on the steeper and more compliant portion of the pressure volume curve. Gas exchange occurs with diffusion and pendelluft and patients have to be deeply sedated and paralyzed while on this mode of ventilation.

### Negative Pressure Ventilation

Negative pressure ventilation creates a pressure gradient between the mouth and alveoli by lowering the body surface pressure below atmospheric pressure. This allows air to flow into the lungs without needing endotracheal intubation. The negative pressure is generated around the patient's chest wall or abdomen using a tank (the so-called *iron lung* that was used in polio epidemic in 1950s), body suit or poncho, or as a cuirass or shell. The negative intrathoracic pressures also enhance venous return as opposed to traditional positive pressure ventilators that reduce venous return. This may be an option for patients who require long-term respiratory support but want to avoid the use of a tracheostomy or facial masks used with other noninvasive ventilation devices.

### Extracorporeal Membrane Oxygenation

For patients with severe refractory respiratory failure that is not improving despite high levels of positive pressure support, gas

exchange can be achieved with an artificial membrane instead of the alveolar capillary membranes. This is done by diverting blood flow away from the lungs into an extracorporeal (outside the body) device that can oxygenate the blood and then pump it back into the systemic circulation. This can be done until the lungs recover from the primary insult or disease process that caused respiratory failure in the first place. There are two major configurations through which ECMO support is provided; venoarterial or venovenous. Both approaches require the placement of large cannulas in the major blood vessels to allow blood to be withdrawn and returned to the patient after oxygenation. Systemic anticoagulation is used to prevent clotting of the blood in the circuit but it increases the risk of bleeding as well. It also requires frequent monitoring to ensure the level of anticoagulation is maintained appropriately. Complications from ECMO include infection, bleeding, circuit failure or rupture and fluid retention. Once the patient recovers, ECMO support can be weaned and the patient's vessels are decannulated. Providing ECMO support requires a whole multidisciplinary team of cardiothoracic surgeons, respiratory therapists, intensivists and nurses.

## OUTCOME AND PROGNOSTIC FACTORS

The overall prognosis of children with respiratory failure depends on the underlying cause and predisposing conditions/risk factors mentioned above. Acute respiratory failure related to infectious disorders, when treated with adequate respiratory support while the infection resolves, is generally associated with good outcomes. However, ARI still accounts for the largest number of deaths in children worldwide. For patients with chronic respiratory failure, provision of long-term therapies and supplemental oxygen/positive pressure support (if needed) can help prevent secondary complications. When an acute process/exacerbation causes respiratory failure in someone with an underlying chronic lung or systemic disorder, then prognosis is generally dependent on the severity of the underlying condition.

## PREVENTION

Prevention of respiratory failure involves timely initiation of therapies for ARIs. Ensuring timely and age-appropriate immunizations for common vaccine-preventable diseases is an important public health strategy for all healthy children and is especially important for children with chronic lung, heart or neuromuscular conditions. Use of appropriate controller medications for asthma can help prevent acute severe exacerbations that could progress to respiratory failure if not promptly treated. Preventive care also involves planning of respiratory support for patients with chronic respiratory conditions or progressive neuromuscular disorders. Ongoing monitoring of lung function by spirometry can be helpful in tracking the decline in lung function over time. Most patients with neuromuscular weakness whose forced vital capacity has dropped below 30% of normal predicted values are at risk for nocturnal hypoventilation and may require night time support with BiPAP. If their end tidal  $\text{CO}_2$  level is more than 45 mm Hg while awake or if they have difficulty in breathing along with daytime oxyhemoglobin saturations less than 95%, then further

support may still be needed during daytime as well. Paying close attention to use of airway clearance techniques (postural drainage, huff cough or the use of mechanical insufflation-exsufflation device or CoughAssist) to prevent atelectasis and mucus plugging in patients with neuromuscular disorders can also help to minimize respiratory morbidity. Placement of tracheostomy for use of long-term positive pressure support may be considered for those with chronic respiratory failure with careful weaning of support as the underlying condition improves.

### IN A NUTSHELL

1. Respiratory failure is the inability of the respiratory system to maintain adequate oxygenation of the blood and body tissues, or the loss of its ability to ventilate adequately.
2. The four major causes of hypoxemia are ventilation perfusion mismatch, diffusion block, hypoventilation and shunt.
3. Acute respiratory failure can occur with several respiratory and non-respiratory acute illnesses, while chronic respiratory failure tends to occur in children with underlying conditions that affect ventilation or gas exchange.
4. Clinical assessment of a child in respiratory distress should involve an assessment of their appearance, perfusion to the skin and work of breathing.
5. Differential diagnosis of respiratory failure includes several acute or chronic disorders that cause tachypnea, metabolic acidosis or inadequate tissue perfusion.
6. Arterial blood gases are an important tool for initial assessment as well as for monitoring of the response to therapy in patients with respiratory failure.
7. Management involves treatment of underlying cause and supportive care.
8. Noninvasive ventilatory support should be considered in patients with acute or chronic respiratory failure as a means to avoid intubation.
9. Outcomes for children with respiratory failure depend on the severity of the underlying disease process.
10. Prevention involves protection against respiratory pathogens and prompt recognition of impending respiratory failure to initiate therapies.

### MORE ON THIS TOPIC

- Dobyns EL, Carpenter TC, Durmowicz AG, Stenmark KR. Acute respiratory failure. In: Chernick V, Boat TF, Wilmott RW, Bush A. *Kendig's Disorder of the Respiratory Tract in Children*. 7<sup>th</sup> ed. Philadelphia: Saunders; 2006. pp. 224-42.
- Gutierrez JA, Duke T, Henning R, South M. Respiratory failure and acute respiratory distress syndrome. In: Taussig LM, Landau LI. *Pediatric Respiratory Medicine*. 2<sup>nd</sup> ed. Philadelphia: Mosby; 2008. pp. 253-74.
- Malley WJ. *Clinical Blood Gases: Assessment and Intervention*. 2<sup>nd</sup> ed. St Louis: Elsevier; 2005.
- Weiner DJ. Respiratory failure in children. In: Panitch H. *Pediatric Pulmonology: Requisites in Pediatrics*. Philadelphia, PA: Elsevier; 2005. pp. 208-22.
- West JB. *Respiratory Physiology: The Essentials*. 9<sup>th</sup> ed. Baltimore: Lippincott Williams and Wilkins; 2012.

## Chapter 8.5

# Mechanical Ventilation

*Dinesh Raj, Rakesh Lodha*

Mechanical ventilation refers to artificially blowing gases into the patients' lungs to maintain oxygenation and remove carbon dioxide. Ventilators have evolved from negative pressure ventilation in the 1950s to the current generation of positive pressure ventilation. During mechanical ventilation, the ventilator either alone or in conjunction with the patient's effort generates a force to move gases into the lungs. For movement of gas through the airways, the force should overcome the elastic and resistive components of the lung, airways, and chest wall. The current era of mechanical ventilation focuses on making the child comfortable on mechanical ventilation, minimizing asynchrony, and using noninvasive route wherever possible. Different strategies of mechanical ventilation in different diseases have improved the outcome of critically ill children. This chapter aims to familiarize the reader with the physiologic basics and different modes of mechanical ventilation. The chapter also discusses the initial settings for various diseases and the common strategies used for common lung conditions needing mechanical ventilation. Indications of mechanical ventilation are listed in **Box 1**.

### BOX 1 Indications of mechanical ventilation

1. Any condition causing hypoxemia and/or hypercarbia [pneumonia, acute severe asthma, acute lung injury (infections, inhalational injuries), respiratory distress syndrome, pulmonary edema, heart diseases like myocarditis, congenital heart disease]
2. Increased work of breathing (septic shock, pneumonia, bronchiolitis, heart diseases)
3. Decreased respiratory drive (head trauma, poisonings, apnea, altered mentation due to any cause)
4. Neuromuscular diseases (Guillain-Barré syndrome, spinal muscular atrophy, etc.)
5. Reduction of raised intracranial pressure in certain conditions
6. Issues related to chest wall, diaphragm and pleura (flail chest, congenital diaphragmatic hernia, pneumothorax, massive pleural effusion)
7. Elective ventilation for surgeries, invasive procedures, etc.
8. Postoperative state.

## PHYSIOLOGY OF GAS EXCHANGE AND LUNG MECHANICS

All the air that is inspired does not take part into gas exchange. The volume of air in the airways which does not take part into gas exchange due to lack of a diffusing membrane is called anatomical dead space. Physiological dead space or total dead space is the combination of anatomical dead space and the alveoli which are ventilated but not perfused. The presence of endotracheal (ET) tube/mask (for noninvasive ventilation) adds to the dead space in ventilated children. Alveolar ventilation is a direct determinant of pulmonary gas exchange. Alveolar ventilation is given by:

$$\text{Alveolar ventilation} = (V_T - V_D) \times \text{RR}$$

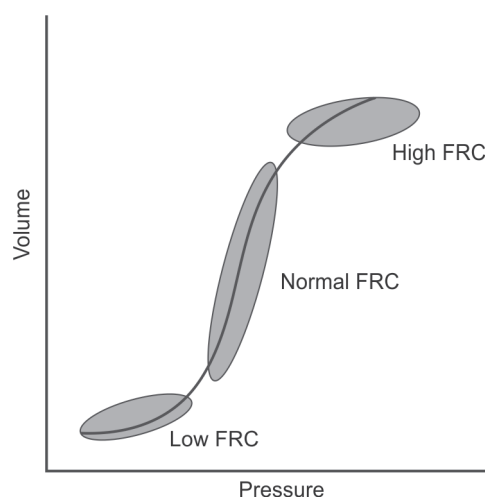
where,  $V_T$  is tidal volume,  $V_D$  is dead space and RR is respiratory rate. Alveolar ventilation can be increased by increasing tidal volume or respiratory rate.

The causes of hypoxemia in a ventilated child include ventilation-perfusion mismatch, right to left shunting, diffusion

abnormalities and hypoventilation. Inadequate ventilation relative to perfusion is responsible for ventilation-perfusion mismatch leading to hypoxemia in majority of cases. Determinants of oxygenation include mean airway pressure (MAP) and fraction of inspired oxygen concentration ( $\text{FiO}_2$ ). MAP can be increased by increasing peak inspiratory pressure (PIP), inspiratory time and positive end-expiratory pressure (PEEP), and changing the flow to attain a square waveform. Increase in MAP beyond a certain extent leads to overdistension and may not improve oxygenation.  $\text{CO}_2$  removal depends on alveolar minute ventilation. Increasing the respiratory rate and tidal volume (TV) improves  $\text{CO}_2$  removal. In pressure-controlled ventilation (PCV), TV can be increased by increasing the pressure difference (PIP-PEEP).

The targets for partial pressure of arterial oxygen ( $\text{PaO}_2$ ) and partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) are 50–80 mm Hg and 40–50 mm Hg, respectively. Higher  $\text{CO}_2$  (up to 60 mm Hg) are accepted in certain scenarios, like chronic lung disease, severe hyaline membrane disease (HMD), and acute respiratory distress syndrome (ARDS) as a part of lung protective strategy (permissive hypercapnia). Compliance, an indicator of the elastic property of the lung, is a ratio of the change in volume with change in pressure ( $\Delta V/\Delta P$ ). Compliance can change in different disease processes. Furthermore, it can change during the disease process in a patient, either recovering or worsening. The slope of the pressure volume curve at any point in time gives the compliance at that particular point (**Fig. 1**). Static compliance is measured at zero airflow and dynamic compliance is measured during airflow through the lungs. Dynamic compliance reflects lung and chest wall stiffness, besides airway resistance. In a stiff lung (e.g., pulmonary edema, consolidation), both are low. If only the dynamic compliance has decreased, it means that the airway is obstructed, e.g., ET tube obstruction or bronchospasm.

Airway resistance is the obstruction to airflow in the airways. It is given by the ratio of change in the pressure to airflow ( $\Delta P/V$ ). The resistance to the flow of air through a tube is proportional to the length of the tube and inversely proportional to the fourth power of radius, as given by the Poiseuille's equation. The airway resistance is affected by the lumen/patency of the airways, presence of secretions, ET tube characteristics, and airway tone. Increase in airway resistance leads to increase in work of breathing. The largest appropriately sized ET tube (as per age) should be put and patency maintained to keep airway resistance minimum.



**Figure 1** Pressure-volume curve—compliance curve  
Abbreviation: FRC, functional residual capacity



The condensations in the ventilator circuits should be avoided. Airway resistance can be monitored on a ventilated child using the pressure-volume (PV) loops (discussed later).

Time constant is the product of compliance and resistance. It is a measure of the time taken for pressure to equilibrate between the proximal airways and the alveoli. In simple terms, it indicates how quickly the lungs can inflate and deflate. Inspiratory time constant is nearly half as long as expiratory time constant. In diseases with longer time constants, meconium aspiration, e.g., the inspiratory time should be kept adequate to allow TV to be delivered, and adequate expiratory time for exhalation. Respiratory distress syndrome (RDS), on the other hand, is typically associated with shorter time constants.

## EQUATION OF MOTION

The relation between volume of gas ( $\Delta V$ ) going to any part of the lung, gas flow ( $V$ ) and applied pressure ( $\Delta P$ ) is given by the equation

$$\Delta P = \Delta V/C + V \times R \times k$$

where  $C$  is lung compliance,  $R$  is airway resistance and  $k$  is a constant, which defines the end expiratory pressure. This equation is known as the equation of motion for the respiratory system. In simple terms, the pressure (exerted by the respiratory muscles and ventilator) should overcome the elastic load ( $\Delta V/C$ ) and the resistive load ( $V \times R$ ). Elastic load is the pressure needed to overcome the chest wall recoil, and resistive load is the pressure needed to overcome the flow of air through the airways. From this equation of motion, we can see that change in pressure will lead to change in volume and flow, if the compliance and resistance are constant; similarly, if volume is changed, pressure and flow will change.

## VENTILATION CONTROLLERS

Inspiration is controlled in mechanical ventilation, whereas expiration is passive. The four variables which can be controlled during inspiration are pressure, volume, flow and time. And the manner in which each of these is controlled, decides the mode of ventilation.

### Pressure Control (Fig. 2)

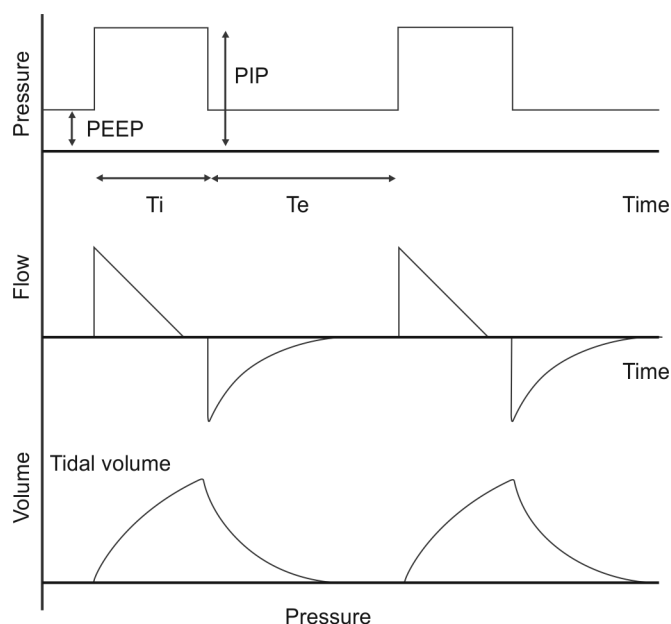
A constant pressure is maintained during inspiration irrespective of the compliance and resistance of the respiratory system. During PCV, volume and flow are dependent variables. With changes in compliance and resistance, the delivered TV may vary. The flow utilized is of a decelerating pattern, with high flow in initial part of inspiration with gradual decline. The expiration starts after the inspiratory time is completed. In the current ventilators, once flow decreases to a predetermined fraction (usually 25%) of the initial flow, expiration ensues (flow cycling).

### Flow/Volume Control (Fig. 3)

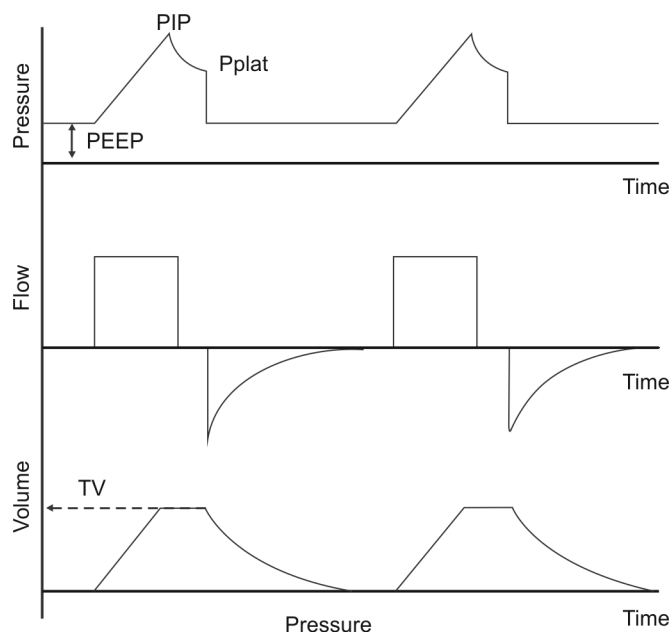
In flow control, the flow is controlled as a function of preset TV. Flow control is also called volume control by some as a preset volume is delivered. However, flow control is an appropriate term as these ventilators measure flow and calculate volume from flow measurement. The flow and volume remain constant with variable pressure. A comparison of volume and pressure control is given in Table 1.

### Phase Variables

Phase variables control the various phases of the respiratory cycle, i.e., initiation of inspiration, maintaining inspiration, switching from inspiration to expiration, and through expiration.



**Figure 2** Scalar waveforms for pressure-controlled ventilation  
Abbreviations: PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; Ti, inspiratory time; Te, expiratory time



**Figure 3** Scalar waveforms for volume-controlled ventilation  
Abbreviations: PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; TV, tidal volume; Pplat, plateau pressure

### Trigger Variable

Trigger variable is responsible for the initiation of the inspiration. Mandatory breaths initiated by the ventilator are time-triggered. However, ventilator can assist the breaths initiated by the patient by sensing change in pressure or change in flow. In pressure triggering, the ventilator detects a drop in pressure in the circuit and initiates inspiration. In flow triggering, the ventilator detects a reduction in flow in the expiratory limb of the circuit. The trigger setting needs to be set appropriately as a very sensitive setting may result in inappropriate ventilator triggering with even cardiac pulsations. On the other hand, an insensitive trigger setting may increase the

**Table 1** Comparison of volume control and pressure control ventilation

	Volume control	Pressure control
Tidal volume	Set	Variable
Airway pressure	Variable	Set
Inspiratory flow	Constant	Decelerating
Minute ventilation	Set	Variable
Advantages	Less risk of volutrauma Automatic weaning as compliance improves	Less risk of barotrauma Initial high flow (decelerating flow) better for stiff lungs
Disadvantages	Risk of barotrauma in stiff lungs with unmonitored peak pressures Flow starvation in air hungry patients due to constant flow	Variable tidal volume Volutrauma can result if peak inspiratory pressure not decreased with improvement in compliance

patient's work of breathing. Work of breathing and patient's comfort are better with flow triggering as lesser effort is needed for changing flow than for changing the pressure in the circuit.

#### Limit Variable

During inspiration, if a variable is not allowed to exceed a preset level, it is referred to as a limit variable. The limit variable once reached is maintained during inspiration. Pressure, volume or flow is used as a limit variable.

#### Cycle Variable

Cycle variable determines the switch from inspiration to expiration. The commonly used cycle variable is time. Pressure, volume and flow can also be used as cycle variable. Using flow as a cycle variable facilitates synchronization of expiration.

#### Baseline Variable

The variable controlled in expiration is called baseline variable, i.e., end-expiratory pressure.

### VENTILATOR TERMINOLOGY (FIG. 4)

#### Peak Inspiratory Pressure

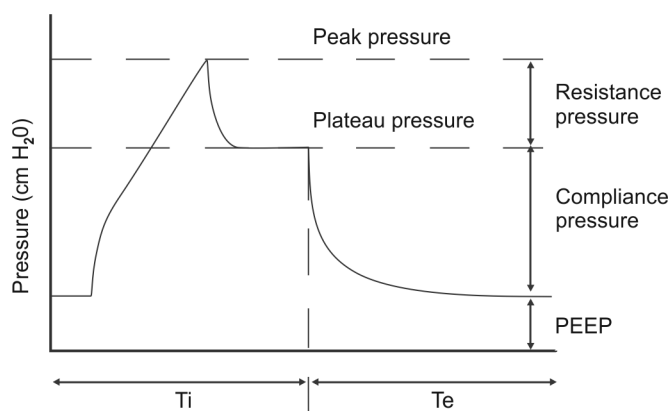
It is the maximum pressure during the inspiratory phase of the breath ventilating the child. PIP is needed to inflate alveoli and improve oxygenation. High PIP may lead to barotraumas.

#### Positive End-expiratory Pressure

It is the pressure maintained in airways at the end of exhalation to keep alveoli open. PEEP is needed to improve functional residual capacity, oxygenation, and avoiding reopening and closing of alveoli which can cause atelectotrauma. Excessive PEEP can lead to overdistension, and reduced venous return and TV.

#### Respiratory Cycle

One respiratory cycle includes inspiration and expiration. The duration for which patient is inhaling is inspiratory time. The duration for which patient is in expiration is expiratory time. I:E ratio is the ratio of inspiratory time and expiratory time. Normally, I:E ratio is kept at 1:2. Inverse ratio ventilation may be needed in ARDS to improve oxygenation.



**Figure 4** Pressure-time waveform for volume-controlled ventilation  
Abbreviation: PEEP, positive end-expiratory pressure

#### Tidal Volume

Volume of each breath, set in volume-controlled ventilation (VCV). It is needed for oxygenation and CO<sub>2</sub> removal.

#### Rise Time

The beginning of a breath can be either fast or slow depending on the flow rate. A faster rise is needed for patients who are air hungry. A slower rise provides laminar flow and better gas distribution.

#### Mean Airway Pressure

The average airway pressure during one complete respiratory cycle is known as mean airway pressure and is given by:

$$MAP = \frac{K (Ti \times PIP) + (Te \times PEEP)}{Ti + Te}$$

where k is a constant depending on the shape of the waveform, Ti is inspiration time and Te is expiration time. Increasing MAP improves oxygenation.

#### Plateau Pressure

Plateau pressure (Pplat) is the pressure at equilibrium applied to small airways and alveoli during inspiration. In normal lungs, PIP is slightly above Pplat. With increasing TV and worsening compliance, both PIP and Pplat increase proportionately. Increased airway resistance due to any cause leads to increase in PIP with no change in Pplat.

#### Intrinsic Positive End-expiratory Pressure/ Auto-positive End-expiratory Pressure

If the expiratory time is not long enough, the exhalation may not be completed. A fresh breath may be given to the patient while the expiratory flow has not become zero. This leads to air trapping and auto-PEEP. Auto-PEEP also increases the work of breathing as the patient has to generate pressure above the sum of auto-PEEP and trigger pressure to trigger a breath from the ventilator.

#### FiO<sub>2</sub>

It is the fraction of inspired oxygen. It can range from 0.2–1.

### TYPE OF BREATHS

Type of breaths in a ventilated patient could be mandatory, assisted or spontaneous. If inspiratory cycling is determined by the ventilator, such a breath is designated as mandatory breath, which is initiated and terminated by the ventilator. If the breath is triggered by the patient, it is referred to as triggered or assisted breath. In spontaneous breathing, cycling (inspiratory and expiratory) and

limit, both are determined by the patient. In supported breaths, inspiratory and expiratory cycling is determined by the patient, but the breaths are supported by the ventilator to a preset limit.

## MODES OF VENTILATION

### Intermittent Mandatory Ventilation

Intermittent mandatory ventilation is a ventilation mode in which the machine delivers control (mandatory) breaths and allows the patient to take spontaneous breaths in between. As machine frequency is preset and independent of the patient's own efforts, breath stacking may occur. The control could be either volume control or pressure control. IMV has now been replaced by more sophisticated modes which allow synchronization and other benefits.

### Synchronized Intermittent Mechanical Ventilation

Synchronized intermittent mandatory ventilation (SIMV) is a ventilation mode which gives either assisted breaths (patient-triggered) or time-triggered machine breaths. The control could be either pressure or volume control. Just prior to time-triggered breath, there is a synchronization window, during which if the patient triggers a breath, it is assisted. If no effort is observed from the patient, the machine delivers the time-triggered breath. In between mandatory breath, patient is free to take spontaneous breaths which are limited by the patient. Synchronization prevents breath stacking (i.e., mandatory breath over and above spontaneous breath). SIMV has the advantages of lowering MAP, decreasing respiratory muscle atrophy and facilitating weaning. The disadvantages include rapid weaning leading to muscle fatigue. However, this can be offset by adding pressure support to SIMV. SIMV is indicated in actively breathing patient to provide partial ventilatory support.

### Assist/Control Ventilation

Assist ventilation (AV) is a ventilation mode in which patient determines the respiratory rate and minute ventilation. It is used in patients with a spontaneous and stable respiratory drive. The ventilator delivers a breath of a preset TV in response to patient's trigger (assist). If the patient triggers less than the set frequency, the machine delivers time-triggered mandatory breaths (control). The patient is not allowed to breathe spontaneously. Advantages include decreased work of breathing, and ability to control the minute ventilation by the patient. However, it can lead to respiratory alkalosis in an anxious child due to excessive triggering, as all breathing efforts detected will trigger the ventilator to deliver the breath. AC mode can be used to provide full ventilatory support in a child with a stable drive.

### Pressure Support Ventilation

Pressure support ventilation (PSV) is a ventilation mode which allows supporting of spontaneous breaths with pressure; the child triggers the breath and controls the cycling to expiration by change in flow. The breaths are supported to a preset pressure support level, and terminated when the patient's inspiratory flow demand decreases below a threshold. Herein, the patient controls the rate, TV and flow. Advantages include decreased work of breathing and enhanced patient comfort due to spontaneous breathing. It can also be used as a weaning tool by a gradual reduction in pressure support. However, it can only be used in a spontaneously breathing individual.

### Pressure-regulated Volume Control

Pressure-regulated volume control (PRVC) is a dual control mode of mechanical ventilation in which a preset TV is delivered at the lowest possible PIP by alterations in flow rate

and inspiratory time. In conventional VCV, the flow is constant, so increase in airway resistance leads to increase in PIP to deliver the volume. However, in PRVC, with an increase in airway resistance, the flow decreases to prevent PIP from rising, but to deliver the set volume, inspiratory time is increased. In a way, both pressure and volume can be controlled in PRVC. The advantages of PRVC include delivering a constant TV while minimizing PIP. However, ventilator support may be decreased in patients breathing at a high respiratory rate. PRVC can be utilized in patients with fluctuating lung mechanics.

### Continuous Positive Pressure Ventilation

This is not a ventilation mode but a commonly used respiratory support modality. Continuous positive pressure ventilation (CPAP) delivers PEEP above the atmospheric pressure. CPAP internally splints the lungs and prevents the alveoli from collapsing. There is improvement in lung compliance and reduction in work of breathing. Alveolar recruitment improves oxygenation and prevents atelectasis. However, hyperinflation and air leaks may occur if PEEP is kept inappropriately high. CPAP can be administered noninvasively on spontaneously breathing patients by nasal and oronasal/nasopharyngeal route. CPAP is indicated in postextubation states, mild HMD, apnea of prematurity, and weaning-prolonged ventilator-dependent infants.

### Bilevel Positive Airway Pressure

Bilevel positive airway pressure (BiPAP) is similar to CPAP with the difference being those two different levels of pressure for inspiration and expiration. Due to the difference in levels of pressure, positive pressure breath is delivered. The switch from one level to other is synchronized with the patient. The triggering in BiPAP can be spontaneous, spontaneous/timed or timed. BiPAP can be used noninvasively to support children with chronic problems like neuromuscular disorders, obstructive sleep apneas, and obesity-hypoventilation syndromes. It can also be utilized in acute conditions including pulmonary edema and pneumonia.

## VENTILATOR SETTINGS

**Table 2** highlights the parameters to be adjusted in pressure- and volume-controlled modes and the initial settings. However, the strategy for different lung diseases is different and initial settings should take into consideration the underlying lung pathology. The various parameters determining oxygenation and CO<sub>2</sub> removal are given in **Table 3**.

## MECHANICAL VENTILATION IN CERTAIN COMMON SCENARIOS

### Ventilation of Nondiseased Lungs

Ventilation of children with healthy lungs is usually not difficult. Not much can be attained by choosing one mode over another. Ventilation can be done using physiological rates with either volume or pressure mode. A TV of 6–8 mL/kg is appropriate. If pressure mode is chosen, a pressure level guided by adequate chest rise and optimal saturation is acceptable; this is usually 8–10 cm H<sub>2</sub>O above PEEP. Physiological PEEP of 3–4 cm H<sub>2</sub>O is appropriate. Inspiratory time should also be based on the age of the child (0.4 sec for newborns and infancy, 0.6 sec for toddlers and preschool children, and 0.8–1 sec for older children and adolescents).

### Asthma

Asthma is characterized by increased airway resistance due to bronchospasm, mucosal edema and airway secretions. Obstruction

**Table 2** Initial settings for pressure- and volume-controlled mode

Settings	Pressure-controlled mode	Volume-controlled mode
Rate	Age-related	Age-related
PEEP	3–5 cm H <sub>2</sub> O (lower for obstructive diseases)	3–5 cm H <sub>2</sub> O (lower for obstructive diseases)
Volume	-	6–10 mL/kg
PIP	Titrate to chest rise	-
Ti	Usually I:E ratio of 1:2, can increase Te in case of obstructive diseases	Usually I:E ratio of 1:2, can increase Te in case of obstructive diseases
FiO <sub>2</sub>	Target adequate oxygenation	Target adequate oxygenation

Abbreviations: FiO<sub>2</sub>, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; Ti, inspiratory time; Te, expiratory time.

to airflow predominantly during expiration is the problem in asthma. Hence, ventilating a child with obstructive lung disease is difficult because in conventional mechanical ventilation, expiration is passive. The idea is to prolong expiration by keeping low rates with long expiratory time; the initial rates are usually about half the physiological rates. Air trapping (auto-PEEP) is to be avoided. Low levels of PEEP are advised. PCV is avoided as the TV delivered may vary greatly with changes in airway resistance and bronchospasm. VCV with constant flow may be better than pressure modes. VCV also allows the measurement of PIP and Pplat which can be used to assess response to therapy. Permissive hypercapnea should be targeted accepting pH as low as 7.2. Sedation and neuromuscular blockade may be required to minimize air leaks. Ketamine and fentanyl are the preferred drugs for sedation.

### Acute Lung Injury/Acute Respiratory Distress Syndrome

Acute lung injury (ALI)/ARDS is characterized with decreased lung compliance leading to respiratory failure. Although diffuse infiltrates (whiteout in some cases) are evident on chest radiographs, the pattern of involvement is heterogenous with a predominant involvement of dependent regions and sparing of nondependent regions. As there are areas of atelectasis and consolidation interspersed with normal lung parenchyma, the ventilation is difficult and prone to ventilator-induced lung injury (VILI). Alveoli in the dependent areas or consolidated part of lung have a closing volume near end-expiration leading to alveolar collapse. These alveoli need to be reopened during inspiration. The repeated opening and closing lead to alveolar damage (atelectrauma). The strategy in ALI is to recruit lungs and keep the alveoli patent. This can be done using optimal PEEP which is needed to keep lung open and preventing atelectrauma. As a general principle, one can begin with a PEEP of 6–8 cm H<sub>2</sub>O and increase in increments of 1–2 cm H<sub>2</sub>O till adequate oxygenation (saturation of 90–92%) is attained. FiO<sub>2</sub> should be kept at 60% or below to prevent oxygen toxicity. Low TV (4–6 mL/kg) with low Pplat (< 30 cm H<sub>2</sub>O) are used to prevent volutrauma and barotraumas. These lung protective strategies can cause hypercapnea which is acceptable provided the pH is above 7.2 (permissive hypercapnea).

### Pneumonia

The principle of ventilation in pneumonia is similar to that of ALI/ARDS. The approach is to titrate the FiO<sub>2</sub> and PEEP to the severity and extent of the lung disease.

**Table 3** Measures to increase oxygenation and ventilation

Oxygenation	
Parameter	Comment
<b>Oxygenation</b>	
FiO <sub>2</sub>	Increasing FiO <sub>2</sub> beyond 0.6 increases oxygen toxicity
Mean airway pressure ↑ PIP ↑ PEEP ↑ Ti ↑ Flow (square waveform) ↑ Rate	High PIP may cause barotrauma High PEEP may decrease venous return May need to decrease rates Square waveform increases barotrauma May lead to auto-PEEP
<b>Ventilation</b>	
Minute ventilation ↑ TV (↑ΔP)  ↑ Rate ↑ Flow ↓ Te	High PIP causes barotrauma, low PEEP affects oxygenation and causes alveolar collapse May lead to auto-PEEP Increases barotrauma Leads to decrease in Ti causing ↓MAP/oxygenation

### Air Leak

While ventilating a child with air leak, the aim should be to reduce MAP as much as possible. FiO<sub>2</sub> can be increased to attain optimum oxygenation. Higher rates may be tried as alveoli have much shorter time constant than the interstitial air. If reduction in MAP is not tolerated, high frequency oscillatory ventilation (HFOV) may be attempted.

### WEANING OFF THE VENTILATOR

Weaning is defined as the transition from ventilatory support to complete spontaneous breathing. At the end of weaning, patient should be able to breathe spontaneously to maintain adequate gas exchange, following which the patient can be extubated. On one hand, prolonged ventilation is associated with complications [VILI, ventilator associated pneumonia (VAP), glottic edema], premature extubation can also be risky. The duration of weaning may be affected by a number of factors. The underlying disease for which ventilation was needed has a bearing on the duration of weaning. Weaning for elective ventilation for procedures or ventilation in the postoperative period may be rapid. However, ALI/ARDS may have to be weaned slowly once the stormy phase is over. Critically, ill children develop fluid overload which may decrease lung compliance affecting oxygenation and may prolong/delay weaning. Level of sedation may also affect extubation readiness. Presence of pulmonary hypertension and compromised cardiac function may also complicate weaning. **Box 2** lists some of the prerequisites for weaning.

#### BOX 2 Prerequisites for weaning

1. Cause of respiratory failure is passive or has improved substantially
2. Adequate oxygenation—able to maintain arterial oxygen saturation and partial pressure of arterial oxygen above 90% and 60 mm Hg, respectively on a fraction of inspired oxygen of < 0.4
3. Hemodynamic stability
4. Absence of anemia
5. Adequate mental status.



## Techniques of Weaning

Gradual reduction of ventilatory support (SIMV) is the commonly used technique of weaning as SIMV permits spontaneous breaths between machine breaths. The frequency of mandatory breaths is gradually reduced by 1–3 breaths per minute at each step. During this period, saturation must be monitored, and  $\text{PaCO}_2$  must be measured 30 minutes after decreasing the rates. The rapidity with which the rates can be lowered depends on the cardiopulmonary function of the patient. Once a frequency of mandatory breaths of 10–15 breaths per minute is reached, and blood gases and vital parameters are normal, the weaning prerequisites are fulfilled, extubation can be attempted.

### Spontaneous Breathing Trials

Spontaneous breathing using T-tube is frequently used for weaning. Spontaneous breathing trials (SBT) are usually tried either alone or with low levels of pressure support (5–7 cm  $\text{H}_2\text{O}$ ) or with CPAP for around half-an-hour. Most patients who fail an SBT usually do so within 20–30 minutes.

### Pressure Support Ventilation

Pressure support ventilation either alone or in combination with SIMV is sometimes used to facilitate weaning. PSV is started at around 5–10 cm  $\text{H}_2\text{O}$  and titrated upward to achieve a desired spontaneous TV (10–15 mL/kg) and desired frequency of 25/min or less. If patient tolerates this well, then pressure support can be gradually reduced.

### Automatic Tube Compensation

Sometimes, the resistance due to artificial airway increases the work of breathing, hampering weaning process. Automatic tube compensation available in some ventilators alleviates the resistance due to artificial airway, facilitating spontaneous breathing.

## Weaning Failure

Weaning failure is defined as the need to be put back on the ventilator (either as a failure of spontaneous breathing trial, or need to reintubate within 48 hours of extubation). Weaning failure is associated with signs of increased work of breathing (tachypnea, accessory muscle use, paradoxical abdominal breathing). The patient may have developed altered mentation, become agitated and diaphoretic.  $\text{CO}_2$  retention, hypoxemia and hypo/hypertension may develop. If the child fails a trial of spontaneous breathing, he should be put back on ventilation and one should wait for 24 hours to attempt a fresh SBT. For these children, other modalities of weaning may be tried including PSV and/or SIMV.

### Cuff Leak Test

As upper airway obstruction is one of the commonest causes of extubation failure, cuff leak test may be done to predict stridor postextubation. After deflating the cuff, an attempt is made to hear leak around the ET tube. A leak audible to the ear with the patient's head in neutral position may predict successful extubation.

## MONITORING

Meticulous monitoring is important to optimize respiratory support and prevent the potential complications of mechanical ventilation. Continuous monitoring of child's vital parameters, including heart rate, respiratory rate, oxygen saturation and blood pressure, is required. End-tidal  $\text{CO}_2$  monitoring if available is desirable. Clinical evaluation at regular intervals to assess child's respiratory efforts, air entry, capillary refill, increased work of breathing, and asynchrony with ventilation should be done. Arterial blood gas should be done to monitor  $\text{PaO}_2$  and  $\text{PaCO}_2$  at least 12 hourly or

half hour after change of settings. Chest radiograph may be needed at frequent intervals to assess the disease status, detection of complications, and the position of ET tube. Pulmonary graphics monitoring allows assessment of the change in mechanics of the respiratory system.

## Ventilator Graphics Monitoring

Ventilator graphics monitoring (**Box 3**) allows real-time measurements of the patient-ventilator interactions. Flow, volume and pressure are measured and displayed real time. From these measurements, compliance, resistance and work of breathing can be calculated. There are two types of graphics: scalars and loops. Scalars represent waveforms of pressure, volume or flow (y-axis) versus time (x-axis). Loops represent waveforms of pressure versus volume or flow versus volume.

### BOX 3 Ventilator graphics

1. Scalar waveforms: control variables (y-axis) versus time (x-axis)
  - Pressure waveform
  - Flow waveform
  - Volume waveform
2. Loop waveform: one control variable plotted against another
  - Pressure-volume loop
  - Flow-volume loop
3. Calculated values
  - Compliance
  - Resistance.

### Pressure Waveform

The shape of the pressure-time waveform depends on the breath type (square in PCV, and triangular in VCV). A negative deflection just preceding inspiration suggests triggering. Peak pressures and Pplat can also be estimated by measurements on the y-axis. Changes in compliance and resistance can affect the level of peak pressure and Pplat attained in VCV. The area under curve of the pressure waveform is the MAP. A significant rise in peak pressure relative to Pplat suggests airway obstruction. **Figures 2 and 3** depict pressure-time scalars for pressure and VCV, respectively.

### Flow Waveform

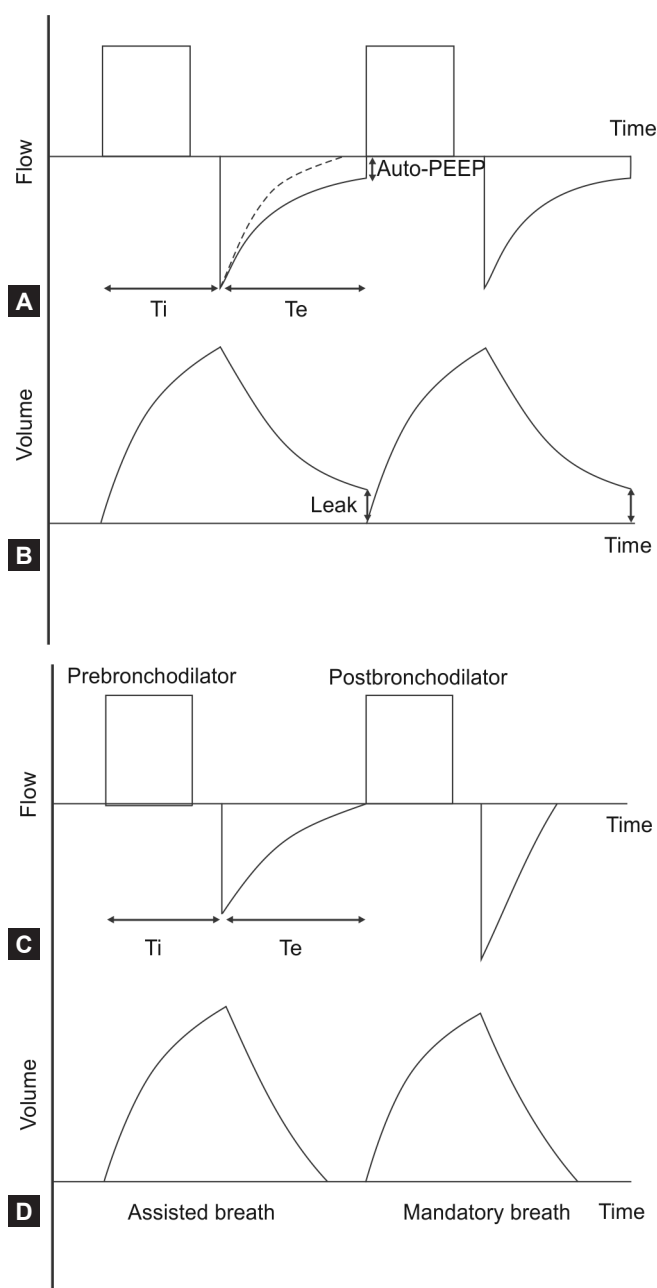
The type of flow, and hence the breath type, can be identified by looking at the flow waveform. Flow is decelerating in PCV and constant in VCV. Auto-PEEP can be identified if the expiratory flow is not reaching baseline. If the expiratory flow is deeply curved and takes long to reach baseline, it suggests airway obstruction. Decreased peak expiratory flow suggests air leak. Rise time can also be assessed by looking at the inspiratory flow limb. **Figures 2 and 3** depict flow-time scalars for pressure and VCV, respectively.

### Volume Waveform

The upstroke in volume waveform indicates inspiration and downstroke indicates expiration. Failure of the expiratory limb to reach baseline suggests ET leak, bronchopleural fistula, or auto-PEEP. **Figures 2 and 3** depict volume-time scalars for pressure and VCV, respectively. **Figures 5A to D** shows the information provided by scalars in monitoring patients on mechanical ventilation.

### Pressure-volume Loops

The slope of the PV loop indicates the elasticity of the lung. The difference in the inspiratory and expiratory limb of the PV loop, also known as hysteresis, indicates the resistive work of breathing. **Figure 6** depicts the loops observed in different breath types. The changes in compliance and resistance can be picked up by a careful look at the PV loops. With overdistension, the terminal



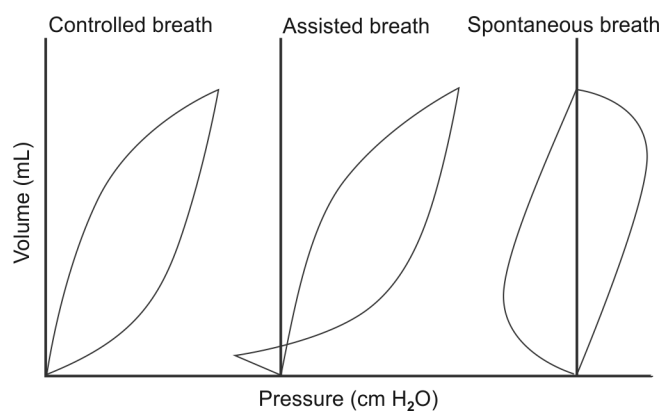
**Figures 5A to D** (A) Auto-PEEP; (B) Leak; (C) Bronchodilator response; (D) Assisted breath

**Abbreviations:** PEEP, positive end-expiratory pressure;  $T_i$ , inspiratory time;  $T_e$ , expiratory time.

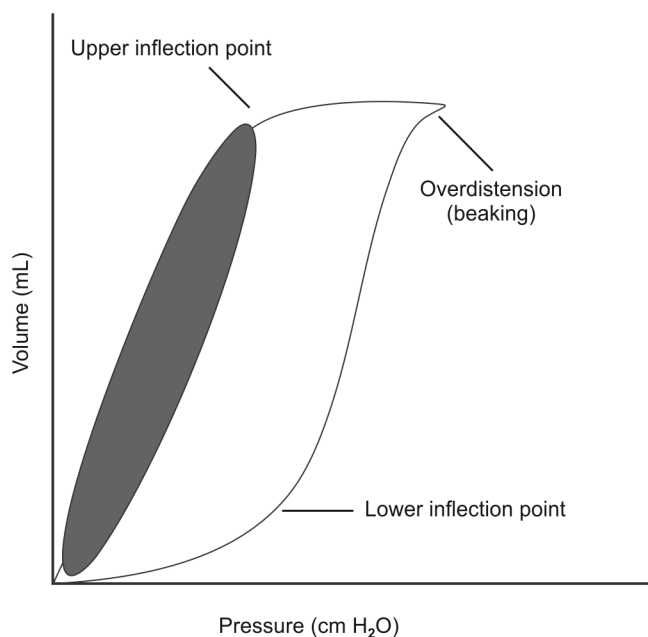
part of the inspiration assumes a beaked shape due to less volume change with the change in pressure (**Fig. 7**). With decrease in lung compliance in PCV, the loops shift downward and to right leading to fall in TV, while reverse is seen with improvement in lung compliance. However, in VCV, with decreased compliance the loop is shifted to right but needs higher pressure to achieve same volume (**Fig. 8**).

### Flow-volume Loops

The flow-volume loops depict the pattern of airflow during breathing (**Fig. 9**). The curve above x-axis is inspiratory limb and



**Figure 6** Pressure-volume loops for different types of breaths

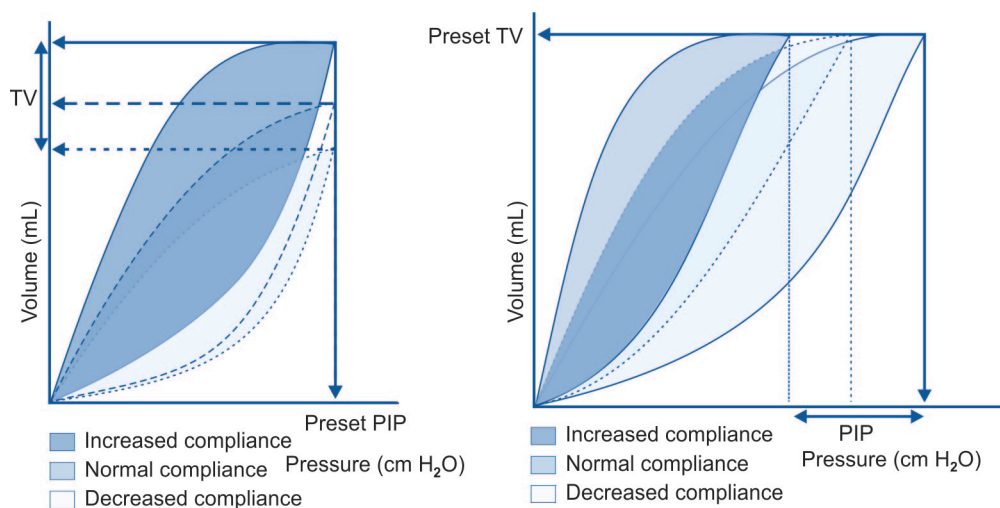


**Figure 7** Pressure-volume loop depicting the upper and lower inflection points and overdistension

the one below x-axis is the expiratory limb. Alteration in airway resistance due to various causes can be identified from these loops. Leak can be identified if the expiratory limb achieves the baseline prematurely. Presence of secretions leads to irregularities in the inspiratory limb.

### HIGH-FREQUENCY VENTILATION

High-frequency ventilation (HFV) utilizes supraphysiologic frequencies with small TV close to or below the anatomical dead space. As the TVs are small (around 1–3 mL/kg), peak pressures are low, and maximal MAP and alveolar recruitment in HFV is one of the lung protective strategies. HFOV is the common mode of HFV used in neonates and children. HFOV employs an oscillatory diaphragm which generates a rapidly altering gas flow to provide active inspiration and expiration. As the diaphragm moves back and forth, gas is pushed into the lungs and actively withdrawn. The frequency with which the diaphragm moves is the breathing frequency, and the magnitude of oscillations is called amplitude (or  $\Delta P$ ).



**Figure 8** Effect of change in compliance on pressure-volume loops for pressure-controlled ventilation (left) and volume-controlled ventilation (right)

Abbreviations: TV, tidal volume; PIP, peak inspiratory pressure.

The mechanism by which gas exchange is achieved in HFV is complex and differs from conventional ventilation. Initiation of HFOV can be associated with hypotension and hemodynamic instability because of the increased MAP leading to decreased venous return. Therefore, it is recommended that patient be hemodynamically stable and volume loaded before switching to HFOV.

High frequency oscillatory ventilation is generally used as a rescue mode in patients who fail on conventional ventilation primarily due to poor oxygenation. HFOV has been used with success in ALI and persistent pulmonary hypertension of the newborn (PPHN). Use in obstructive diseases should be cautious as HFOV may lead to intrinsic PEEP and active expiration may not be very effective in these scenarios.

The settings of HFOV include frequency, amplitude, MAP, percent inspiration, inspiratory bias flow and  $\text{FiO}_2$ . Oxygenation can be increased by increasing MAP and  $\text{FiO}_2$ .  $\text{CO}_2$  elimination is achieved by decreasing the frequency or by increasing the amplitude, inspiratory time and bias flow.

## COMPLICATIONS OF MECHANICAL VENTILATION

### Ventilator-induced Lung Injury

Ventilator-induced lung injury is the lung damage secondary to positive pressure ventilation. Mechanisms of VILI include physical disruption of cellular membranes and alveolar spaces due to mechanical forces and aberrant cellular response leading to inflammation. Degree of lung inflation is an important determinant of lung injury. Volutrauma and barotrauma, both are implicated in VILI. Atelectrauma, due to repeated opening and causing (recruitment-derecruitment) of alveoli is also implicated in VILI when ventilating at lower lung volumes. High inspired oxygen, due to oxidant stress, also contributes to lung injury. To

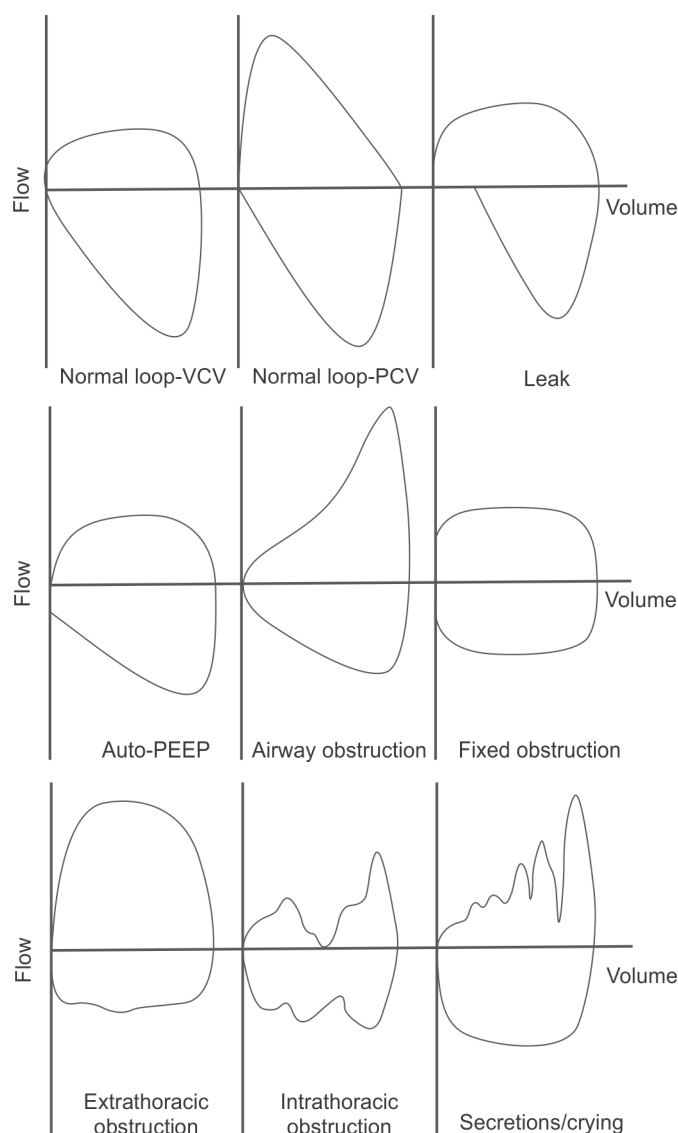
prevent VILI, oxygen must be judiciously used, PEEP should be optimal, Pplat must be limited, and overdistension should be avoided.

### Ventilator-associated Pneumonia

Nosocomial pneumonia diagnosed in patients ventilated for 48 hours or more with signs of a new lower respiratory infection is known as VAP. VAP occurs in 3–20% of all mechanically ventilated children, and risk of VAP increases at around 1% per day of ongoing ventilation. The risk factors of VAP include colonization of upper respiratory tract, microaspiration of oropharyngeal secretions and contaminated equipment or aerosolized medications. Prevention of VAP includes elevation of head end by 30 degrees, avoidance of gastric distension by nasogastric tubes, frequent oropharyngeal suctioning, oral hygiene with antiseptics, in-line suctioning, and changing ventilator circuits only when visibly soiled or malfunctioning.

### Air Leaks

Respiratory epithelium can rupture during positive pressure ventilation leading to air entering the lung parenchyma or the pleural space. From the lung parenchyma, air can track proximally along the bronchovascular bundle causing pulmonary interstitial emphysema, and subsequently pneumomediastinum and pneumopericardium. Escape of air into the pleural cavity causes pneumothorax. A pneumothorax must be considered when a child has deterioration in respiratory function. If pneumothorax is suspected in a child with cardiorespiratory compromise, immediate needle decompression must be attempted, followed by a chest drain insertion. If even after 48 hours of putting the chest drain the lung does not reexpand or air continues to bubble through the drain, a bronchopleural fistula is the likely possibility.



**Figure 9** Patterns of flow-volume loops observed in different scenarios  
 Abbreviations: VCV, volume-controlled ventilation; PCV, pressure-controlled ventilation; PEEP, positive end-expiratory pressure.

### IN A NUTSHELL

1. Mechanical ventilation is of utmost importance in the management of critically ill children.
2. As there are multiple ventilator modes, it is desirable to understand how the modes operate, in terms of inspiratory/expiratory cycling, control, limit and feedback.
3. As compliance and resistance of the respiratory system can change with time, ventilator graphics monitoring which allows real-time measurements of the patient-ventilator interactions should be utilized to optimize ventilator settings.
4. High-frequency ventilation is increasingly being used as a rescue mode in patients who fail on conventional ventilation primarily due to poor oxygenation, especially in ALI, air leaks and PPHN.
5. Although mechanical ventilation is life-saving, it can lead to complications (VILI, air leak, VAP), which can be prevented by close monitoring.
6. Pressure control mode utilizes a decelerating flow pattern which is useful in stiff lungs and air hungry patients.
7. Volume control has the benefits of automatic weaning with improvement in compliance.
8. Pressure-regulated volume control, a dual control mode, delivers a preset TV at the lowest possible PIP by alterations in flow rate and inspiratory time, thereby minimizing barotrauma.
9. Mechanical ventilation in acute asthma involves low rates with prolonged expiratory time and low PEEP.
10. Strategy of ventilation in ALI/ARDS involves low TV and optimal PEEP to recruit lungs and keeping the alveoli patent.

### MORE ON THIS TOPIC

- Chang DW. Clinical Application of Mechanical Ventilation. 4th ed. New York: Delmar Cengage Learning; 2014.
- Hasan A. Understanding Mechanical Ventilation. 2nd ed. London: Springer; 2010.
- Mackenzie I. Core Topics in Mechanical Ventilation. New York: Cambridge University Press; 2008.



## Chapter 8.6

# Sedation and Analgesia

Venkat Shankar

The field of pediatric procedural sedation and analgesia has seen a rapid evolution in the last 20 years. There is an increased awareness among health care providers and parents that even the smallest of the infants perceive pain and anxiety. Increasingly, parents insist on being present and witnessing the procedures being performed on their children and have rising expectations of a relative anxiety and pain-free experience for the child and family. Additionally, the number of invasive and noninvasive procedures performed on children outside the operating room environment has grown exponentially in the recent years fuelling the need for safe, effective and efficient sedation and analgesia. Consequently, a large number of nonanesthesiologists are called upon to provide these services.

Till recently, the area of pain perception in young infants and newborns did not receive much attention. On the other hand, there have been concerns about the safety of administering potent sedatives and analgesics to children due to the potential of respiratory depression and airway compromise. Moreover, unlike adults, children can often be physically overpowered by adult health care providers for restraining them for a painful procedure and culturally it seems that many providers justify inadequate sedation and analgesia by accepting that “it is natural for children to be afraid and cry”. Children are often not in a position to refuse consent or even express their fears and apprehension.

There are many different models and systems of providing procedural sedation and analgesia to children that use different resources, manpower and drugs. In this chapter, some fundamental principles involved in providing safe, effective, predictable sedation in varying settings are described.

### Goals of Procedural Sedation

A good procedural sedation plan attempts to achieve many of these goals (**Box 1**). One should customize the specific sedation or analgesia plan for each situation based on factors like the child's age, co-morbidity, developmental maturity, nature and length of procedure.

#### BOX 1 Goals of procedural sedation

- Allay the fear and anxiety in both the child and the parents
- Induce unawareness and amnesia, if needed
- Obtain the cooperation of the child
- Achieve the necessary degree of immobilization
- Minimize pain and discomfort
- Keep the child safe during sedation
- Minimize the residual effects of sedation after the procedure.

### LEVELS OF SEDATION

Often the term *conscious sedation* is used incorrectly to describe any level of sedation that does not require an endotracheal intubation and respiratory support. As a matter of fact, the term *conscious sedation* is an oxymoron for most pediatric settings and should not be used. Many leading organizations have agreed to a standardized definition for four levels: minimal, moderate and deep sedation, and general anesthesia. These four are not discrete categories, but they are a continuum of a spectrum where a child could easily lapse from one level of sedation to a much deeper one without any warning (**Table 1**). An important fact to remember is that these levels are not specific to any drug and virtually any level

of sedation can be achieved by any agent or any route. The term conscious sedation is no longer recommended as in most children the goal of procedural sedation is to achieve a state where the child is non-responsive to vocal commands and stays still during interventions. This level is more accurately described as deep sedation.

### Skills Training

It is not feasible in most situations to have trained anesthesiologists perform all procedural sedation. Consequently, there is a need to train and ensure appropriate skills for the providers who are doing procedural sedation in children. A large amount of literature exists about skills training and competency verification for various levels of providers.

The person performing the procedure should preferably not be the primary person providing sedation and monitoring the patient. The person performing sedation should not be distracted by other tasks that impair his ability to remain focused on the child's cardiorespiratory status. The individual performing sedation or monitoring the sedated patient should be skilled in recognition of early signs of airway obstruction and hypoventilation or apnea and able to intervene by maintaining airway patency and providing adequate assisted ventilation. The person should have familiarity with the pharmacology of the sedative agents and their antagonists. It is also recommended that any person who intends to provide sedation at a particular level should be skilled enough to rescue the child from next deeper level of sedation.

### PATIENT SELECTION AND SCREENING

Appropriate patient selection is essential for ensuring safe and effective sedation for any situation. It is essential for a focused, standard assessment of the child before the plan for sedation is finalized. It is helpful to follow the American Society of Anesthesiologists (ASA) physical status classification guidelines to stratify the risk of sedation (**Table 2**). A brief and focused evaluation of child should include few essential elements of medical history (**Table 3**) and physical examination (**Table 4**). A child classified as ASA physical status IV or higher should be referred to anesthesiologist for safe administration of sedation or analgesia. Such structured presedation assessment systems have been shown to correlate with good clinical outcomes and reduction of adverse events in the hands of nonanesthesiologists.

It is recommended to follow the commonly accepted fasting guidelines to minimize the risk of vomiting and aspiration (**Table 5**). However, in many emergent situations, it is difficult to wait for the appropriate period of fasting and delay an essential procedure. In such cases, the risk versus benefits of sedation must be assessed to decide about the appropriate plan, and this should be discussed with the family. Based on this assessment, the available options could be: 1. Delay the procedure, 2. Use a lighter level of sedation, if appropriate, 3. Use general anesthesia after securing the airway using a rapid sequence endotracheal intubation.

### EQUIPMENT AND MONITORING

All appropriate equipment and supplies needed for airway management and resuscitation of a pediatric patient should be available at the location of the actual sedation. A suggested list of equipment and supplies is listed in **Table 6**. Depending on the clinical situation, the provider should modify the list. It is recommended that the equipment be checked just prior to the sedation to ensure it is in working condition.

The child undergoing sedation should be continuously monitored using a pulse oximeter with audible and visible signal

**Table 1** Levels of sedation

Factors	Minimal sedation	Moderate sedation/Analgesia (conscious sedation)	Deep sedation	General anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation*	Purposeful response following repeated or painful stimulation*	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

\* Reflex withdrawal from a painful stimulus is NOT considered a purposeful response

from the time sedative agents are administered till complete recovery occurs. Ventilatory adequacy can be monitored by close observation, auscultation or preferably using a continuous nasal capnography. Use of impedance plethysmography to monitor breathing may be unreliable due to its inability to detect early airway obstruction. In situations where direct observation of the child is not possible (i.e. during an MRI scan), continuous capnography is essential to monitor for any apnea or airway obstruction. The pulse oximeter is not a substitute for a robust and independent ventilation monitor. To the extent possible, it is preferable to have the child's face and mouth visible to the observer during the procedure.

Although controversial, it is generally a good practice to administer supplemental oxygen during any deep sedation as it has been shown to reduce the incidence of hypoxemia and bradycardia. However, one should be cognizant that this may delay the detection of an airway obstruction or apnea. Continuous monitoring of heart rate and frequent blood pressure measurements are recommended during moderate and deep sedation. However, use of routine continuous electrocardiography has not been shown to be of any added value. A time-based contemporaneous recording of child's level of consciousness, pulse oximeter reading, capnography, heart rate, respiratory rate and blood pressure should be recorded in a legible manner, preferably on a preformatted documentation flow sheet. These should be recorded at least every 5 minutes during the sedation. In addition, the names of drugs, routes, doses and times of administration should be documented.

Children receiving sedatives are at risk for delayed manifestation of respiratory depression, and can have airway related complications after the procedure is over and no one is closely monitoring the child. This is especially true for oral and rectal routes of administration, where unpredictable absorption can lead to a later than expected peak effect of the drug. Some of the commonly used drug regimens, e.g., chloral hydrate and *lytic cocktail* are notorious for prolonged sedation and are no longer preferred. There should be appropriate level of monitoring of any sedated child recovering from procedure and clearly defined discharge criteria (**Table 7**) should be established.

## ADVERSE OUTCOMES

Many large studies have shown that when performed by appropriately skilled and trained nonanesthesiologists, the incidence of serious adverse outcomes secondary to pediatric procedural sedation are extremely low. The majority of the complications result from respiratory depression or airway obstruction. This could lead to Hypoventilation or hypoxemia, and if not detected and corrected promptly, could lead to serious cardiovascular compromise and neurological injury. A list of usual adverse events seen is given in **Table 8**. An important fact to remember is that all classes of medication and all routes have been associated with adverse outcomes and no provider should be

**Table 2** American Society of Anesthesiologists physical status classification

Class	Status
I	A normal healthy patient
II	A patient with mild systemic disease (no functional limitation)
III	A patient with severe systemic disease (with functional limitation)
IV	A patient with severe systemic disease that is a constant threat to life
V	A moribund patient who is not expected to survive without the operation

**Table 3** Essential elements of premedication history

1.	Any major medical illness affecting the respiratory, cardiovascular, renal or hepatic systems
2.	History of any sedations, anesthesia exposure, surgeries and outcomes
3.	Drug allergies and current medications
4.	History of snoring, sleep apnea or hypoventilation
5.	Last oral intake (nature and timing)
6.	Review of organ systems

**Table 4** Elements of focused physical examination

1.	<i>Vital signs:</i> Heart rate, respiratory rate, pulse oximetry, blood pressure, temperature
2.	Weight
3.	Auscultation of heart and lungs
4.	<i>An evaluation of airways:</i> Facial dysmorphism, retrognathia, micrognathia, trismus, macroglossia, loose teeth, dental appliances, tonsillar hypertrophy, visibility of uvula, short neck, tracheal deviation and obesity.

**Table 5** American Society of Anesthesiologists preprocedure fasting guidelines

Type of food	Fasting period
Clear liquids	2 hours
Breastmilk	4 hours
Light solids	6 hours

complacent about any sedative agent, dose or route. The following factors have been correlated with increased risk of adverse outcomes: multiple sedative agents, inadequate premedication screening and medical evaluation, inadequate/inconsistent

**Table 6** Suggested list of equipment and supplies for pediatric sedation

Emergency medications
Amiodarone
Atropine
Calcium chloride or gluconate
Diphenhydramine
Epinephrine (1:1000, 1:10,000)
Flumazenil
Glucose (50%)
Hydrocortisone, dexamethasone, methylprednisolone
Lidocaine
Naloxone
Salbutamol
Sodium bicarbonate
Vasopressin
Equipment
Adhesive tape
Alcohol wipes
Endotracheal tubes (2.5-, 3.0-, 3.5-, 4.0-, 4.5-, 5.0-, 5.5-, 6.0-, 6.5- and 7.0-mm internal diameter)
Face mask (infant, child, small adult)
Gloves
Hypodermic needles
Intraosseous needle
Intravenous catheters (24-, 22-, 20- and 18-gauge)
Intravenous fluids, including normal saline and lactated ringer solutions
Intravenous tubing and burette drip set
Laryngoscope blades (straight numbers 1, 2 and 3 and curved numbers 2 and 3)
Laryngoscope handles
Oral and nasal airways (pediatric sizes)
Oxygen regulator, flow meter and tubing
Self-inflating or anesthesia bag-valve set (0.5-, 1- and 2-L sizes)
Source of compressed oxygen (e.g., a tank with at least 60 min of supply at high flows or a wall outlet)
Stylets
Suction device (portable or wall outlet)
Suction tubing and canisters
Syringes (1-, 3-, 5- and 10-mL)
Tourniquets
Yankahuer and soft-tip suction catheters (5-, 8-, 10- and 12-F)
Monitors
Capnometer (end-tidal CO <sub>2</sub> monitor) with bi-nasal cannula
Defibrillator with pediatric pads or paddles
Monitor with leads and sensors (respiratory rate, heart rate and ECG)
Pulse oximeter with sensors

**Table 7** Guidelines for discharge of a child recovering from sedation

1. The child should be back to his or her preprocedural mental status and able to be aroused easily.
2. Respiratory and cardiovascular status should be stable, and airway protective reflexes should be intact and airway patent.
3. The child should be able to sit up unaided or should be back to the pre-procedural motor function status.
4. At least 2 hrs should have elapsed since the last administration of any pharmacologic antidote such as flumazenil or naloxone to prevent a re-sedation phenomenon.
5. The child should be discharged with a responsible adult who will accompany the child and be able to understand and react to any postprocedural complications.
6. Written instructions regarding postprocedural diet, activities, precautions, and warning signs and an emergency number should be provided.

**Table 8** Common adverse events during procedural sedation

• Inadequate sedation
• Airway obstruction
• Hypoxemia
• Apnea
• Vomiting
• Hypotension
• Prolonged sedation
• Laryngospasm

physiologic monitoring, lack of independent observer, medication errors and inadequate recovery procedure. In addition, premature infants and infants less than 6 months of age are prone to higher incidence of respiratory depression and apnea. Certain areas like MRI scanner pose unique challenges in terms of monitoring and pose additional risk and require specialized MRI-compatible monitors, devices and infusion pumps.

## SELECTED SEDATIVE AGENTS

There are a large number of sedative and analgesic drugs that can be used to achieve the intended level of sedation and analgesia (**Table 9**). It is generally preferred to use intravenous route for deep sedation. A practitioner should become familiar with a few of the agents and develop a complete understanding of the pharmacokinetics, doses and side effects of the agent being used.

### Chloral Hydrate

Chloral hydrate has been used orally and rectally for many decades. It is an effective sedative agent but provides no analgesia. It has been used extensively in radiology procedures with good results. Traditionally, chloral hydrate is regarded as a very safe agent, and this has often led to complacency on the part of the practitioner in terms of dosing and monitoring principles. The drug can often produce deep levels of sedation and has been associated with adverse outcomes of death and neurologic injury. It has active metabolites including trichloroethanol, which may have a prolonged half-life in younger infants and neonates. Because this drug may lead to a prolonged need for observation after a short radiology procedure, it is not recommended to use chloral hydrate in younger infants who will be discharged home after the procedure.

### Benzodiazepines

Midazolam is the most commonly prescribed drug in this class of agents. It can be administered through oral, intranasal, rectal, intramuscular or intravenous routes. Recently, multiple studies have demonstrated the safety and efficacy of the intranasal route of midazolam administration. It has potent amnesic and anxiolytic properties and is a short-acting sedative. It does not have any analgesic properties and often needs to be combined with topical, local or regional analgesia or systemic analgesia, using narcotic agents or ketamine. The combination of midazolam with an opioid such as fentanyl has been popular but can cause immense respiratory suppression. Respiratory depression caused by midazolam can be reversed by using antagonist flumazenil.

### Barbiturates

Pentobarbital (Nembutal) has been used for many years for sedating children who are undergoing noninvasive radiology procedures. It produces a deep sleep with minimal movement for up to approximately 1 hour and is popular for use during

**Table 9** Suggested dosages and routes for pediatric procedural sedation

Drug	Dose	Onset of action (min)	Duration of action (min)	Common indications	Comments
Chloral hydrate	PO or PR: 25–100 mg/kg, maximal dose 2g	20–30	45–90	Diagnostic radiology procedures in infants and toddlers	Unpredictable effect, paradoxical agitation seen often, prolonged sedation in neonates, may cause emesis
Dexmedetomidine	IV: 1–2 mcg/kg loading dose over 10 minutes, followed by infusion 0.5–2 mcg/kg/h	10–15	10	Diagnostic radiology procedures	Expensive, limited experience, needs infusion pumps, may cause severe bradycardia
Midazolam	IV: 0.05–0.1 mg/kg (maximum of 0.4 mg/kg)	2–5	30–60	For anxiety-producing procedures, bone marrow aspiration, spinal tap with additional analgesia	Excellent amnesia and anxiolysis; combination with fentanyl may produce profound respiratory depression; younger children (5-year) may occasionally need up to 0.6 mg/kg; flumazenil reverses oversedation
	IM: 0.1–0.2 mg/kg	15–20	45–90		
	PO: 0.5 mg/kg	15–30	60–90		
	IN: 0.2–0.6 mg/kg	10–20	30–60		
	PR: 0.3–0.5 mg/kg	15–30	60–90		
Pentobarbital	IV: 1–6 mg/kg total in increments of 1–2 mg/kg	3–5	30–45	Diagnostic radiology procedures including MRI	Excellent hypnotic, although occasionally leads to paradoxical excitement; no analgesic effect; not reversible with antidotes; oral pentobarbital is effective in infants and toddlers
	IM: 1–6 mg/kg (maximum 100 mg)	10–20	45–90		
	PO: 4–6 mg/kg (maximum 100 mg)	20–40	45–90		
Methohexital	PR: 25 mg/kg	10–15	60	Diagnostic radiology procedures	Good immobilization and hypnosis; not reversible
Fentanyl	IV: 1–4 mcg/kg total in increments of 1 mcg/kg	2–3	20–60	Painful procedures	Excellent analgesia; may produce itching (nasal area) and nausea; can cause profound respiratory depression when combined with midazolam; rapid push can cause chest wall rigidity; reversible with naloxone
Ketamine	IV: 1–2 mg/kg loading dose, 0.25–1 mg/kg maintenance q 10–15 minutes	2–5	15–60	Painful procedures, fracture reduction, laceration repair, thoracostomy tube insertion, burn care	Dissociative state, excellent analgesia; can lead to increased bronchial and salivary secretions; produces emergence hallucinations in older (> 10 y) children; contraindicated in children with raised intracranial pressure; effects not reversible
	IM: 2–5 mg/kg	5–10	15–60		
Propofol	IV: 1–1.5 mg/kg loading; 0.25–0.5 mg/kg every 3–5 min; or infusion of 50–150 mg/kg/min	1–2	5–10	Diagnostic radiology procedures, especially MRI; in combination with local/systemic analgesics for painful procedures, e.g., endoscopy	Can rapidly induce state of general anesthesia; apnea on induction seen often; burns in peripheral veins, may be reduced by 1:10 addition of 1% lidocaine; myoclonus seen occasionally; not approved for prolonged sedation in children; not reversible
Flumazenil	IV: 0.02 mg/kg/dose, q 1 min to a maximum of 1 mg	1–2	20–60	Benzodiazepine-induced respiratory depression	Rebound sedation may occur; can precipitate seizures, withdrawal in long-term benzodiazepine users
Naloxone	IV/IM: 0.1 mg/kg/dose, q 1 min to maximum of 2 mg/dose	IV: 1–3 IM: 10–15	20–40	Opioid-induced respiratory depression	Rebound sedation may occur; can precipitate acute withdrawal in long-term opioid users, and one-tenth dose aliquots should be used in them

*These doses are intended only as broad guidelines; each individual patient may have varying needs depending on clinical condition, associated drugs and other confounding factors. It is always a good practice to titrate intravenous drugs slowly to achieve the required effect.*



MRI scanning. Paradoxically, it does cause a small proportion of children, usually in the preschool age, to unpredictably become agitated and dysphoric. Traditionally, pentobarbital has been administered through the intravenous and intramuscular routes; however, more recently, the oral route has been used, and this approach has shown results that are superior to chloral hydrate. Barbiturates do not have any analgesic effects and are unsuitable for sedating children who are undergoing painful procedures.

### Opioids

Opioids such as fentanyl and morphine are commonly used, often in conjunction with a sedative, to achieve analgesia for painful procedures. The fentanyl and midazolam combination is very effective in achieving rapid onset sedation and analgesia, although the combination can result in profound respiratory depression. Fentanyl has been a preferred choice of many practitioners because of its rapid onset of action, shorter duration of effect, lack of histamine release and less cardiovascular depressant action. Respiratory depression, pruritus, nausea and emesis, and hypotension are major side effects of all the agents in this class. Chest wall rigidity is a rare effect from rapid intravenous administration of fentanyl. Naloxone is an effective antidote for the respiratory depression induced by opioids.

### Ketamine

Ketamine is a dissociative anesthetic and produces excellent analgesia, amnesia and sedation for pediatric procedures. It is commonly used in the emergency room setting for fracture reduction and casting, laceration repair and other painful procedures. It is regarded as relatively safer than other sedatives because of its less pronounced depressant effects on respiratory drive and airway protective reflexes. However, it does produce excessive salivation and airway secretions, and there is the risk of aspiration or airway obstruction. It can be administered by intramuscular route with good efficacy. Ketamine has been associated with emergence of dysphoria and hallucinations in adults. However, this phenomenon does not appear to be as prominent in children, and there are recent reports suggesting that no additional benefits are gained by the concurrent use of benzodiazepines.

### Propofol

The use of propofol outside the operating room and by non-anesthesiologists has been steadily increasing over the past few years. There are multiple reports of its efficacy and safety in pediatric procedural sedation. Propofol is a potent ultra-short-acting agent used to induce general anesthesia and is associated with rapid deepening of sedation level to that of general anesthesia. Propofol is a diisopropylphenol. Its actual mechanism of action is unknown, but it is postulated that propofol mediates activity of the gamma aminobutyric acid receptors. All children receiving propofol should be monitored identically to those receiving intravenous general anesthesia, and nasal prong capnography is required.

Propofol has no analgesic property, and topical or local analgesia is needed for painful procedures. It is well suited for brief painful procedures such as spinal taps and bone marrow aspiration in oncology clinics and long nonpainful procedures such as MRI scanning in the radiology department. The short half-life of propofol results in shorter postprocedural recovery time compared with other agents. Propofol often causes a burning

sensation when it is injected in peripheral veins; this effect may be reduced by mixing 1 mL of 1% lidocaine in every 10 mL of propofol and by injecting the drug slowly.

### Dexmedetomidine

Dexmedetomidine is a relatively new drug that has a central alpha 2 agonist activity. Many recent studies have suggested its safety and efficacy. It is particularly useful in radiological procedures. It has rapid onset, short acting with quick and smooth emergence, making it an attractive agent. Although respiratory depression is not common with this agent, severe bradycardia and hypotension is commonly reported. It can produce a paradoxical hypertensive response when given with atropine or glycopyrrolate. The utility of this drug is still being evaluated in the context of procedural sedation.

### MORE ON THIS TOPIC

- American Society of Anesthesiologists. Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by nonanesthesiologists. *Anesthesiology*. 2002;96:1004-17.
- American Academy of Pediatrics. Committee on Drugs. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: addendum. *Pediatrics*. 2002;110:836-8.
- Cote CJ, Notterman DA, Karl HW, et al. Adverse sedation events in pediatrics: a critical incident analysis of contributing factors. *Pediatrics*. 2000;105: 805-14.
- Cravero JP, Beach ML, Blike GT, et al. The incidence and nature of adverse events during pediatric sedation/anesthesia with propofol for procedures outside the operating room: a report from the Pediatric Sedation Research Consortium. *Anesth Analg*. 2009;108:795-804.
- Krauss B, Green SM. Procedural sedation and analgesia in children. *Lancet*. 2006;367:766-80.
- Shankar V, Deshpande JK. Procedural sedation in the pediatric patient. *Anesthesiol Clin Am*. 2005;23: 635-54.

### IN A NUTSHELL

1. Procedural sedation and analgesia is increasingly required for children for invasive and noninvasive procedures. Pediatricians should be familiar with the principles of safe sedation.
2. Although various levels of sedation are described, a child can lapse into a deeper plane of sedation than intended, and the practitioner should have the ability to recognize and intervene.
3. Appropriate patient selection, focused history and examination are essential for good outcomes.
4. Appropriate equipment and monitoring should be provided for all sedations.
5. Children are at a high risk for prolonged effects of sedatives and postprocedure complication and need to be observed till they are back to baseline state prior to discharge.
6. A variety of agents can be used to achieve the specific goals of immobility, anxiolysis, analgesia, hypnosis and amnesia. The practitioner should be familiar with the pharmacokinetics of the agents he chooses to use.
7. Standard guidelines for fasting should be followed to reduce the risk for aspiration.

# Section 9 POISONING AND ENVENOMATION

**Section Editor** Rakesh Lodha

## Chapter 9.1

### Clinical Approach to a Poisoned Child

P Ramesh Menon

Poisoning is a process of unintentional self-injury, by a xenobiotic exposure through skin and mucosal surfaces, associated with accumulation of toxins in the body due to derangements in the metabolic processes of homeostasis. Identification of the same in a child needs a clinical suspicion, laboratory evaluation and sometimes relevant imaging. Majority are accidental oral exposures at home by toddlers (exploratory ingestion).

Poisoning is a common medical emergency in childhood. In India, accidental poisoning (majority of poisoning in children) has been very frequent below 5 years of age with male dominance. In older children and adolescents, suicide attempts or gestures are more common. From India, there are no community-based data regarding incidence of poisoning. In a retrospective analysis of poisoning from eight regional hospitals in different part of India, pediatric poisonings constituted 0.23–3.3% of the total poisoning. The mortality ranged from 0.64% to 11.6%. Accidental poisoning was common involving 50–90% of children below 5 years of age and males outnumbered the females. Suicidal poisoning was seen after 13 years of age and was due to drugs and household chemicals. Drugs are an important cause of poisoning in children; the drugs consumed usually belong to phenothiazines, antiepileptic and antipyretics. Iron poisoning was seen in younger children. Kerosene was one of the causes of accidental poisoning at all hospitals except Shimla and rural Maharashtra where probably wood charcoal is widely used. Pesticide poisoning was more prevalent in Punjab and West Bengal whereas plant poisoning was very common in Shimla. Significant number of snake envenomation has been recorded from rural Maharashtra. Other less common accidental poisonings in children included alcohol, corrosives, heavy metals, rodenticides, detergents and disinfectants. Thus various regions in the country showed some variation in types and frequency of childhood poisoning which could be attributed to different geographical and socioeconomic background.

#### WHEN TO SUSPECT?

An awareness of the local pattern of poisons (availability/usage) is helpful. A positive history may be available in up to 50%. Any hyperacute onset of (multiple organ) symptoms (in a cluster) and rapid progression in a child are usual clues to poisoning in a child. History of medications or drug availability in house or intake for co-morbid conditions in child or others should be documented as corroborative evidence (even if negative). The index of suspicion should be higher if the child is at risk (age: 1–4 years and/or has a previous history of ingestion).

*Toxidromes* are a cluster of clinical features which often occur together in a patient and may indicate poisoning with specific agents (**Table 1**).

#### WHAT TO SUSPECT?

Pediatric unintentional injuries due to chemical agents are classified as follows:

*Exploratory ingestion* Previously described as accidental ingestion, it signifies a complex interplay of child/substance and environmental factors (injury model). Pica-prone hyperactive victim (1–5 years) with easy access to medicines, cosmetics, detergents or pesticides is the usual clinical situation.

*Child abuse by poisoning* Common in children less than 1 year or more than 5 years, when the history is inconsistent or arouses discomfort. Previous history of poisoning may be available or siblings may have been poisoned; massive overdoses or multiple ingestion; exposure to illicit drugs or alcohol; unusual poisonings with household substances (salt or water, pepper, etc.); other evidence of child abuse or neglect; any of these should lead to the suspicion of abuse. Morbidity of such cases tends to be higher.

*Pediatric medication errors* Due to weight-based dosing (mg/kg dosing) or age-based dosing. Young infants cannot express early symptoms of allergy or adverse reactions. Up to 10% of poisoning deaths are due to these. Multiple pediatric oral suspensions with different concentrations exist such as phenytoin, verapamil, atenolol, tacrolimus and various antibiotics.

*Toxin (Lethal in small doses) ingestion* (**Table 2**) New products (household or medication formulations)

#### HOW TO MANAGE?

Higher body surface area or weight, increased skin perfusion, hydration, greater susceptibility for dehydration and insensible losses are distinct considerations in the management of a young child with poisoning. Increased respiratory rate and minute ventilation deliver a higher dose for airborne toxins by inhalation. Higher risk of respiratory fatigue and failure due to mechanical reasons and physiological sensitivity to hypoxia, metabolic toxins, with a lower reserve (cardiovascular, acid-base, glycogen stores) distinguish children from adults.

Airway patency and protection (ET intubation) should be performed in all children in whom it is threatened. Higher adrenergic tone may result in tachycardia as the lone vital sign abnormality for cardiac output maintenance. Calcium channel blockers (CCBs)/organophosphate (OP) pesticides may precipitate circulatory arrest in very small doses. Hypotension is to be managed with fluids initially. Vasoactive drugs, most commonly dopamine and epinephrine or norepinephrine, are used when hypotension remains fluid unresponsive. Norepinephrine or glucagon is preferred in hypotension due to beta-blocker or tricyclic antidepressants (TCA) induced hypotension. Developmental pharmacodynamics results in enhanced central nervous system

**Table 1** Toxicidromes, mnemonics and examples

Type	AVPU/Mental status	Vitals (Temp/HR/RR/BP)	Pupils	Other manifestations	Examples of toxic agents
Sympathomimetic	Excitation, hallucinations, paranoia	↑↑/↑/↑ wide pulse pressure	Mydriasis	Diaphoresis, tremors, hyper-reflexia, seizures	Cocaine, amphetamines, theophylline, caffeine
Anticholinergic <i>Hot as a hare/dry as a bone/red as a beet/mad as a hatter/blind as a bat/bowel bladder lose their tone and heart runs alone</i>	Excitation, hallucinations, delirium with mumbling speech, coma	↑↑/↑/↑	Mydriasis	Dry flushed skin/mucosa, ileus, urinary retention, myoclonus, choreoathetosis, picking behavior, seizures (rare)	Antihistamines, TCA, antispasmodics, atropine, scopolamine, belladonna alkaloids
Hallucinogenic	Agitation, synesthesia, Hallucinations, depersonalization	↑↑/↑/↑	Mydriasis (usually)	Nystagmus	Phencyclidine, LSD, (e.g., MDMA ["Ecstasy"], MDEA)
Opioid	CNS depression, coma	↓↓/↓↓/↓	Miosis	Hyporeflexia, pulmonary edema, needle marks	Opioids (e.g., heroin, morphine, oxycodone, hydromorphone), diphenoxylate
Sedative-hypnotic	CNS depression, confusion, stupor, coma	↓↓/↓↓/↓	Miosis (usually)	Hyporeflexia	Benzodiazepines, barbiturates, carisoprodol, alcohols, zolpidem
Cholinergic <i>SLUDGE +DUMBELS wheezing/diaphoresis/bronchorrhea/bradycardia/miosis</i>	Confusion, coma	↓↓/↓/↑/↑/↓	Miosis	Salivation, urinary + fecal incontinence, diarrhea, GI cramps, emesis, muscle fasciculations, seizures	Organophosphate and carbamate insecticides, nicotine, pilocarpine, physostigmine, edrophonium
Serotonin syndrome	Confusion, agitation, coma	↑↑/↑/↑	Mydriasis	Tremor, myoclonus, diarrhea hyper-reflexia, clonus, rigidity diaphoresis, flushing, trismus	MAOIs alone or with: SSRIs, meperidine, dextromethorphan, TCAs, L-tryptophan

Abbreviations: AVPU, alert/voice/pain/unresponsive; TCA, tricyclic antidepressant; Temp, temperature; HR, heart rate; RR, respiratory rate; BP, blood pressure.

**Table 2** Small dose toxins, and their major effects

Drug	Lethal effects at	Major effects			
Benzocaine	<20 mg/kg	Seizures	CNS depression	Arrhythmia	Methemoglobinemia,
Calcium antagonists	<40 mg/kg				Bradycardia, hypotension
Camphor	Approximately 50 mg/kg	+	+		Respiratory depression
Chloroquine	<30 mg/kg	+		+	
Diphenoxylate (e.g., Lomotil®)	1.2 mg/kg		+		Respiratory depression
Lindane	Approximately 6 mg/kg	+	+		
Phenothiazines	Approximately 20 mg/kg	+	+	+	
Sulfonyleureas	<1 mg/kg				Hypoglycemia
Theophylline	Approximately 50 mg/kg	+		+	Arrhythmias
Tricyclic antidepressants	Approximately 15 mg/kg	+		+	Hypotension
Toxic alcohols (e.g., methanol, ethylene glycol)	0.3 mL/kg		+		

(CNS) depression with clonidine, codeine, dextromethorphan cough syrups; paradoxical reactions to benzodiazepines and QTc prolongation with sotalol, etc. Neonates require other considerations, e.g., carboxyhemoglobin (COHb) concentrations are higher at 2–5% because carbon monoxide (CO) is a by-product of protoporphyrin metabolism. Neonates are also more susceptible to OP poisoning since their baseline red cell cholinesterase is 50–70% lower.

### EMERGENCY DEPARTMENT: GENERAL LIFE SAVING MEASURES

Stabilization of the ABC immediately is a priority. Screen for occult trauma, ocular and dermal exposures in addition before initiating decontamination. Assess mental status (AVPU), vital signs, pupillary size, skin and look for specific clues (**Tables 1 and 2**).

**A: Airway** (Look for secretions/cough/gag) Caustics/plants containing Calcium oxalate crystals (Philodendron houseplants) have higher airway threat. Intubate the child if there is a (higher) risk of airway compromise.

**B: Breathing** (Look for  $SpO_2$ , breathing pattern) OP poison/cocaine poisoning can sensitize the child to scoline resulting in apnea of up to 7 hours. Try and maintain  $SpO_2$  greater than 95%. Perform a blood gas analysis.

**C: Circulation** (Look for HR, rhythm and blood pressure) Inotropes may worsen cardiovascular toxicity and antiarrhythmics may be proarrhythmic and negatively inotropic. Establish at least two large bore lines in the unstable patient.

**D: CNS depression/excitation** Classify the physiologic status as excited (with increase in temperature, heart rate, blood pressure, respiratory rate); depressed (hypoglycemia, opiate intoxication or thiamine deficiency) or mixed. Hypoxemia, hypoglycemia, opiate intoxication, thiamine deficiency are amongst common causes of altered mental status. Depression of CNS may lead to threat to airway patency.

Do NOT use antipyretics; external or internal cooling measures may be used with muscle relaxants or benzodiazepines. Take samples for serum electrolytes, renal function test (RFT), liver function test (LFT), blood glucose, pH, ECG (**Table 3**). Point of care test (urine, blood, gastric aspirate/vomit) to identify the agent of injury or path of injury are available and should be utilized simultaneously (if not a remote setting). These are nonspecific with respect to the time of exposure to the toxin. Plasma drug levels are not routinely sought except in acetaminophen, salicylate, iron (Fe), lithium (Li), digoxin, theophylline, methanol and anticonvulsants poisonings. The resultant delay in specific management in acute

poisoning is avoidable. A widening of the QRS complex may be the first sign of TCA toxicity.

### MANAGING IN HOSPITAL OR INTENSIVE CARE UNIT

Optimal management of the poisoned child depends upon the specific poison involved, severity of illness and elapsed time between exposure and presentation (**Table 4**). Certain poisons can produce symptoms that mimic common diseases (**Table 5**). Household products (kerosene; insect repellents; pesticides) are the commonest cause of poisoning in children. Medications (drugs) especially anticonvulsants (carbamazepine, phenytoin) and other miscellaneous products including dyes, antiseptics, herbal medicines, button batteries, adhesives are also consumed by children. Consider the maximum amount of substance that could have been ingested by comparing the number of tablets, volume of liquid remaining, details on packaging. When children share a poisonous substance, it is presumed that each child has taken the maximum amount. Supportive care, the mainstay of therapy, variably involves decontamination, antidote therapy, and enhanced elimination techniques. Coupled with decontamination, it is usually sufficient for complete recovery.

#### Decontamination

Decontamination refers to the techniques used to prevent the absorption (in the early stages) of the toxic substance by the body. It is NOT an *always* (to be done) procedure in children.

Emetics and antiemetics are best avoided. Syrup of ipecac is no longer recommended. Gastric lavage is not routinely recommended. It is contraindicated in corrosive ingestion or volatile hydrocarbon poisoning. Adequate airway protection is essential. Gastric lavage is less effective than activated charcoal in reducing the absorption of simulated toxins, but is roughly equivalent in efficacy to ipecac. Gastric lavage in combination with activated charcoal (administered either before lavage or both before and after lavage) is more effective in reducing drug absorption than is activated charcoal given alone, but studies have not confirmed a clinical benefit of gastric lavage. *Activated charcoal has become the preferred method of gastrointestinal decontamination in children.* Voluntary ingestion is preferred to nasogastric administration. It may be ineffective in Fe, Li, bleach, petrochemicals and alcohols (**Table 6**). Specific exposures are dealt in subsequent chapters.

Activated charcoal is an insoluble, nonabsorbable, fine carbon powder made from the burning and crushing of wood, coconut shells, coal and petroleum products, which are then heated with steam, air, or carbon dioxide in the *activation* process, which adds surface area. This enhances the network of inter-connecting



**Table 3** Laboratory clues to diagnosis of poisoning

<i>Lab abnormalities</i>	<i>Chest X-ray</i>	<i>Blood gas</i>	<i>Anion Gap</i>
<b>Rhabdomyolysis</b> Sympathomimetics Anticholinergics Central hallucinogens Neuroleptics (NMS) Malignant hyperthermia Serotonin syndrome Corticosteroids	<b>Irritant gases</b> NH <sub>3</sub> , Cl <sub>2</sub> , H <sub>2</sub> S N <sub>2</sub> oxides Phosgene Smoke SO <sub>2</sub> Metal oxides Acid and alkaline gases Volatile inhalants (hydrocarbons)	<b>Increased osmolal gap</b> (normal 5 ± 7 [SD] mOsm/L) Acetone Ethanol Ethylene glycol Glycerol Hypermagnesemia (>9.5 mEq/L) Isopropyl alcohol Mannitol Methanol	<b>Increased anion gap with metabolic acidosis</b> (>13 mEq/L)* Methanol Ethylene glycol Ethanol Salicylates Isoniazid Cocaine Theophylline
<b>Hepatotoxicity</b> Acetaminophen Ethanol Phenytoin Halogenated hydrocarbons CCl <sub>4</sub> Heavy metals Erythromycin estolate Pyrrolizidine alkaloids (plants)	<b>Radiopaque toxins (CHIPES)</b> C-Chlorinated hydrocarbons (e.g., chloral hydrate, CCl <sub>4</sub> ), Ca salts (e.g., calcium carbonate), Crack vials H-Heavy metals (e.g., Fe, Ar, Hg, Pb, Tl) I-Iodinated compounds (e.g., thyroxine) P-Psychotropics (e.g., phenothiazines, Li, cyclic antidepressants), Packets of drugs (e.g., cocaine and heroin), Play-Doh, K salts E-Enteric-coated tablets (e.g., aspirin) S-Salicylates, Na salts, Sustained-release preparations	<b>Increased oxygen saturation gap</b> (>5% difference) CO, CN SulfHbemia H <sub>2</sub> S MetHb	<b>Decreased anion gap</b> (<6 mEq/L) HyperMg Hypercalcemia Bromide Nitrates Lithium Iodide Spironolactone NH <sub>4</sub> Cl Acetazolamide
<b>Methemoglobinemia</b> Nitrates Nitroglycerin Aniline dyes Nitrous gases (arc welders) Arsine			
<i>pH</i>	<i>Hypoxia</i>	<i>Dyselectrolytemia</i>	
<b>Respiratory alkalosis</b> Aspirin (early) Methanol (delayed)	<i>By CNS depression</i> Opiates Barbiturates, Ethanol, ethylene glycol, methanol, isopropyl alcohol <i>Sedative-hypnotics</i> Tricyclic antidepressants Clonidine Opiates Salicylates Hydrocarbons Smoke inhalation Phosgene and chlorine <i>By paralysis of the ventilatory muscles</i> Neuromuscular blockers Tetanus toxin	<b>Hyperkalemia</b> Cardiac glycosides Hypokalemia Beta-adrenergic agonists Albuterol Theophylline Epinephrine Caffeine Diuretics	
<b>Respiratory acidosis</b> Opiates Combinations of sedative-hypnotics Neuromuscular blocking agents		<b>Hyperglycemia</b> Beta-adrenergic agonists Theophylline Epinephrine Caffeine Calcium blockers Iron	
<b>Metabolic acidosis</b> Iron, isoniazid Lactate (CN, CO theophylline, methemoglobin inducers), Ethanol		<b>Hypoglycemia</b> Beta blockers Insulin Oral hypoglycemic agents Ethanol Quinine Salicylate	
<b>Metabolic alkalosis</b> Diuretics Milk alkali syndrome	<i>Simple asphyxiants</i> (Displace oxygen in the lungs) Methane, Propane N <sub>2</sub> , CO <sub>2</sub> , CO, CN, H <sub>2</sub> S Cellular asphyxiants MetHbemia SulfHbemia	<b>Hypocalcemia</b> Ethylene glycol Oxalate	
<b>Combined respiratory alkalosis and metabolic acidosis</b> Aspirin			

**Table 4** Indications for PICU management (few criteria, in intoxicated patients)

Glasgow coma scale $\leq 6$ ; Agitation requiring restraint
$PCO_2 > 45$ mm Hg, hypoxia or respiratory failure (ARDS), and/or endotracheal intubation
$SBP \leq 80$ mm Hg
Metabolic acidosis with $pH \leq 7.2$
Hyperthermia with $T > 104^\circ F$
Poisoning with a "toxic time bomb" - Ingested drug packets, sustained-release preparations
Need for invasive hemodynamic monitoring ; Need for whole bowel irrigation to enhance GI elimination of poison
Need for emergency hemodialysis, hemoperfusion, hemofiltration
Need for emergency antidote which requires close monitoring (e.g., antivenom, Digibind, physostigmine, naloxone drip)
Ischemic chest pain from toxin (e.g., cocaine, carbon monoxide)
TCA or other drug exposure with $QRS > 120$ ms or $QTc > 500$ ms

**Table 5** Toxins that mimic common illnesses

Acute liver failure	Paracetamol	Idiopathic hepatic failure
Hyperthermia, tachypnea, sudden onset	Salicylates	Pneumonia
Hyperglycemia, ketosis, drowsiness	Theophylline	Diabetic ketoacidosis
Non-ketotic hypoglycemia, collapse	Ethanol	Glycogen storage disease

**Table 6** Agents for which activated charcoal is not recommended

Heavy metals: Ar, Pb, Hg, Fe, Zn, Cd
Inorganic ions: Li, Na, Ca, K, Mg, F, I
Boric acid
Corrosives acids, alkali
Hydrocarbons alkanes, alkenes, alkylhalides, aromatic hydrocarbons
Alcohols, acetone, ethyleneglycol, isopropanol, methanol
Essential oils

pores which bind (adsorb) and trap chemicals within minutes of contact, thereby preventing their systemic absorption and toxicity. Activated charcoals (AC) have a binding surface area of 950–2000  $m^2/g$  and can absorb between a few mg and 1 g of intoxicant per gram of activated charcoal. The amount of drug bound by charcoal is dependent upon:

- The characteristics of the ingested substance. Most poisons bind well to AC with the exception of small, highly ionized chemicals such as metals, electrolytes, acids, and alkali;
- The surface area of the specific AC preparation employed; and
- The relative amounts of AC and the intoxicant.

More than 90% of an intoxicant generally is adsorbed when the ratio of AC to intoxicant is 10:1 or greater. Larger doses of activated charcoal, either as single or multiple doses are more effective at preventing drug absorption by mass action. Multiple doses of activated charcoal are used to enhance pre-absorptive and post-absorptive elimination by exploiting the effects of certain drugs that slow gastrointestinal motility (e.g., anticholinergics drugs), interrupting enterohepatic circulation, or "gastrointestinal dialysis." Cathartics (sorbitol) may be administered with the first dose of AC, amongst the multiple doses.

## Enhancing Elimination

Active techniques are restricted to prolonged exposures to high concentrations of toxins. Repeated doses of activated charcoal, where indicated is one such (**Box 1**). It may result in bowel obstruction and perforation).

### BOX 1 Indications for enhancing elimination

Active elimination techniques may be indicated in poisoning with carbamazepine, barbiturates, dapsone, quinine, theophylline, salicylates, Amanita phalloides, slow release preparations, digoxin, phenylbutazone, phenytoin, and piroxicam

*Whole bowel irrigation* is another technique of decontamination for patients who have ingested large amounts of nonabsorbable substances, iron, sustained release preparations and illicit drug packets. It is based on enteral administration of large quantities (30 mL/kg/h) of osmotically balanced polyethylene glycol electrolyte solution to induce a liquid stool. Treatment is continued till rectal effluent clears. This typically takes 4–6 hours. The maximum recommended doses for children older than nine months are 9 months to 6 years: 500 mL/h; 6–12 years: 1000 mL/h; Older than 12 years: 1500–2000 mL/h.

*Forced diuresis*, urinary alkalization or acidification is preferably avoided. Cathartics are also avoided and never used alone for decontamination or enhanced elimination. They are better replaced by Dialysis, hemoperfusion and hemofiltration. Extracorporeal elimination is worthwhile if it increases total body clearance by 30% or more. Substances not amenable to extracorporeal elimination include benzodiazepines, TCA, phenothiazines, chlordiazepoxide and dextropropoxyphene.

## Endoscopy and Surgery

Endoscopic removal should be considered for children who have a life-threatening amount of a substance in the stomach (e.g., bezoars, concretions) that cannot be safely removed by other means. Endoscopy also can be used to remove foreign bodies such as large coins or batteries; however, some of these materials are difficult to grasp with the endoscope and may require surgical removal. Surgical removal also is indicated for plastic packets/pouches because the packets may rupture if endoscopic removal is attempted, and for life-threatening gastric iron bezoars.

## Dilution

Dilution is utilized only for ingestions of corrosive substances such as acids or alkali. The recommended pediatric doses are 120–180 mL of water. Larger doses may induce vomiting. Airway patency must always be assessed before giving fluids by mouth.

## ANTIDOTES

Diagnostic trial of antidotes improved alertness in response to flumazenil for benzodiazepine ingestion; improved alertness in response to glucose for oral hypoglycemic ingestion; physostigmine for anticholinergic agent ingestion (C/I: Wide QRS on ECG); naloxone for opiate ingestion; diphenhydramine for PTZ ingestion. Details are discussed with specific agents or can be obtained from poison centers ([www.who.int/gho/phe/chemical\\_safety/poisons\\_centres/en/index.html](http://www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html)). Antidotes reverse or reduce poison effects by different mechanisms (**Table 7**).

**Table 7** Examples of antidotes and indication, for uncommon poisons

<i>Antidote</i>	<i>Poisoning indication</i>
Calcium gluconate and calcium chloride (10%) , high-dose insulin euglycemia, IV lipid emulsion	Calcium channel blocker Hydrogen fluoride (HF)
Cyanide antidote kit (may contain sodium nitrite 3%, sodium thiosulfate, + hydroxocobalamin)	Cyanide
Dimercaprol (BAL)	Acute arsenic Inorganic mercury Lead (with encephalopathy)
Ethanol (10%)	Methanol/Ethylene glycol
Fomepizole (4-methylpyrazole)	Methanol Ethylene glycol
Glucagon, norepinephrine infusion	Beta-adrenergic antagonist Calcium channel blocker
Methylene blue	Methemoglobinemia
Propranolol	Thyroxine
Pyridoxine, NaHCO <sub>3</sub>	Isoniazid (INH)
Flumazenil	Benzodiazepines
Na replacement, low dose dopamine	Lithium
Procyclidine	Metoclopramide
Dextrose, octreotide	Sulfonylureas

**IN A NUTSHELL**

1. Evolving homeostatic machinery and developmental shifts places children (including adolescents) at special risk of exposure and risks (exploratory exposure) to injurious agents.
2. Poisoning is a common medical emergency in childhood, in India.
3. Ingestion, ocular and dermal exposures in order of occurrence are the routes of exposure commonly encountered.
4. Activated charcoal and whole bowel irrigation are the only validated decontamination procedures in children (pre-toxic phase).
5. Specific antidotes are available for most (common) pediatric toxins.
6. Outcomes are better with protocol based management in dedicated/ experienced ICUs with close liaison with Poison care centres (e.g : National Poisons Information Centre - +(91)-11-26589391, 26593677; National Health Portal- <http://www.nhp.gov.in> )

**MORE ON THIS TOPIC**

- Dutta AK, Seth A, Goyal PK, et al. Poisoning in children: Indian scenario. Indian J Pediatr. 1998;65:365-70.
- Velez LI, Shepherd JG, Goto CS. Approach to the child with occult toxic exposure. From: <http://www.uptodate.com/contents/approach-to-the-child-with-occult-toxic-exposure>. Accessed September 25, 2014.
- Velez LI, Shepherd JG, Goto CS. Decontamination of poisoned children. From: <http://www.uptodate.com/contents/decontamination-of-poisoned-children>. Accessed September 25, 2014.
- VV Pillay, Comprehensive Medical Toxicology, 2<sup>nd</sup> ed. Paras Medical Publisher, Hyderabad, India.

## Chapter 9.2

# Poisonings by Common Drugs

Indumathy Santhanam, Sharada Sathish

Young children and infants, unlike adults and adolescents, ingest tablets more out of curiosity with a tendency to orally explore small objects. Unfortunately, even ingestion of one to two tablets can have life-threatening consequences in infants and toddlers. Early recognition, appropriate resuscitation and decontamination is essential to ensure optimal outcomes. Children presenting to the emergency department (ED) with history of tablet ingestion must be evaluated for airway instability, respiratory compromise, bradycardia, tachyarrhythmias, hypotension, convulsions, posturing and pupillary abnormalities within the first minute of arrival. Simultaneously, lifesaving maneuvers are initiated if necessary. Timed documentation of physiological status is mandatory, both for medical management and medico-legal purposes. Even if initially stable, physiological status can rapidly change. Thus frequent monitoring and documentation is essential. The child should be observed at least for 12 hours. If the ABCs are stable, the physician should look for toxidromes or signs that are specific for toxin ingestion.

## RISK ASSESSMENT

History taking, should not delay stabilization of the ABCs. History should include age, sex, approximate time of ingestion (if not witnessed), nature of tablets and whether the ingestion was accidental, suicidal or homicidal. Efforts should be taken to confirm name of the drug by inspecting the original containers, and prescriptions. All potentially accessible medications (purses, pill boxes) of both family members and visitors should be examined. Risk assessment should be based on the *worst case scenario*. It is wise to assume that the time of ingestion was the latest time possible and that all agents that were unaccounted for or missing had been ingested. Though spillage is difficult to estimate, one should presume that all the missing volume was consumed. When more than one child has ingested, then it is assumed that all the children have consumed all the missing drugs. If the ingested drug has been identified, a Poison Control Center (e.g. National Poison Control Centre, All India Institute of Medical Sciences, New Delhi) can be contacted for advice.

The commonest *two pills can kill* list includes, sodium channel blockers such as chloroquine, dextropropoxyphene, propranolol, tricyclic antidepressants, calcium channel blockers, diphenoxylate/atropine, dextropropoxyphene, beta-blockers, sulphonylureas and theophylline slow release (SR). **Table 1** summarizes possible causes of various clinical features.

**Table 1** Drugs and their toxic effects

Cardiac dysrhythmias	Chloroquine Anti-arrhythmic agents Anti-psychotics, anti-depressants
Hypotension and cardiogenic shock	Calcium channel blockers (large doses, sustained release preparations)
Coma	Opioids (direct CNS depression) Sulphonylureas (CNS depression due to drop in blood sugar)
Convulsions	Camphor (excitation)
Metabolic: Hypoglycemia, acidosis	Sulphonylurea, Aspirin

*Toxic effects that occur within a few hours* Chloroquine: Rapid onset of coma, seizures, cardiovascular collapse; Dextropropoxyphene: Ventricular tachycardia; Propranolol: Coma, seizures, ventricular dysarrhythmias, hypoglycemia; Tricyclic antidepressants: Coma, seizures, ventricular tachycardia, hypotension.

*Toxic effects occurring within 8–12 hours* Hypoglycemia occurring within the first 8 hours point towards sulphonylurea toxicity. Slow release formulations take up to 12 hours to start acting. These include the following: Calcium channel blockers (verapamil, diltiazem): Late onset conduction defects, bradycardia, Hypotension and refractory shock; Opioids: Coma, respiratory depression, pin point pupils; Theophylline SR: vomiting, seizures, supraventricular tachycardia.

## INVESTIGATIONS

An urgent glucose estimation is recommended, if a child presents with unknown tablet ingestion. It is also mandatory following ingestion of sulphonylureas and for children presenting with altered mental status. If capillary blood glucose is less than 80 mg/dL, rapid dextrose correction is initiated. If intravenous access is unavailable, intramuscular glucagon (1.0 mg) is recommended. In addition, a 12-lead ECG should be taken for ingestion of cardiac drugs such as digoxin, calcium channel blockers, beta blockers and antiarrhythmic agents. If ECG abnormalities are noted, continuous monitoring is necessary until recovery. If the nature of the ingested drug is unknown, ECG is performed as a screening test. It may be repeated if the child appears unwell or the cardiopulmonary assessment shows instability.

## TREATMENT

### Gastric Decontamination (Table 2)

Gastric lavage and activated charcoal are not routinely performed except in the most severe cases. Since, the potential risks of stomach wash or activated charcoal far outweigh the benefits, decontamination is not recommended.

### Gastric Lavage

Gastric lavage is performed by placing a large bore orogastric tube through which normal saline is administered. The saline is aspirated until the effluent is clear. Though orogastric tubes recover significant amounts of gastric contents, its use is limited due to poor tolerance, stimulation of the gag reflex, risk of aspiration and perforation. The American Academy of Clinical Toxicology (AACT) and European Association of Poison Centres and Clinical Toxicologists (EAPCCT) recommend that gastric lavage may employed, if a large amount of toxin has been ingested and if the patient has been brought within 1h of ingestion.

**Table 2** Drugs used for gastric decontamination

Drug	Dose	Problems during administration	Avoid in the following conditions
Activated Charcoal	1–2 g/kg (max 50–60 g)	Vomiting, Aspiration,	Unprotected airway, Altered mental status
Gastric lavage	10–15 mL/kg	Vomiting, Aspiration	Persistent vomiting
Polyethylene glycol (PEGLEC)	500 mL/h < 5 years 1000 mL/h > 6 years	Vomiting, crampy abdominal pain	GI bleed Intestinal obstruction, ileus Perforation



### Activated Charcoal

Activated charcoal has been used to reduce absorption of a wide variety of toxins from the stomach and the intestinal tract. It acts by interrupting enterohepatic and enteroenteric re-circulation of drugs in the gut lumen. The drugs that can be eliminated are carbamazepine, phenobarbitone, phenytoin, valproate, dapson, theophylline and salicylates. It is difficult to use in children since its lack of palatability and unattractive appearance causes vomiting. The AACT discourages the routine use of activated charcoal except if the ingestion had occurred within 1 hour. The recommended dose of charcoal to drug is 10:1. A dose of 1–2 g/kg is advised if the quantity of the ingested drug is not clear.

### Whole Bowel Irrigation

Polyethylene glycol (PEGLEC) is used for irrigation following ingestion of iron tablets and sustained release medications. It is an electrolyte lavage solution, formulated to prevent extensive absorption or secretion of fluid across the gastrointestinal (GI) mucosa. Large volumes of this solution are administered enterally, until the rectal effluent is clear. The head end is elevated head to at least 45° to prevent aspiration. If emesis occurs, the infusion is discontinued for 30 min, and restarted at half the previous rate and increased as tolerated. Metoclopramide may be given if needed. Whole bowel irrigation (WBI) is safe in children; volumes as large as 44L have been administered without ill effects. Typical rates of administration are 500–1000 mL/h, orally or by nasogastric tube. The adverse effects associated with this procedure consist of vomiting, abdominal cramps and bloating.

### Cathartics

Currently, cathartic agents are contraindicated. The risk of hypernatremic dehydration and cardiovascular collapse is high with sorbitol, while hypermagnesemia is a hazard in children with renal disease.

### Enhanced Elimination

Elimination is not a preferred technique in the management of children presenting with drug ingestion. Theophylline toxicity is the only exception where hemodialysis is recommended. This modality of elimination is employed when clinical evidence of tachyarrhythmias and seizures occur in association with elevated serum theophylline levels.

### Antidotes

Table 3 lists the antidotes for some of the drugs.

### SPECIFIC DRUG INGESTIONS

#### Chloroquine

Chloroquine has a very small toxic-to-therapeutic margin. Fatality has been reported for ingestion of 300 mg of base of chloroquine. Respiratory depression often occurs. Apnea, hypotension, and cardiovascular compromise can occur quickly. Electrocardiographic abnormalities include QRS prolongation, AV block, ST- and T-wave depression, increased U waves, and QTc interval prolongation. Significant hypokalemia may be associated with the cardiac manifestations. Hypokalemia results from chloroquine induced intracellular shifts. Neurologic manifestations include central nervous system (CNS) depression, dizziness, headache, and convulsions. Management is symptomatic. Oro-gastric lavage and activated charcoal are recommended. Enhanced elimination has no role. There is no antidote.

#### Theophylline

Serum levels of 5–15 mcg/mL is considered toxic. Toxic effects are due to adenosine antagonism, release of endogenous norepinephrine resulting in adrenergic receptor stimulation and phosphodiesterase inhibition. Toxicity affects the GI, cardiovascular, CNS, musculoskeletal system. It also causes

**Table 3** Antidotes for common drug poisoning

Poison/overdose	Antidote	Route	Dosage	Adverse effects
Paracetamol	N-Acetyl Cysteine	IV	150 mg/kg over 1 hour followed by 50 mg/kg over 4 hours followed by 100 mg /kg over 16 hours	Nausea, vomiting
		PO	140 mg/kg loading followed by 70 mg/kg Q4h for 17 doses	Anaphylactoid reactions
Benzodiazepines	Flumazenil	IV	0.2 mg over 30s; if response inadequate repeat q1 min to 1 mg max	Nausea, vomiting, facial flushing, agitation, headache, dizziness and seizures
Beta blocs	Glucagon	IV	0.15 mg/kg bolus followed by infusion of 0.05–0.15 mg/kg/h	Hyperglycemia, nausea and vomiting
Calcium channel blockers	Insulin	IV	1 U/kg bolus followed by infusion of 0.5–1 U/kg/h	Hypoglycemia, follow serum potassium and glucose closely
	Calcium	IV	Dose depends on the specific calcium salts*	
Iron	Deferoxamine	IV	Infusion of 5–15 mg/kg/h; maximum 6 g/24 h	Hypotension(minimized by avoiding rapid infusion rates)
Isoniazid	Pyridoxine	IV	Empirical dosing-70 mg/kg; maximum 5 g If intake dose is known 1 mg per milligram of INH	Can be given by NG tube and IM also
Sulfonylureas	Octreotide	IV/SC	1–2 mcg/kg/dose (adults: 50–100 mcg) q6-8h	
Antihistamines/ Anti-cholinergics	Physostigmine	IV/IM	0.02 mg/kg over 5 min may repeat q5-10 min to 2 mg max	Bradycardia, asystole, seizures, bronchospasm, vomiting, headache

\*: Calcium chloride- 100 mg/mL (10%): 20 mg/kg/dose not to exceed 45–90 mg/kg/h with a maximum concentration of 20 mg/mL  
Calcium gluconate- 200–500 mg/kg IV or PO

metabolic derangements. Intractable vomiting, ventricular extrasystoles, tachyarrhythmias, peripheral vasodilation, hypotension, hyperventilation, respiratory alkalosis, respiratory failure and acute lung injury may be precipitated. CNS toxicity is characterized by headache, anxiety, agitation, insomnia, tremor, irritability, hallucinations, and seizures. Hypokalemia can also occur. Fluids and vasopressors are given for hypotension and beta blockers are used to control arrhythmias. Benzodiazepines (BDZ) and barbiturates are recommended for convulsions. Hypokalemia is corrected if identified. Ondansetron is useful for vomiting. There is no role for orogastric lavage since absorption is rapid. However, activated charcoal plays an important role. Whole bowel irrigation helps in elimination of sustained release formulations. Hemodialysis is indicated for serum theophylline level more than 90 µg/mL or serum level more than 40 µg/mL and seizures/hypotension unresponsive to intravenous fluid/ventricular dysrhythmias.

### Iron Toxicity

Ferrous salts have a propensity to cause more toxicity than the nonionic iron preparations. Toxicity occurs when more than 20 mg/kg of elemental iron is ingested. Direct mucosal irritation can cause GI bleeding. Ingestion of a large quantity of iron tends to overwhelm the normal storage sites and proteins. Since iron takes part in redox reactions, free iron, leads to generation of a large amount of free oxygen radicals. Oxidative damage of the various organs results in congestion, edema, necrosis, and hemorrhage. Iron being an intracellular poison affects almost every organ in the body. It can cause acute periportal hepatic necrosis, pancreatic necrosis, and pulmonary and renal damage.

The free iron ions in circulation also disrupt the mitochondrial oxidative phosphorylation leading to generation of excessive H<sup>+</sup> ions leading to metabolic acidosis. Furthermore, iron also causes massive postarteriolar dilatation, increased capillary permeability and coagulopathy leading to shock, within the first few hours after ingestion. Myocardial failure, caused by reactive oxygen species induced myocardial damage further contributes to shock. Clinical features are summarized in **Table 4**.

### Laboratory Parameters

Laboratory values including chemistries, hemoglobin, iron concentration, coagulation, and hepatic profiles are necessary in the sickest patients. An arterial blood gas, venous blood

**Table 4** Clinical stages in iron intoxication

Stages	Time	Manifestation	Remarks
Stage I Local toxic stage	0–6 hours	Nausea, vomiting, abdominal pain, and diarrhea, hematochezia melena and hematemesis	Absence of vomiting excludes serious toxicity
Stage II Latent stage	6–24 hours	Resolution of previous symptoms	Ongoing cellular damage
Stage III Shock stage	12–24 hours	Shock, lethargy, seizures coma	May occur in first few hours following massive ingestion
Stage IV	2–3 days	Hepatic failure	Uptake of iron by the reticuloendothelial cells of liver
Stage V	2–8 weeks	Gastric outlet obstruction	Rarely seen

gas, or stat electrolytes rapidly detects a metabolic acidosis. Anion gap metabolic acidosis, elevated leukocyte counts more than 15000/mm<sup>3</sup> and hyperglycemia greater than 150 mg/dL suggest iron intoxication. Toxic ingestion is characterized by peak concentrations of iron at 2–6 hours after ingestion. Serum iron concentrations between 300 µg/dL and 500 µg/dL usually correlate with significant GI toxicity and modest systemic toxicity. Concentrations between 500 µg/dL and 1000 µg/dL are associated with pronounced systemic toxicity and shock. Concentrations more than 1000 µg/dL is associated with significant morbidity and mortality. Lower concentrations cannot exclude the possibility of serious toxicity.

### Management

Stabilization of airway breathing and circulation takes the priority. Large bore intravenous access should be established while decontamination procedures are started simultaneously. Fluid resuscitation should take place along with WBI. History should include time of since ingestion and the percentage of elemental iron in the preparation and how much of iron per kg body weight had been ingested. Consumption of iron more than 30 mg/kg warrants admission and investigation (**Table 5**).

**Table 5** A triage based on alleged amount of consumption of elemental iron

Dose	Risk for toxicity	Procedure
<20 mg/kg	Little risk	Decontaminate Observation for 6 hours
20–60 mg/kg	Moderate risk	Decontaminate Observe for 6 hours consider desferrioxamine chelation
>60 mg/kg	High risk	Decontaminate Start chelation therapy

**Gastrointestinal decontamination** Activated charcoal does not bind iron and hence should not be used for decontamination. Gastric lavage may be employed. Endoscopic removal is an alternative strategy for removal of large ingestions.

**Enhance elimination** Whole bowel irrigation is the preferred method for iron ingestion. The usual dose of WBI with polyethylene glycol electrolyte lavage solution is 500 mL/h in children. This rate is best achieved by starting slowly and increasing as tolerated, often using a nasogastric tube and an infusion pump to administer large volumes. Antiemetics such as metoclopramide or serotonin antagonists can be used to treat nausea and vomiting. Irrigation must be continued until abdominal films are clear.

### Antidote

The specific antidote for iron toxicity is deferoxamine. In the presence of ferric iron (Fe<sup>3+</sup>), deferoxamine forms the complex ferrioxamine, which is excreted by the kidneys, imparting a reddish-brown color to the urine (vin rosé). Deferoxamine chelates only the free iron and not the iron present in transferrin, hemoglobin, or hemosiderin. 100 mg of deferoxamine mesylate chelates approximately 8.5 mg ferric iron. Intravenous administration of deferoxamine should be considered in patients with persistent vomiting, toxic appearance, lethargy, signs of shock, hypotension and metabolic acidosis. Deferoxamine administration also should be considered for any patient with a serum iron concentration more than 500 µg/dL. In patients manifesting serious signs and symptoms of iron poisoning, deferoxamine should be initiated as an intravenous infusion, starting slowly and gradually increasing to a dose of 15 mg/kg/h (maximum daily dose 360 mg/kg, and total 6 g). Hypotension is the rate-limiting factor as more rapid infusions

are used. Infusions are continued until the urine returns to normal color. Occasionally, normal urine color in presence of high serum iron has been reported making the decision regarding the end point difficult. Stable clinical state of the patient combined with urine color in response to deferoxamine, and serum iron less than 100 µg/dL is probably the more appropriate end-point.

### Antihistamine and Cough Medication Toxicity

Sympathomimetic agents are also major ingredients of cough preparations. Severe toxicity is characterized by hypertension, reflex bradycardia, arrhythmias, convulsions and coma. Paracetamol is the next major ingredient and should not be overlooked when evaluating toxicity. Opioids are also commonly found in cough syrups. Dextromethorphan, another common drug in cough mixtures, has low toxic potential. Codeine, another common ingredient causes toxicity when large amounts are ingested. Anti-histamines in cough syrups may cause CNS depression and cardiovascular toxicity. The presence of several active ingredients in a single preparation may produce a confusing clinical picture and potentiate adverse effects. A variety of arrhythmias can occur due to blockade of the sodium channel.

### Management

Seizures are controlled using benzodiazepines. Hypotension should be corrected with fluids and inotropes. Adrenaline should be avoided since paradoxical hypotension has been noted. Asymptomatic children should be observed for a minimum of 4 hours. Multiple dose activated charcoal can be administered since anticholinergic agents decrease GI motility.

Physostigmine (0.02 mg/kg slowly IV over 3–5 min) is the recommended antidote for treating anti-cholinergic toxicity. Magnesium sulphate may be administered in arrhythmias due to terfenadine and astemizole.

### Paracetamol Poisoning

When toxic dose of paracetamol has been ingested, absorption occurs within 2 hours and peak plasma levels are attained within 4 hours.

**Phase 1: 30 min–24 hours after overdose** During this phase children demonstrate malaise, anorexia, nausea, vomiting, pallor, and diaphoresis. Rarely, following massive overdoses resulting in direct toxic effect on the liver, metabolic acidosis and coma could occur.

**Phase 2: 24–72 hours after overdose** The phase 1 symptoms subside. Right upper quadrant tenderness develops due to hepatic damage. Liver enzymes and INR (International Normalized Ratio) are elevated. Renal functions begin to deteriorate, although blood urea remains normal secondary to decreased hepatic urea formation.

**Phase 3: 72–96 hours after overdose** In this phase, on-going hepatic centrilobular necrosis progress to fulminant hepatic failure. The clinical features reflect this process resulting in coagulation defects, hypoglycemia, metabolic acidosis, and jaundice. Renal and cardiac failures, along with hepatic encephalopathy lead to death.

**Phase 4: 4 days–2 weeks after overdose** If the victim survives phase 3, complete resolution of hepatic and renal function is possible.

### Risk Assessment

The clinician must attempt to predict the likely clinical course and potential complications following ingestion. History should focus on the dose and concentration of paracetamol ingested and whether there is history suggestive of increased susceptibility to toxicity. Examination and investigations should be aimed at recognizing evidence of liver damage (**Table 6**). Clinical or biochemical evidence of liver injury may not be apparent for up to 24 hours after acute paracetamol overdose. Serum paracetamol

**Table 6** Paracetamol dosing that may be associated with hepatic injury\*

	Adults and children >6 years	Children aged 0–6 years
Acute single ingestion	>200 mg/kg or 10 g whichever is less over a period of less than 8 hours	≥200 mg/kg over a period of less than 8 hours
Repeated supra therapeutic ingestion	>200 mg/kg or 10 g (whichever is less) over a single 24 hours period >150 mg/kg or 6 g (whichever is less) per 24 hours period for the preceding 48 hours. >100 mg/kg or 4 g/day (whichever is less) in patients with predisposing risk factors**	>200 mg/kg over a single 24 hours period >150 mg/24 hours period for the preceding 48 hours >100 mg/kg/24 hours period for the preceding 72 hours period in patients with predisposing risk factors**

\* Adapted from Dart RC, Erdman AR, Olson KR et al. Acetaminophen poisoning; and evidence-based consensus guidelines for out of hospital management. Clin Toxicol. Philadelphia: 2006;44:1–18.

\*\* predisposing risk factors are use of enzyme inducing drugs, malnutrition, prolonged fasting

levels should be used to assess the need for *N*-acetylcysteine (NAC) administration in all patients with deliberate paracetamol self-poisoning, regardless of the stated dose. The best surrogate marker indicating the potential for injury is a timed serum paracetamol level plotted on a nomogram. However, the nomogram cannot be applied for repeated or staggered doses, or if the time of ingestion cannot be determined with confidence.

The most important risk factor for liver damage and death after acute paracetamol ingestion is the extent of delay beyond 8 hours until treatment with NAC commences. Treatment within 8 hours will prevent all serious hepatic injury. However, NAC has frequent adverse effects, is moderately expensive and requires hospitalization, so it is not reasonable to administer it to every patient with possible paracetamol overdose.

The treatment nomogram (available from Daly FF1, Fountain JS, Murray L, et al. *Med J Aust.* 2008;188:296–301) is to simplify decision making. This provides both a margin of safety for patients who may possess risk factors and a small margin of error for estimation of time of ingestion, and avoids the need for potentially confusing additional lines.

### Management

Gastric lavage or induction of emesis is not useful. A single dose activated charcoal may be administered at a dose of 1 g/kg mixed into a slurry with water or juice if the ingestion has occurred within 2 hours, more than 200 mg/kg ingestion or the toxic dose has been ingested in tablet form. Specific antidote is *N*-acetylcysteine. NAC, when administered within 8 hours of ingestion can prevent fatality. Beyond 8–10 hours of ingestion, efficacy decreases. Risk assessment for patients presenting within 8 hours can be plotted on a nomogram when they present with known time of ingestion along with serum paracetamol levels. For those who present beyond 8 hours after ingestion, NAC should be commenced immediately if the dose exceeds the threshold for possible toxicity or the patient shows clinical signs suggestive of paracetamol toxicity (nausea, vomiting, right upper quadrant pain or tenderness). Evaluation of serum paracetamol and alanine aminotransferase (ALT) levels should also be performed as soon as possible. If serum paracetamol level is subsequently found to be below the nomogram line, *N*-acetyl cysteine may be stopped; if above the line, it should be continued.

The baseline serum ALT level helps to evaluate level of risk and provides useful baseline data if NAC is indicated. Additionally, when NAC is commenced, baseline international normalised ratio and platelet count provide data regarding severity of hepatic failure. *If the time of ingestion is unknown*, or the treating clinician is not confident of the history of ingestion, it is safest to treat the patient as a delayed presentation. NAC infusion appears to preserve cerebral blood flow and perfusion better than traditional therapies such as mannitol and hyperventilation. With the exception of established liver failure, where the intravenous route has been investigated, intravenous and oral NAC administration is equally efficacious in treating paracetamol toxicity. Oral NAC has fewer severe side effects than IV NAC. Discontinuation of NAC is based on reduction of serum paracetamol level to  $<10$  mcg/mL and the absence or resolution of liver injury. Once these conditions can be assured, discontinuation of NAC therapy is appropriate. Outcomes following use of the 20-hour, 48-hour and 36-hour IV NAC dosing protocols and other short-course dosing protocols suggest that all therapies are safe and effective the patients are treated within 8 hours of an acute ingestion. **Flow chart 1** summarizes the management of paracetamol poisoning.

### Salicylate Poisoning

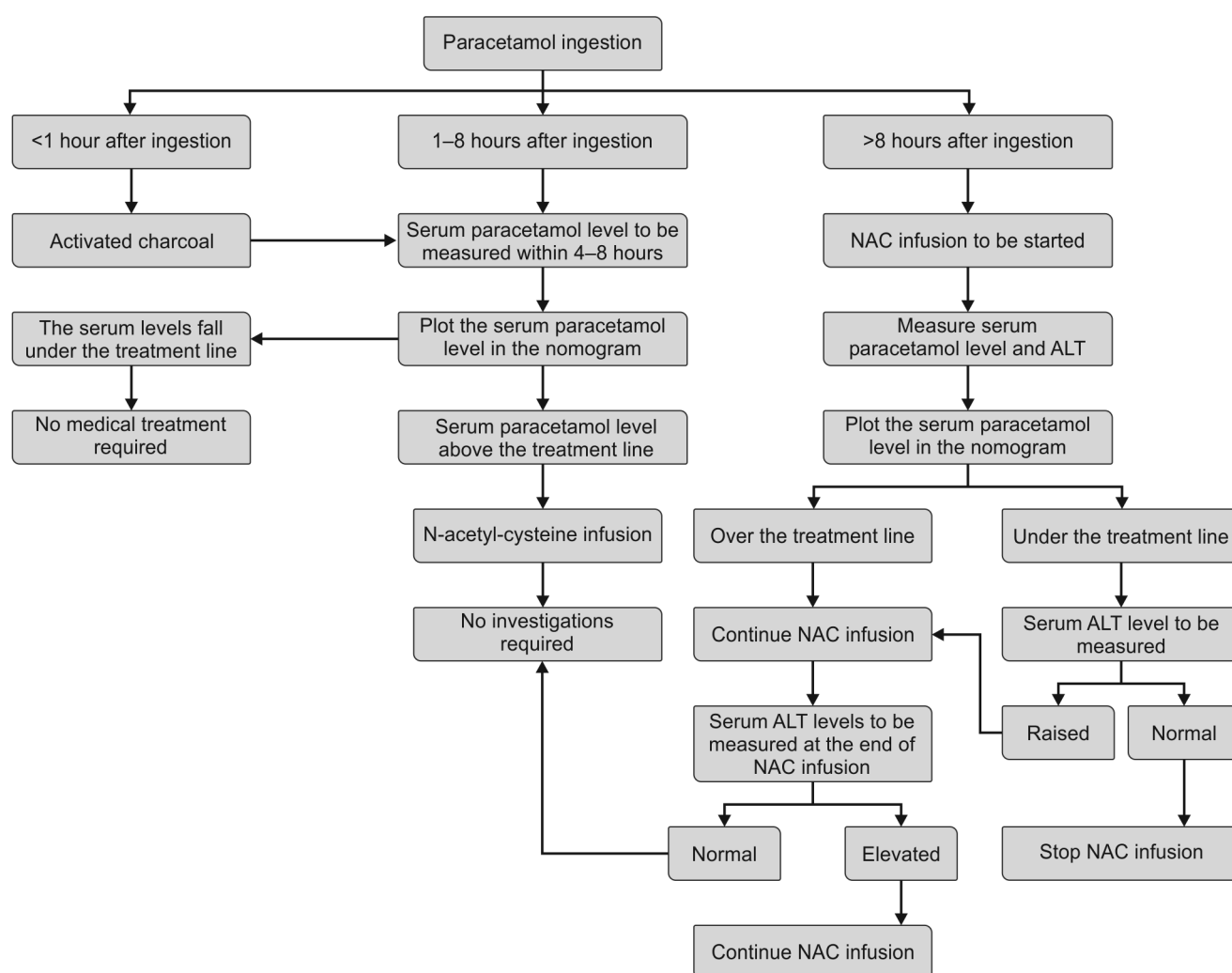
In addition to ingestion of acetyl salicylic acid (aspirin), salicylate poisoning may also result from application of salicylate containing

ointments, keratolytic agents, or other agents containing methyl salicylate (oil of wintergreen). Liniments and ingredients used in hot vaporizers contain high concentrations of methyl salicylate (up to 30% in liniments and 100% oil of wintergreen). The intentional or unintentional ingestion of such topicals is usually disastrous: approximately 1–2 teaspoons (5–10 mL) of methyl salicylate can be lethal for a young child. Onset of symptoms usually occurs within 2 hours of ingestion. In a child, weighing 10 kg, the minimum toxic salicylate dose of approximately 150 mg/kg body weight. One milliliter of oil of wintergreen contains 140 mg/kg of salicylate.

### Clinical Features (Box 1)

Salicylates stimulate the respiratory center in the brainstem, leading to hyperventilation and respiratory alkalosis. CNS effects may include vertigo, hyperactivity, agitation, delirium, hallucinations, convulsions, lethargy, and stupor. Coma is rare and generally occurs only after massive ingestions (serum salicylate concentrations  $>100$  mg/dL) or mixed overdoses. In addition, salicylates are weak acids and in toxic concentrations replace 2–3 mEq/L of plasma bicarbonate. Impaired renal function resulting from salicylate toxicity leads to accumulation of sulfuric and phosphoric acids. The latter interferes with the Krebs cycle limiting the production of adenosine triphosphate (ATP). Uncoupling of oxidative phosphorylation, causes accumulation of pyruvic and lactic acids and generates large amounts of heat. Salicylate induced increased

**Flow chart 1** Algorithm for acute paracetamol poisoning with known time of ingestion





**BOX 1 Features of Salicylate Poisoning**

**Coagulation abnormalities:** Hypoprothrombinemia, inhibition of factors V, VII, X, platelet dysfunction.

**Gastrointestinal:** Nausea, vomiting, hemorrhagic gastritis, decreased motility, pylorospasm.

**Hepatic:** Abnormal liver enzymes, altered glucose metabolism.

**Metabolic:** Diaphoresis, hyperthermia, hypoglycemia, hyperglycemia, hypoglycorrhachia, ketonemia, ketonuria.

**Pulmonary:** Tachypnea, respiratory alkalosis, acute lung injury.

**Renal:** Tubular damage, proteinuria, sodium and water retention, hypouricemia.

fatty acid metabolism generates ketone bodies: beta-hydroxybutyric acid, acetoacetic acid, and acetone. The net result is a wide anion gap metabolic acidosis. A significant component of this metabolic acidosis is a ketoacidosis. The pH of salicylic acid offers a unique opportunity to increase elimination by alkalinizing the urine.

### Treatment

The rapid cardiopulmonary cerebral assessment is performed. Fluid losses following salicylate poisoning can be huge, especially in children, and can be attributed to tachypnea, vomiting, fever, a hypermetabolic state, hyperpnea, and insensible perspiration. Shock or dehydration must be adequately assessed and corrected if necessary, along with any glucose and electrolyte abnormalities. Multiple dose of activated charcoal may help. Forced alkaline diuresis helps rapidly remove salicylates. Hemodialysis may be needed in severe toxicity.

### Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The commonest NSAIDs used for children are ibuprofen, mefenamic acid and diclofenac. Most of the acute toxicity due to NSAIDs is due to inhibition of COX 1 enzyme in the GIT. This inhibits the formation of cytoprotective prostaglandins PGE<sub>2</sub> and PGI<sub>2</sub> resulting in decreased production of mucus and bicarbonate, promotes HCl secretion, decreases gastric blood flow. All these lead to reduced GI protection. The acidosis associated with NSAID overdose occurs infrequently and usually is a high-anion-gap metabolic acidosis. The most common effects of toxicity are due to GI distress and CNS depression. Other CNS effects may include changes in cognition, hallucinations, muscle twitching, or seizures and are most frequent after mefenamic acid overdose. Children who ingested more than 400 mg/kg are more likely to develop seizures, apnea, hypotension, bradycardia, metabolic acidosis, and renal and hepatic dysfunction.

### Management

The cardiopulmonary cerebral assessment should be performed to determine the physiological status. If the physiological status is unstable, resuscitate the ABCDs. Benzodiazepines are necessary for control of seizures following large dose consumption of mefenamic acid. Acid base status should be evaluated and managed. Fluid and electrolyte imbalances are corrected. Proton pump inhibitors are administered to treat or prevent GI toxicity. As the absorption of NSAIDs is very rapid, gastric lavage is not indicated. Children who have consumed more than 100 mg/kg of ibuprofen and more than 25 mg/kg of mefenamic acid should receive activated charcoal. Hemodialysis is ineffective. There is no specific antidote.

### Isoniazid (INH) Poisoning

INH is rapidly absorbed via GI tract (GIT) and attains peak concentrations within 2 hours. INH alters the metabolism of pyridoxine, creating a functional deficiency of pyridoxine that

results in impaired activity of pyridoxine-dependent enzyme systems, as well as a decrease in catecholamine synthesis. INH also interferes with the synthesis of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. Acute intoxication of INH leads to a triad of refractory seizures, hyperglycemia and metabolic acidosis. The clinical features appear within 30 min of ingestion. Seizures occur following ingestion of 20 mg/kg of INH and persist until GABA is regenerated. Protracted coma (24–48 hours) occurs following seizures. Metabolic acidosis occurs due to increased lactic acid levels.

### Management

Gastric lavage is performed and activated charcoal is administered if ingestion of drug has occurred within an hour. Asymptomatic patients who present to the ED within 2 hours of ingestion may be observed for a 6 hours period for signs of toxicity. There is no role for increased elimination. If comatose or convulsing, the airway is secured and ventilation is provided. If shock is identified, small volume aliquots are administered. If convulsing, standard protocol for status epilepticus is started. Benzodiazepines complement the action of pyridoxine in the control of seizures and are the drugs of choice. As phenytoin has intrinsic GABA-ergic activity they are contraindicated. Gastric lavage is withheld until airway is stabilized. Pyridoxine (1 g per 1 g of INH) is the antidote of choice. In children, if unknown quantities have been ingested 70 mg/kg of pyridoxine to a maximum of 5 g may be administered at a rate of 1 g every 2–3 min.

### Benzodiazepines

Benzodiazepines (BDZ) are the most common sedative hypnotics prescribed and used. Intentional poisoning is more common in adolescents. BDZ overdose by itself is safe in children, but when it is taken in combination with other drugs, may result in depressed level of consciousness. Combination of drugs with BDZ is more toxic due to their synergistic effects and cause more CNS depression.

### Clinical Features

Significant overdoses manifest as slurred speech, ataxia, and incoordination. Moderate to severe toxicity manifests as stupor or coma. In the most severe cases, all neurologic responses may be lost and respiratory depression parallels CNS depression. Hypoventilation produces respiratory acidosis and contributes to cardiovascular depression. The vast majority of children develop symptoms within 4 hours of BDZ ingestion. 90% of the children develop ataxia, as the most common sign of toxicity. Only 10% children develop respiratory depression.

### Management

Gastric lavage may be performed if the ingestion has occurred within the past 1 hour. Activated charcoal has a doubtful role. Flumazenil rapidly reverses the sedative effects of BDZ. Flumazenil's onset of action is within 1–3 min. Its maximum effect lasts for 6–10 min. Dosage: 0.01 mg/kg (maximum dose: 0.2 mg) with repeated doses of 0.01 mg/kg given every minute to a maximum cumulative dose of 1 mg. It is administered rapidly IV injection over 15–20 in a large IV line. Care is taken not to exceed 0.2 mg/minute.

### Phenytoin Poisoning

Clinical features include nausea, vomiting, dizziness, vertigo, lethargy, weakness, cardiac arrhythmias, abdominal distention or ileus, and renal failure. Acute overdose predominantly causes neurotoxicity affecting cerebellar and vestibular functions. CNS drug levels correlate with serum drug levels: serum phenytoin levels

>15 mg/dL: nystagmus; >30 mg/dL: ataxia; >50 mg/dL: lethargy, slurred speech, pyramidal and extrapyramidal manifestations.

### Management

If the child is stable, serum phenytoin levels are evaluated. The therapeutic serum drug levels are 10–20 mg/mL. Gastric lavage is performed within the first hour of ingestion. Multidose activated charcoal is indicated, to prevent drug absorption. However, there is no role for increased elimination and no specific antidote is available. Deaths from phenytoin toxicity are rare.

### Beta-Blockers

Beta-blockers are rapidly absorbed from the GIT with their peak effect ranging from 1 hour to 4 hours. Toxicity results in blunting of the chronotropic and dromotropic response. There is interference in the uptake of calcium into the sinus node leading to stimulation of calcium-sensitive outward potassium channels and subsequent refractory bradycardia. Toxicity also results in centrally mediated respiratory depression, the mechanism of which is unknown. Other clinical features include hypotension, unconsciousness, hypoglycemia and seizures. Propranolol is the commonest agent associated with fatality.

### Management

If the physiological status is stable, decontamination using activated charcoal is advised. If ingestion had occurred less than an hour ago, gastric lavage may be performed. If sustained release tablets had been ingested PEGLEC should be considered. If bradycardia is noted, in addition to the steps taken above, injection atropine is advised. Glucagon is the antidote of choice (start with 50 mcg/kg IV, increase to maximum 10 mg till a response occurs at 1–2 min intervals). Then a glucagon infusion is started at the response dose/hour. Calcium infusion is initiated. Supportive management is given for shock. Supra-physiological doses of vasopressors may be needed, if shock is refractory to fluids.

### Calcium Channel Blockers

Diltiazem and verapamil are the most toxic of calcium channel blockers (CCB). They inhibit the L-type calcium channels leading to reduction in the myocardial calcium flux, decreased force of contraction, and bradycardia. Decrease in the vascular smooth muscle calcium influx leads to vasodilatation. Toxic doses can lead to hyperglycemia. Toxicity features appear within 2–3 hours of the ingestion (delayed up to 6–8 hours in sustained release CCBs). If child presents with bradycardia, hypotension or cardiogenic shock, provide ventilation, small aliquots for shock resuscitation and early inotropes, if needed. Orogastric lavage and WBI is advised. Therapy is symptomatic. There is no specific antidote.

### Anti-diabetics and Hypoglycemics

Sulfonylureas act by binding to the potassium ATP channels and inhibiting the potassium efflux stimulated insulin release. Biguanides inhibit gluconeogenesis. Clinical features are due to hypoglycemia mediated CNS symptoms. Single dose activated charcoal may be useful in children with metformin overdose. Gastric lavage has a doubtful role. Therapy focuses on maintenance of euglycemia by ensuring oral feeds or administration of dextrose

infusion. Despite dextrose infusion, if hypoglycemia persists, octreotide is administered at 4–5 µ/kg/day SC divided in 6 hourly doses. If blood glucose (BG) is greater than 60 mg/dL and the child is asymptomatic, observation is recommended for at least 8 hours. Hemodialysis may help in children with severe metabolic acidosis due to metformin ingestion.

### MORE ON THIS TOPIC

- Chang TP, Rangan C. Iron poisoning: a literature-based review of epidemiology, diagnosis, and management. *Pediatr Emerg Care*. 2011;27:978-85.
- Craig S. Phenytoin poisoning. *Neurocrit Care*. 2005;3:161-70.
- Daly FF, Fountain JS, Murray L, et al. Guidelines for the management of paracetamol poisoning in Australia and New Zealand—explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres. *Med J Aust*. 2008;188:296-301.
- Ho J, Jackson Johnson D. Massive levothyroxine ingestion in pediatric patient: case report and discussion. *CJEM*. 2011;13:165-8.
- Juurlink DN, Tenenbein M, Koren G, et al. Iron poisoning in young children: association with the birth of a sibling. *CMAJ*. 2003;168:1539-42.
- Kreshak AA, Tomaszewski CA, Clark RF, Cantrell FL. Flumazenil administration in poisoned pediatric patients. *Pediatr Emerg Care*. 2012;28:448-50.
- Love JN, Sikka N. Are 1-2 tablets dangerous? Beta-blocker exposure in toddlers. *J Emerg Med*. 2004;26:309-14.
- Ranniger C, Roche C. Are one or two dangerous? Calcium channel blocker exposure in toddlers. *J Emerg Med*. 2007;33:145-54.
- Riordan M, Rylance G, Berry K. Poisoning in children 2: painkillers. *Arch Dis Child*. 2002;87:397-9.

### IN A NUTSHELL

1. The “two pills can kill” list includes, sodium channel blockers such as chloroquine, dextropropoxyphene, propranolol, tri-cyclic anti-depressants, calcium channel blockers, diphenoxylate/atropine, dextropropoxyphene, beta-blockers, sulphonylureas and theophylline SR.
2. Paracetamol dose less than 150 mg/kg does not warrant further action.
3. Ideally, N-acetylcysteine (NAC), should be administered within 8 hours of ingestion of paracetamol to prevent fatality. Beyond 8–10 hours of ingestion, its efficacy decreases.
4. The intentional or unintentional ingestion of topical agents having methyl salicylate as ingredient is usually disastrous. Approximately, 1–2 teaspoons (5–10 mL) of methyl Salicylate can be lethal for a young child.
5. Gastric decontamination such as gastric lavage and activated charcoal are not routinely performed in asymptomatic children with normal cardiopulmonary cerebral assessment unless a large quantity has been ingested and the presentation is within 1 hour.
6. Dextrostix and ECG should be performed as part of screening for unknown toxicity and repeated as needed.
7. Activated charcoal is useful for drugs such as carbamazepine, phenobarbital, phenytoin, valproate, dapsone, theophylline and salicylates.
8. Polyethylene glycol (PEGLEC) is useful in ingestion of iron tablets and sustained release medications.

## Chapter 9.3

# Hydrocarbon Poisoning

Jayashree M, Karthi N

Hydrocarbon ingestions account for about 5% of all accidental poisonings and 25% of all fatal ingestions in the under-5 children, globally. The hydrocarbon compounds commonly implicated in toxic exposures are as depicted in **Table 1**. Accidental kerosene poisoning remains a serious problem in India and other developing countries with incidence varying from 25% to 60%. In a recent study from India, kerosene ingestion accounted for 27% of all poisoning admissions to pediatric intensive care unit (PICU) though a decreased incidence has been noted in the recent 5 years. Data from USA for hydrocarbon related injuries in the past decade has also shown a decline from 19.5 ED to 13.8 ED visits per 100,000. Despite the declining trend, hydrocarbons still present a high-risk for injury in children younger than 5 years. The accessibility depends on factors such as demography, socioeconomic status, education, local belief and customs. Hydrocarbons especially kerosene is commonly used as fuel for cooking and lighting in rural homes. Inappropriate storage in unmarked soft drink or beverage bottles and attractive color (blue color additive) coupled with children's desire to explore, account for the high incidence of hydrocarbon exposures. Higher incidence during summer months is because the kerosene stored in soft drink bottles is mistakenly consumed for water by the thirsty children. The morbidity and mortality associated with hydrocarbon ingestion are related to pulmonary aspiration and its complications.

## HYDROCARBON COMPOUNDS

Hydrocarbons are broadly classified into aliphatic (straight chain) and aromatic (with a benzene ring) hydrocarbons. The former derived as byproducts of petroleum distillation are the most commonly implicated hydrocarbons in toxic exposures. The potential for pulmonary aspiration depends primarily on the triad of viscosity, volatility and surface tension. Compounds with low viscosity (flow easily), high volatility (aids pulmonary absorption) and low surface tension (allows the substance to spread easily over the contacted surface) carry the highest risk for aspiration. Of the three, the most important determinant for pulmonary aspiration is the viscosity as it facilitates entry and deeper penetration. Substances with viscosity less than 45–60 SSU (Saybolt seconds

universal) are considered at high-risk for aspiration. There is no correlation between volume of hydrocarbon ingested and severity of aspiration. Kerosene has a bad taste which precludes large volume ingestions. Ingestion of even small amounts poses a risk of serious pulmonary toxicity especially in young children. Although vomiting often precedes and precipitates aspiration, lack of vomiting does not rule out the possibility of aspiration. Gastrointestinal absorption is minimal and systemic toxicity is rare even with ingestion of large doses (12–18 mL/kg).

*Halogenated hydrocarbons* are used in households and industries as solvents, dry-cleaners, degreasers and vehicles for paints and varnishes. They are highly volatile (ability to vaporize) and toxic exposures occur mainly by inhalation. Intentional inhalation can be encountered in adolescents when taken for recreational purposes. Halogenated hydrocarbons also possess high aspiration potential, but differ from aliphatic agents in their ready absorbability from GI tract and increased potential to produce systemic toxicity of CNS, cardiac, hepatic and renal systems. *Aromatic hydrocarbons* are a less frequent cause for childhood poisoning and their exposure occur primarily in occupational settings. Intentional inhalation abuse may be seen in older children. Pulmonary and CNS manifestations predominate in acute toxicity.

It is however important to remember that a mixture of different hydrocarbons may be present in the exposed product and is often difficult to isolate the unique effects of a single substance. Many insecticides, metals and other toxic chemicals may be contained in a petroleum vehicle making it very important to identify every ingredient within a commercial product before treatment.

## Pathophysiology

The key pathophysiological feature of hydrocarbon toxicity is surfactant destruction which causes alveolar collapse, ventilation-perfusion mismatch and hypoxemia. As the illness progresses, capillary damage and increased permeability lead to diffuse hemorrhagic alveolitis, finally culminating into a chemical pneumonitis. The changes in lungs are similar irrespective of the type of aliphatic hydrocarbon aspirated. Highly viscous hydrocarbons tend to produce a more localized and indolent lipid pneumonia. CNS manifestations, if any, in kerosene poisoning are due to hypoxia and acidosis resulting from pulmonary toxicity rather than due to direct effects. Direct CNS toxicity however is a feature of halogenated and aromatic compounds. The damage to the nerve cell membrane may be brief or permanent depending on the duration of exposure. Fatty infiltration of liver and centrilobular necrosis are observed with halogenated hydrocarbons.

## Clinical Features

More than 90% of the symptoms of hydrocarbon ingestion are related to the respiratory tract. Initial symptoms include coughing, choking and gasping, far more pronounced in large volume ingestions. These then progress to tachypnea, retractions and cyanosis suggestive of aspiration pneumonia. The time from ingestion to onset of respiratory distress is usually about 30 min, peaking over 48 hours and resolving in the next 2–8 days with supportive care. The pungent odor of kerosene may be apparent in the breath. Wheeze and crackles may be heard on auscultation. Fever is common, early in the course due to direct tissue inflammation. However, persistence of fever beyond 2 days suggests bacterial superinfection. CNS symptoms with aliphatic agents are generally secondary to pulmonary involvement and limited to mild irritability, drowsiness and rarely seizures. On the other hand, halogenated compounds produce dose related direct CNS toxicity. An initial excitatory phase is often followed by CNS

**Table 1** Common hydrocarbon compounds

Aliphatic hydrocarbons	Halogenated hydrocarbons	Aromatic hydrocarbons
<i>Low viscosity (&lt; 60 SSU)</i>		
Kerosene	Carbon tetrachloride	Benzene
Gasoline/petrol	Tetrachloroethane	Toluene
Mineral spirits	Chloroform	Xylene
Naphtha products	Trichloroethylene	
Turpentine	Perchloroethylene	
	Methylene chloride	
<i>High viscosity (&gt; 100 SSU)</i>		
Tar and asphalt		
Paraffin wax		
Lubricating oil, grease		
Petroleum jelly		
Diesel oil		

Abbreviation: SSU, Saybolt seconds universal.

Source: Adapted from Tinker TD. Hydrocarbon ingestion in children: its sequelae and management. J Okla State Med Assoc. 1986;79:95-101.



depression, resulting in stupor and coma. Life-threatening cardiac arrhythmias can occur early in the course. Hepatic and renal dysfunction may develop after 2–4 days.

### Investigations

All symptomatic children with suspected aspiration should have a chest radiograph. Maximum radiographic changes can occur from 2 hours to 72 hours after hydrocarbon exposure. Since chest X-ray findings correlate poorly with clinical symptoms, initial radiographs may be normal and in less severely ill, waiting for 4–6 hours before obtaining a chest radiograph may yield more information. The radiographic findings range from unilateral to bilateral lower lobe densities to large areas of consolidation and atelectasis (**Fig. 1**). Pleural effusions and air leaks are uncommon (**Fig. 2**).

Arterial blood gas analysis is indicated in all children with respiratory distress to detect hypoxemia and/or hypercarbia. Leukocytosis can occur even in the absence of infection. In symptomatic patients and those who have ingested toxic additives, laboratory evaluation should include blood count, electrolytes,



**Figure 1** Chest X-ray showing bilateral infiltrates



**Figure 2** Chest X-ray showing bilateral infiltrates and right side pneumothorax [intercostal drainage (ICD) tube in situ]

and liver and renal function tests. Toxicological analysis for hydrocarbons has no value in clinical management.

### Treatment

#### Decontamination

Management of hydrocarbon ingestion is primarily supportive. The main objective is to prevent aspiration. Gastric decontamination is not recommended as these compounds have poor GI absorption. Moreover lavage or induced vomiting increases the risk of aspiration. In cases where lavage has to be done, for e.g., in ingestions that are large volume, multiple toxins or toxins with potential for systemic toxicity like halogenated or aromatic compounds, pesticides, metals camphor, etc., it should be done with a cuffed endotracheal tube in situ. Skin exposure should be treated with removal of contaminated clothes and irrigation with soap and water. Administration of activated charcoal may induce emesis and hence not indicated.

#### Respiratory Support

All children with respiratory symptoms should be treated with supplemental oxygen and vital signs and oxygen saturation monitored. Continuous positive airway pressure may be needed in some children to maintain oxygenation. The need for intubation and ventilatory assistance should be based on clinical assessment and findings on arterial blood gas analysis. The principles of ventilation are the same as for any other parenchymal disease. Chest radiographs may be obtained to identify atelectasis or air leaks. Bronchospasm can be treated with aerosolized beta-2 agonists. Fluid balance should be carefully monitored.

Corticosteroids and prophylactic antibiotics are not recommended due to lack of evidence. Exogenous surfactant administration for acute respiratory distress syndrome due to hydrocarbon pneumonia is of unproven benefit. Successful use of high frequency ventilation and extracorporeal membrane oxygenation has been reported in refractory cases.

### Outcome

Most patients recover fully with supportive care. Mortality has ranged from 1% to 5% in most series. Hypoxemia at admission, prior lavage, need for ventilation and secondary infections have been shown to be predictors of poor outcome. A small percentage of survivors were noted to have minor pulmonary function abnormalities, pneumatoceles and pulmonary fibrosis during follow-up.

### Disposition

In emergency department, children should be observed for at least 6 hours. Children who remain asymptomatic or those who are mildly symptomatic but become asymptomatic during the period of observation can be safely sent home with a follow-up advice. All patients with worsening symptoms, signs of toxicity (hypoxia, altered mental status), markedly abnormal chest radiograph, presence of toxic additives and suicidal intent should be admitted.

### Prevention

Parental education and counseling regarding proper storage with regulatory restraints on packaging and availability of hydrocarbon products are of paramount importance in protecting children from further episodes of exposure.



**MORE ON THIS TOPIC**

- Anas N, Namasonthia V, Ginsburg CM. Criteria for hospitalizing children who have ingested products containing hydrocarbons. *JAMA*. 1981;246:840-3.
- Gupta P, Singh RP, Murali MV, et al. Kerosene oil poisoning—a childhood menace. *Indian Pediatr*. 1992;29:979-84.
- Gurwitz D, Kattan M, Levison H, et al. Pulmonary function abnormalities in asymptomatic children after hydrocarbon pneumonitis. *Pediatrics*. 1978;62:789-94.
- Jayashree M, Singhi S, Gupta A. Predictors of outcome in children with hydrocarbon poisoning receiving intensive care. *Indian Pediatr*. 2006;43:715-9.
- Jayashree M, Singhi S. Changing trends and predictors of outcome in patients with acute poisoning admitted to the intensive care. *J Trop Pediatr*. 2011;57:340-6.
- Jolliff HA, Fletcher E, Roberts KJ, et al. Pediatric hydrocarbon-related injuries in the United States: 2000-2009. *Pediatrics*. 2013;131:1139-47.
- Steele RW, Conklin RH, Mark HM. Corticosteroids and antibiotics for the treatment of fulminant hydrocarbon aspiration. *JAMA*. 1972;219:1434-7.
- Wolfe BM, Brodeur AE, Shields JB. The role of gastrointestinal absorption of kerosene in producing pneumonitis in dogs. *Pediatrics*. 1970;76:867-73.
- Zucker AR, Berger S, Wood LD. Management of kerosene-induced pulmonary injury. *Crit Care Med*. 1986;14:303-4.

**IN A NUTSHELL**

1. Accidental hydrocarbon ingestion, especially kerosene is a significant problem in children.
2. Inappropriate storage, being mistaken for water are chief causes for poisoning, especially in a rural setup.
3. Aliphatic hydrocarbons are mostly implicated in toxic exposures. Triad of viscosity, volatility and surface tension determine the risk of aspiration.
4. Pulmonary manifestations predominate. No correlation between volume of ingestion and severity of aspiration.
5. Hydrocarbons have poor GI absorption. Features of systemic toxicity are largely secondary to hypoxia and acidosis.
6. Management is supportive and mainly to prevent aspiration.
7. Lavage is contraindicated as it tends to worsen severity of aspiration.
8. Corticosteroids and prophylactic antibiotics have no role.
9. Most patients recover fully with supportive care.
10. Hypoxemia at admission, prior lavage, need for ventilation and secondary infections have been shown to predict poor outcome.

## Chapter 9.4

# Poisoning in the Household

Narayanan P, Harikrishnan KN

Household poisoning and other injuries are among the foremost causes of child mortality in India. Most of the poisoning exposures occur in children aged 5 years or younger. This could be attributed to the explorative nature of toddlers, along with curiosity, increasing mobility, and a tendency to put things in their mouths. Instances of pediatric poisoning generally are unintentional (> 99.0% of all poisoning exposures). More than 80% of poisoning exposures occur in the home, the environment in which children of this age spend most of their time.

The common household poisons include agents used for cleaning, plant poisons and those used for destruction of pests or insects (**Table 1**). Many of these act as mild skin and mucosal irritants and exposure to them may be asymptomatic or mildly symptomatic. They usually resolve spontaneously with supportive treatment. However, few among them, particularly pesticides and certain plant poisons may cause life threatening manifestations.

A major part of this chapter is devoted to poisoning with organophosphorus compounds as they are one of the commonest, yet deadly, poisons being dealt with in the pediatric emergency; the second half is devoted to other poisons like plant poisons, phosphorous, naphthalene, etc., some of which may be lethal.

**Table 1** Common household products of low toxicity

Floor cleaner	Bath oil
Toilet cleaner	Silica gel
Laundry blue (washing blue)	Deodorant
Soap	Emulsion paint
Shampoo	Glue (PVA and superglue)
Conditioner	Hair treatments
Bleach	Make up and skin care
Air freshener	Plant care
Baby oil	Polish

## EPIDEMIOLOGY

An analysis of poisoning cases reported to the National Poisons Information Centre, AIIMS, New Delhi revealed that the highest incidence of poisoning was due to household agents (44.1%), followed by drugs (18.8%), agricultural pesticides (12.8%), industrial chemicals (8.9%), animals bites and stings (4.7%), plants (1.7%) and others. Data from south India identified agrochemical pesticides as the most important agent of acute poisoning (49% of cases) followed by drugs (17%). The common predisposing factors responsible for children getting poisoned in the household are highlighted in **Box 1**.

### BOX 1 Predisposing factors for poisoning in the household

- Easy availability of hazardous substances.
- Attractive color, smell and packaging of poisons.
- Storage of such materials in tins/bottles, which previously contained edible items.
- Poor knowledge among parents regarding child-resistant packaging and toxicity of various substances.
- Failure of safe disposal of leftover pesticides after use.

## ORGANOPHOSPHATE AND CARBAMATE POISONING

Organophosphates and carbamates are responsible for an estimated 200,000 deaths in rural Asia annually. According to hospital-based pediatric data on poisoning from India, pesticides constitute a significant proportion of causes ranging from 10% to 56%. The common pesticides reported in poisoning include organophosphates, carbamates, and pyrethroids.

## Pathophysiology

Organophosphates and carbamates are lipid soluble agents. Hence, they are well absorbed through the skin, mucous membranes, gastrointestinal tract and also by inhalation. Since they do not produce any local irritation, substantial exposure can happen undetected through these routes. Once absorbed, they rapidly bind to the enzyme, acetylcholinesterase, found in all cholinergic nerve endings and in red blood cells (RBCs). While carbamates bind reversibly to the enzyme, the phosphorylation of acetylcholinesterase by organophosphate compounds can become irreversible with time (aging). The time taken for aging can vary from few minutes in the case of certain nerve gases to many days for some commercially available pesticides. Oximes are antidotes which can only regenerate acetylcholinesterase that has not aged. Therefore, the effectiveness of oximes may be as short as few hours to as much as days depending on the compound involved.

Inhibition of acetylcholinesterase leads to the accumulation of acetylcholine, thus leading to hyper-stimulation of acetylcholine receptors. This results in the clinical features of cholinergic over activity at the muscarinic and nicotinic receptors and also in the central nervous system (CNS). The nicotinic receptors are primarily distributed in the autonomic ganglia and neuromuscular junctions of skeletal muscles while muscarinic receptors are distributed in the visceral organs, secretory glands and smooth muscles (**Table 2**). The symptoms produced reflect the location of these receptors.

Prolonged excessive stimulation of nicotinic receptors can lead to temporary downregulation and insensitivity to acetylcholine. This temporary insensitivity of varying severity which develops after 24–48 hours after exposure to organophosphates could be the possible explanation for development of the *intermediate syndrome* in organophosphate poisoning; this is seen between the early cholinergic symptoms and the late onset polyneuropathy (see section on clinical features). In addition, inhibition and aging of neuropathy target esterase (different from acetylcholinesterase) is postulated to be the cause of late onset organophosphate induced delayed polyneuropathy (OPIDP), seen more commonly in adults.

## Clinical Features

The clinical spectrum of organophosphate poisoning encompasses three temporarily separated clinical syndromes:

1. The acute cholinergic phase
2. The intermediate syndrome
3. Organophosphate induced delayed polyneuropathy

The first two are life threatening while OPIDP is a disabling disease rarely seen in children. The clinical presentation of organophosphate poisoning can be a challenging diagnosis, as there may not be any history of exposure from the care givers. Moreover, sometimes the offending agent could be a mixture of different compounds (e.g., organophosphate and pyrethroids or organochlorine products) or may contain organic solvents (kerosene, ethanol, ethylene glycol, etc.) which might alter the clinical presentation. However, in most instances, the characteristic constellation of symptoms (*cholinergic toxidrome* as it is known in toxicology) is highly suggestive and relatively easy to

**Table 2** Distribution of muscarinic and nicotinic receptors

Peripheral nervous system			Neuroendocrine system	Central nervous system (CNS)
Autonomic ganglia		Neuromuscular junction (skeletal muscle)	Parasympathetic peripheral junctions (smooth muscles, secretory glands, etc.)	Adrenal medulla
Sympathetic	Parasympathetic	Nicotinic	Muscarinic	Nicotinic
Nicotinic	Nicotinic			

recognize (**Table 3**). The muscarinic [diarrhea, urination, miosis, bradycardia, bronchospasms, emesis, lacrimation, lethargy, salivations, sweating (DUMB BELLS)], nicotinic [mydriasis, tachycardia, weakness, hypertension and fasciculations (MTWHFS)] and CNS features can occur in any combination; the predominant manifestations can vary from patient to patient and also in a given patient during the course of the illness. Practically, the most useful clinical features during routine management are salivation (**Fig. 1**), decreased air entry into the lungs due to bronchorrhea and bronchospasm, constricted pupils, excessive sweating, bradycardia, and hypotension.

The intermediate syndrome can occur in up to 20% of patients with organophosphate poisoning. Though the classical presentation occurs 2–4 days after the exposure, usually once the acute cholinergic crisis is abating, it can occur as early as 12–16 hours also. The classical features are weakness of the neck (neck flop) and proximal muscles of the limbs, progressing to involvement of respiratory muscles resulting in respiratory paralysis. The weakness is lower motor neuron type with flaccidity and diminished reflexes and recovers completely in a week's time with supportive therapy alone.

**Table 3** Signs and symptoms of organophosphate poisoning (cholinergic toxidrome)

Muscarinic	Nicotinic		Both Muscarinic and nicotinic (central nervous system)
Parasympathetic system	Sympathetic system	Neuromuscular junction	
Diarrhea	Mydriasis	Weakness	Confusion
Urination	Tachycardia	Fasciculation	Convulsions
Miosis	Hypertension, hyperglycemia		Coma
Bradycardia, bronchorrhea, bronchospasm	Sweating		
Emesis			
Lacrimation, low blood pressure			
Salivation, secretion, sweating			

**Figure 1** Excessive salivation in a child with organophosphate poisoning

## Differential Diagnosis

In the absence of a definite history of exposure, sometimes the diagnosis can be challenging especially if the clinical presentation is not classical. It should be noted that all pesticides are not organophosphates or carbamates and unless typical cholinergic toxidrome is present, an alternate agent should be suspected. The common differential diagnoses that are considered are encephalitis, CNS infections, kerosene aspiration, organochlorine or pyrethroid poisoning, and status epilepticus. Children with acute heart failure due to myocarditis or scorpion sting can have lung signs (frothing, wheeze) and autonomic features (sweating, tachycardia, hypotension, etc.) which can mimic organophosphate poisoning.

## Approach to Diagnosis

The only laboratory test used in clinical practice for confirmation of the diagnosis is RBC and plasma cholinesterase levels. In addition to nerve endings, cholinesterase is also present in RBCs (acetylcholinesterase) and also in plasma (butyrylcholinesterase, also known as pseudocholinesterase). Since organophosphate

compounds can inhibit these cholinesterases also to varying extent, low levels of these enzymes can indicate exposure to organophosphates. Though they are helpful in confirming the diagnosis, treatment should not be delayed for want of test results. Butyryl cholinesterase levels recover by 7% per day, once the organophosphate is completely eliminated; and may be used for monitoring of therapy.

## Management

The general principles of management are resuscitation at admission, administration of oxygen, blocking the muscarinic effects by administering atropine, regeneration of acetylcholinesterase with the help of oximes and mechanical ventilation for respiratory failure (**Box 2**). Even though there is some controversy regarding the efficacy of oximes, WHO still recommends their use in this setting. Rapid intravenous administration of pralidoxime can produce laryngospasm, muscle rigidity, neuromuscular blockade and paralysis. Hence, it should be administered as an initial loading dose over 5–10 min followed by continuous infusion. If the exact agent is not known and the patient has the classical cholinergic

**BOX 2 Treatment of organophosphate poisoning**

- Check airway, breathing, and circulation. Place patient in the left lateral position, provide oxygen, if available. Intubate if necessary to maintain airway and breathing.
- Administer 0.01–0.04 mg/kg of atropine (minimum 0.1 mg) as a bolus intravenously. Will need higher initial doses in most instances. Start an infusion of isotonic fluids to maintain normal blood pressure and urine output above 0.5 mL/kg/h.
- Record pulse rate, blood pressure, pupil size, presence of sweat, and auscultatory findings at time of first atropine dose.
- Give pralidoxime chloride 20–40 mg/kg intravenously over 20–30 min; followed by an infusion of pralidoxime 5–10 mg/kg/h.
- After 5 min of giving atropine, check pulse, blood pressure, pupil size, sweat, and chest sounds. If no improvement, give double the initial dose of atropine.
- Monitor every 5 min; administer double dose of atropine if no response. Once signs of improvement are present, stop dose doubling. Tachycardia is not a contraindication to atropine since it can be caused by multiple factors. The pupils will usually dilate; however, this sign is not a useful endpoint for initial atropine treatment because a delay exists before maximum effect. However, very dilated pupils are an indicator of atropine toxicity.
- Once the child is stable, start atropine infusion hourly at 10–20% of the total dose required to reverse the muscarinic effects. Monitor hourly to see the degree of atropinization. If dose is less, cholinergic features will reappear. In that case repeat bolus doses of atropine as above and increase the infusion rate. If child becomes agitated and febrile with absent bowel sounds and urinary retention, suspect atropine overdose. Immediately stop the infusion and wait 30–60 min for these features to settle before starting again at a lower infusion rate.
- Continue the oxime infusion until atropine has not been needed for 12–24 hours.
- Assess strength of neck flexors regularly in conscious children by asking them to lift their head off the bed and hold it in that position. Any sign of weakness indicates that the child is at risk of developing peripheral respiratory failure (intermediate syndrome).
- If the child is agitated, review the dose of atropine infusion and provide adequate sedation with diazepam. Physical restraint of agitated patients can result in severe hyperthermia due to the combined effects of atropine (lack of sweating), agitation and warm weather conditions. Hence adequate sedation is important.
- Look for recurring cholinergic crises due to release of fat soluble organophosphorus from fat stores. This can occur for several days to weeks after ingestion of some organophosphorus compounds. These patients will need retreatment with atropine and oxime.

toxidrome, a therapeutic trial with oximes is justified. Gastric lavage is controversial and should be considered only if the child is brought immediately after exposure. Thorough decontamination of skin, mucous membranes and clothing are required in most cases; especially if ingestion was not the primary route of exposure.

Newer modalities of treatments target decreasing the synthesis and release of acetylcholine (magnesium sulfate, clonidine) and removing the organophosphate from blood by hemodialysis or hemofiltration. Scavenging the organophosphate by administration of butyrylcholinesterase and recombinant bacterial phosphotriesterases, or hydrolases also have been tried. These therapies do not have sufficient evidence at present to recommend for routine use.

In most children with organophosphate poisoning, rapid reversal of cholinergic toxidrome is possible within an hour of presentation and the atropine and oxime infusion can be tapered over the next 24–48 hours. A few patients may require ventilator support for a short duration especially if they have prominent CNS manifestations or have suffered prolonged hypoxia. Children who develop intermediate syndrome might require mechanical ventilation for 3–7 days or longer. Oximes and atropine are not effective in treating this condition, which can develop as early as 12–16 hours after exposure.

**Prognosis**

The reported mortality of organophosphate poisoning varies from 15% to 30%. Survival depends not only on the type of organophosphate involved and the delay in initiating therapy, but also on the availability of supportive therapy like mechanical ventilation. The various factors related to the organophosphate compound which affects prognosis are the toxicity, presence of impurities, formulation, need for activation in the body, speed of binding to acetylcholinesterase and aging and the duration of action.

**RODENTICIDE POISONING**

Rodenticides may have many toxic ingredients. The older rodenticides were based on coumarin like compounds which resembled warfarin in its action, leading to coagulopathy and death of rats. Zinc and aluminum phosphide are also commonly used in rodenticides. Aluminum phosphide is commonly known as Celphos<sup>®</sup>, Quickphos<sup>®</sup> and Phostoxin<sup>®</sup> and is available as sealed metal tubes containing pellets. Because of the frequent use, rats are now resistant to such compounds, and hence alternatives are being used, the commonest and highly toxic being yellow phosphorous.

Ratol paste, which contains 3% yellow phosphorous is, nowadays, commonly available and can be rapidly fatal. Elemental phosphorous exists as the red phosphorous, which is nonvolatile, insoluble and nonabsorbable and white or yellow phosphorous which can cause systemic side effects. Yellow phosphorous is a local and systemic toxin causing severe damage to gastrointestinal, hepatic, cardiovascular and renal systems. It is used as rodenticide and in fireworks. Modes of exposure include direct ingestion and absorption through skin, mucous membranes, and inhalational route. It is distributed to all tissues, but around 70% is concentrated in the liver, peak levels being reached 2–3 hours after exposure.

**Pathophysiology**

Phosphorous is a protoplasmic poison. It inhibits oxidative phosphorylation resulting in cellular hypoxia. Phosphine gas (PH<sub>3</sub>), which is released when phosphorous (zinc/aluminum phosphide) comes in contact with gastric hydrochloric acid, also increases oxidative stress by induction of free radicals and inhibition of catalase. The hypoxic insult affects all organs, particularly the liver, heart, kidneys and brain, resulting in multiorgan dysfunction and death. The fatal dose is 1–5 mg/kg; death may occur as early as 24 hours or as late as 6–7 days after exposure.

**Clinical Features**

Clinical features of yellow phosphorous poisoning can be divided into three characteristic phases:

The *first phase* manifests with local effects on the gastrointestinal mucosa and lasts less than 24 hours. Children may be asymptomatic or may complain of burning epigastric pain, vomiting, intense thirst and rarely, diarrhea. Stools are often dark and luminous, often referred to as smoking stool syndrome.

The *second phase* lasts up to 3 days (24–72 hours) postexposure and patients are characteristically asymptomatic. This may give a false impression that there is no significant toxicity and lead to a premature discharge from hospital. However, extreme caution should be exercised, as most patients with significant amount of ingestion will have a catastrophic course of events. Children may have minor gastrointestinal symptoms. Vascular collapse and myocardial dysfunction leading to cardiogenic shock, although rare, can complicate these phases.

The *third phase* is characterized by reappearance of the primary symptoms. Jaundice, often with pruritus and other features of hepatic failure, including bleeding manifestations appear. There may be abdominal distension and worsening sensorium, which heralds the onset of hepatic encephalopathy.



Children may manifest with features of shock because of poor intake, ongoing bleed or myocardial damage. Other neurological manifestations include headache, tremor, impaired vision, cramps, paralysis and coma. Myocardial involvement manifests with hypotension, arrhythmias (including bundle branch blocks, conduction blocks, extrasystoles and repolarization abnormalities) and cardiogenic shock. Echocardiography reveals transient global hypokinesia. Temporary bone marrow suppression, isolated cholestasis and even pulmonary edema have been reported. Acute tubular necrosis leading to acute kidney injury may be seen in more than 50% cases. Liver biopsy shows features of toxic hepatitis with extensive necrosis, ballooning degeneration and steatosis. The causes of death include hepatic and renal insufficiency and cardiogenic shock.

### Management

Ratol (yellow phosphorous) ingestion has a high mortality rate of 27–73% in various case series, which is directly related to the ingested dose. The absence of a specific antidote and lack of good supportive therapies in hepatic failure contribute to the high mortality. Early elevations in transaminases or alkaline phosphatase, more than tenfold rise in alanine aminotransferase, severe derangement in prothrombin time (INR > 6), metabolic acidosis and presence of hypoglycemia signify poor prognosis.

Mainstay of therapy is supportive management and measures to remove as much unabsorbed poison as possible. Caution should be exercised in the emergency room as spontaneous combustion and explosion while attempting RT passage has been reported. Gastric lavage with potassium permanganate to convert phosphorous to harmless oxides is recommended. Patients should be carefully monitored for hepatic encephalopathy and acute kidney injury. It is reasonable to give vitamin K and fresh plasma transfusions in case of spontaneous bleeding. Supportive therapy for hepatic failure, including high carbohydrate, low fat diet, fluids, antibiotics, lactulose should be given. Studies have not shown any clear benefit from steroids, exchange transfusion or N-acetylcysteine (NAC). Liver transplantation should be considered as a lifesaving procedure. However, the prohibitive cost and involvement of other organs are significant limitations, and mortality remains high.

There are recent reports of improved survival following use of NAC as an adjuvant, when patient presented early (mortality 14.3% in NAC group compared to 66% in non-NAC group) to the ER. Magnesium sulfate, because of its membrane stabilizing action may be used intravenously to prevent cardiac conduction abnormalities.

### Prevention of Pesticides and Rodenticide Poisoning

Since most of the instances of pediatric poisoning are accidental in our country, health education regarding safe storage and disposal of these compounds can bring down the occurrence of these unfortunate accidents. Better regulation regarding packaging and sale of existing compounds and also development of pesticides which are safer and nontoxic to humans may be long-term strategies to address this preventable cause of mortality and morbidity in our country.

## PLANT POISONS AND MUSHROOMS

### Oleander Poisoning

Oleander is a common shrub found in South Asia (**Fig. 2**), the common members being white oleander (*Nerium oleander*) and yellow (*Thevetia peruviana*) oleander. Although all parts of the plant are poisonous, the fruits and seeds are responsible for most of the poisoning reported. It is used as an abortifacient and as components of rodenticides or insecticides. Exposure may be



**Figure 2** Pink oleander plant with flowers

accidental or suicidal ingestion of parts of the plant or by inhalation of fumes from the burning leaves.

### Pathophysiology

Cardiac glycosides or cardenolides are the toxins responsible for the characteristic manifestations of oleander poisoning. The cardenolides present in common oleander include oleandrin, digitoxigenin, nerrin, folinerin and rosangenin and those in yellow oleander include thevetin A and B, thevetoxin, peruvoside, ruvoside and neriifolin. These compounds contain a steroid nucleus with a lactone ring, which strongly resembles digitoxin. This structural similarity is responsible for the inhibition of Na-K ATPase enzyme system. This causes conduction block across SA and AV node, and is also responsible for hyperkalemia and intracellular calcium accumulation which leads to ventricular arrhythmias. Other mechanisms of toxicity include activation of sodium channels causing prolonged depolarization and impaired repolarization. Oleandrin is responsible for local irritation of mucosa. The fatal dose is one leaf or one seed and death may occur within 6 days.

### Clinical Features

Oleander poisoning manifests with predominant gastrointestinal and cardiac symptoms. Nausea, vomiting, diarrhea and mucosal erythema develop within an hour. Perioral paresthesias, dizziness, progressive skeletal muscle weakness and excessive salivation have been reported. Cardiac manifestations include hypotension, bradycardia and arrhythmias. Presence of unexplained bradycardia in the presence of heart failure is a paradoxical feature which can make the treating physician suspect oleander poisoning. In a recent observational study, the commonly reported arrhythmias include sinus bradycardia, sinus arrest or exit block, second-degree AV block followed by third-degree heart block and rarely supraventricular arrhythmias and first-degree heart block. ECG was normal in 40% of patients. Ventricular ectopics and ventricular tachycardias are uncommon in contrast to digoxin toxicity.

Metabolic abnormalities documented include hyperkalemia, hypokalemia and hypomagnesemia. The degree of hyperkalemia correlated with the serum digoxin cross reactive cardiac glycoside concentration and with cardiac arrhythmias.

### Management

Children suspected to have ingested oleander should be monitored for at least 12–24 hours because there can be a latent period before manifesting symptoms. Any symptomatic patient

should be admitted for intensive monitoring, preferably in the intensive care unit. Multi-dose activated charcoal (MDAC) is said to decrease absorption of glycosides and also interrupt enterohepatic circulation; however, there is substantial difference between two recent randomized controlled trials on the efficacy of MDAC in oleander poisoning. Hypotension may be managed by appropriate fluids or vasopressor agents. Bradycardia usually responds transiently to atropine (0.02–0.05 mg/kg/dose IV) which may be repeated based on the response. However, temporary pacemakers are required in majority of patients with conduction blocks and persistent bradycardia. Arrhythmias usually resolve within 24 hours, but rarely may persist up to 3–6 days. Indications for temporary pacemakers include complete heart block, Mobitz type II second-degree block, sinus bradycardia with heart rate less than 40/min and sinus arrest with pauses more than 2 sec.

Antidigoxin Fab antibodies were found to significantly reverse arrhythmias early leading to an increase in the heart rate and correction of hyperkalemia. The therapeutic response usually occurs in an hour and sinus rhythm is restored in more than 70% cases in a couple of hours. The dose is 400–800 mg in 200 mL saline IV as an infusion over 20 min under close monitoring. Unfortunately, the exorbitant cost limits its use in developing countries like India.

Rapid correction of electrolyte abnormalities is also important in decreasing mortality. Isoprenaline, magnesium sulfate, phenytoin and recently fructose-1,6-diphosphate are other treatment modalities which have been tried, though there is no substantial evidence to support their routine use.

### Datura Poisoning

Datura, belonging to Solanaceae family is a common plant found all over India (**Fig. 3**). The fruits and seeds are the most toxic, though ingestion of any plant part can cause symptoms. It is misused as a stupefying poison mainly for criminal purposes and as components of home remedies by quacks. Exposure is most commonly by accidental ingestion of fruits.

### Pathophysiology

Datura contains daturine, which is a mixture of alkaloids—hyoscyne, levo-hyoscyamine and traces of atropine. These alkaloids when absorbed after ingestion antagonize the muscarinic effects of acetylcholine. Nicotinic receptors are unaffected. The chief sites of action are cholinergic muscarinic receptors of postganglionic parasympathetic nerves and cortical and subcortical levels in the brain. The fatal dose is approximately half a teaspoon of datura seeds; death may occur within 24 hours.



**Figure 3** Datura fruit

### Clinical Features

Following ingestion, children manifest with excessive thirst, blurring of vision, confusion, agitation and difficulty in swallowing. Tachycardia is a consistent sign, the absence of which should incite a search for an alternate diagnosis. Other signs include dry mucous membranes, flushing of skin, fever or hyperpyrexia, dilated pupils, urinary retention and sluggish bowel sounds. The typical features may be summarized by the famous statement “*hot as a hare, blind as a bat, dry as a bone, red as a beet and mad as a wet hen*”. The neurological features due to central anticholinergic effect include disorientation, ataxia, visual incoordination and visual or auditory hallucinations. The initial restlessness and confusion may progress to stupor and coma within 2–4 hours and may prove fatal. Transient hypertension, arrhythmias and seizures have been described.

### Management

Children who are asymptomatic and those without central anticholinergic effects usually recover spontaneously, and need only observation for around 24 hours. Children with severe poisoning should be admitted. Intensive neurological monitoring and care of airways and breathing is required, especially in comatose patients. Hyperpyrexia responds to tepid sponging and antipyretics. Seizures should be managed with anticonvulsants like diazepam. Children may be very agitated and violent and usually do not respond well to hypnotics. Physostigmine, an acetylcholinesterase inhibitor is the specific antidote. It can cross blood brain barrier, and reverses both central and peripheral antimuscarinic effects of *datura*. It is indicated when child presents with seizures, hallucinations and supraventricular tachycardia. Dose is 0.5 mg IV slowly over a period of 3–5 min, and may be repeated every 10 min (maximum dose 2 mg).

### Mushroom Poisoning

There are many species of mushrooms available, which can lead to varied clinical manifestations, when ingested. *Amanita phalloides* is the worst offender, which can lead to acute hepatic failure. The major classes of mushrooms with their predominant mechanism of toxicity are listed in **Table 4**.

## HOUSEHOLD PRODUCTS OF LOW TOXICITY

### General Household Cleaning Products

Household cleaning products are responsible for a significant proportion of unintentional poisonings in children and are regularly reported among the top five agents implicated in pediatric poisoning exposure. This most likely reflects the ubiquitous nature of these agents within the child's environment and the ease of accessibility to children. Most household cleaning products appear attractive to children because of their color, scent, and brightly colored packaging. Fortunately, the high frequency of exposure to these toxic products is not associated with a similar frequency in morbidity. These agents contribute to less than 2% of the overall mortality due to poisonings in the under-5 age group. Among thousands of innocuous products present within the household, very few are hazardous. The big challenge for pediatricians and toxicologists is to identify the few rare life-threatening situations where definitive intervention is needed.

### Bleach

Household bleach solutions contain approximately 10% sodium hypochlorite. Children usually do not ingest them in significant quantity, as they are extremely unpalatable. The fumes typically release small amounts of hypochlorous acid and chlorine gas. Commonly observed effects include nausea, vomiting, eye irritation and diarrhea. More severe exposures may have burns in the lips, mouth and oropharynx and even laryngeal edema and

**Table 4** Characteristics of poisonous mushrooms

<i>Class</i>	<i>Mechanism of action</i>	<i>Features</i>	<i>Management</i>
Amanita mushrooms	Cyclopeptide alpha-amanitin inhibits RNA polymerase	GI irritation Hepatic failure, encephalopathy Renal toxicity Death by 2–6 days	Supportive Activated charcoal, N-acetylcysteine
Monomethylhydrazie mushrooms e.g., Gyromitra	Gyromitrin/monomethylhydrazine inhibits GABA formation	Mental confusion Progressive ataxia, seizures	Pyridoxine
Hallucinogenic e.g., Psilocybe	Structural similarity to serotonin	Euphoria Hallucinations Tachycardia, hypertension	Self-limiting
Muscarinic e.g., Clitocybe	Cholinergic agonist	Salivation, lacrimation, diaphoresis, urination, diarrhea	Atropine
Coprine mushrooms e.g., Coprinus	Inhibits acetaldehyde dehydrogenase	Edible mushroom, interaction only when taken with alcohol nausea, vomiting, flushing, tachycardia	Self-limiting

Abbreviation: GABA,  $\gamma$ -aminobutyric acid.

stridor. Ingestion of less than 100 mL of household bleach rarely leads to serious problems. Ingestion of fluids, especially milk, should be encouraged.

Esophageal injury is uncommon and is usually associated with concentrated solutions (industrial bleach may contain up to 50% sodium hypochlorite) or the ingestion of large volumes. Children at risk of esophageal damage should be hospitalized with careful monitoring of fluid and electrolyte balance. The presence of more than two symptoms may suggest esophageal involvement though none of the symptoms are 100% accurate in predicting esophageal injury. Early endoscopic examination is warranted where the suspicion is high.

### Disinfectants

These agents contain a variety of potentially toxic ingredients—hydrochloric acid (10%), sodium alkyl benzene sulfonate, sodium alkene sulfonate and others. However, since in most commonly available products, these toxic components are present in very small amounts, serious adverse effects are uncommon. Symptoms are usually mild and limited to areas of direct exposure like irritation of the oral mucosa and brief gastrointestinal upset. Fluid intake should be encouraged in an attempt to dilute and disperse the harmful agents. Children who are asymptomatic especially if they have ingested very small amounts (< 10 mL) may be discharged home. Consumption of large quantities of these agents, or even small quantities of concentrated solutions can lead to life threatening manifestations like local corrosive effects, aspiration pneumonia, metabolic acidosis, CNS depression and hepatic as well as renal injury. Phenol based derivatives pose the greatest risk (e.g., chloroxylenol, active ingredient of Dettol).

### Detergents

These are ubiquitous agents in every household and can be classified based on their chemical properties into three main categories—nonionic, anionic, and cationic. The first two categories (non-ionic, anionic) of detergents have low toxicity and children need to be observed only if respiratory symptoms are present (can result from foam aspiration). Most domestic cleaners do not contain cationic detergents, such as benzalkonium chloride and cetrimide. Concentrated solutions of these chemicals can produce corrosive effects. Like in the case of bleach, oral fluids should be encouraged and after a brief period of observation, asymptomatic children can be discharged. Management of corrosive ingestion is discussed elsewhere.

### Alcohol, Perfumes and Mouthwash

Ethanol is a common organic solvent found in alcoholic drinks, perfumes, aftershaves, mouthwash, etc. In children, most cases of ethanol poisoning result from ingestion of large quantities of household substances having a low concentration of ethanol such as mouth wash. Concentrated solutions, being more irritant, are rarely ingested by children.

Ethanol being a CNS depressant, can lead to respiratory compromise. Alcohol dehydrogenase present in the liver metabolizes ethanol with nicotinamide adenine dinucleotide (NAD) as cofactor. As NAD is required for multiple metabolic pathways, competition from large quantities of ethanol impairs several metabolic processes resulting in acidosis and impaired gluconeogenesis. Hypoglycemia can result from impaired gluconeogenesis especially in young or fasted children as a result of depleted glycogen stores.

Activated charcoal is not indicated as it does not absorb organic solvents like ethanol. Gastric lavage and induced emesis also may be ineffective as ethanol is rapidly absorbed across mucous membranes. If facilities are available, blood samples should be taken at least 1 hour after ingestion for estimating blood ethanol levels. However, treatment is determined on clinical grounds and mainly supportive. Dehydration and hypoglycemia should be corrected with careful attention to fluid balance as cerebral edema also can occur. A multitude of specific therapies have been tried, largely in adult patients with ethanol poisoning. Most of these aim to decrease the need and duration of supportive therapy. Drugs like flumazenil and naloxone for reversing CNS depression and forced alkaline diuresis for rapid elimination of ethanol are ineffective. Fructose can increase availability of NAD and has been tried as an intravenous infusion to enhance ethanol metabolism. But it can result in adverse effects like lactic acidosis and osmotic diuresis. Hemodialysis, though invasive, is very effective in treating patients with documented high blood ethanol levels (> 300 mg/dL).

### Nail Varnish Removers

These cosmetic agents usually contain acetone or ethyl acetate. Acetone, being an organic solvent is easily absorbed from the stomach and mucous membranes. Similar to other organic solvents, it causes local irritation in exposed areas, vomiting, and CNS depression. Metabolic derangements observed with acetone ingestion include ketosis, acidosis, and hyperglycemia. An estimate of the amount ingested, if possible, can be helpful. Those who have consumed more than 2 mL of pure acetone should be



kept under observation for 2 hours and if asymptomatic can then be discharged. Activated charcoal may not be beneficial as organic solvents like acetone bind poorly to acetone.

Symptomatic children should be hospitalized and offered supportive measures. Insulin may be required to control hyperglycemia and significant alteration in sensorium may necessitate mechanical ventilator support. Acetone can damage renal tubules and hence renal function should be monitored carefully. Ethyl acetate also can cause mucosal irritation, but unlike acetone, large quantities are required to produce CNS toxicity.

Nail varnish is usually available in small containers and ingestion of such small volumes is unlikely to produce significant damage though it contains a variety of potentially toxic ingredients.

### Toothpaste

Most of the children exposed to toothpaste with fluoride ( $> 6$  mg of fluoride/kg is toxic) typically have a benign course of recovery in the hospital. The most commonly observed adverse effects being nausea and vomiting resulting from gastric irritation. Large exposures ( $> 40$ – $50\%$  of the paste tube) are unusual, but can result in significant toxicity, including hypocalcemia, hypomagnesemia, cardiac rhythm disturbances and CNS features such as tremors or seizures. Treatment is primarily supportive.

### Naphthalene Poisoning

Naphthalene is a polycyclic aromatic hydrocarbon that is commonly encountered in indoor and outdoor environments. It exists primarily as a vapor at ambient pressure due to its high vapor pressure and has a strong, characteristic odor. It is insoluble in water, but highly soluble in oil, which may lead to its absorption through skin, especially in babies. There are numerous sources of naphthalene in the environment. It is a component of crude oil, and is used as a pesticide in mothballs, as deodorant in lavatories and in dyes. Naphthalene mothballs contain 99.9% naphthalene, and can range in weight from 0.5 g to 5 g.

The majority of exposure to naphthalene in the environment occurs through inhalation, while other pathways include dermal contact with and ingestion of naphthalene-containing products. Dermal exposure can occur from direct contact with mothballs, as well as items stored in enclosed spaces with naphthalene-containing mothballs. Incidents of serious medical outcomes, including acute hemolytic anemia, have been reported in association with dermal exposure in newborns to diapers and blankets that have been stored with mothballs.

### Pathophysiology

Naphthalene undergoes hepatic metabolism, and is oxidized to alpha-naphthol and other metabolites. It has recently been reported that certain cytochrome P450 enzymes that are highly expressed in the human respiratory tract are also capable of catalyzing these metabolic transformation reactions. The metabolites of naphthalene produce oxidative stress, leading to the formation of methemoglobin and the oxidation of hemoglobin which results in the formation of visible Heinz bodies and increased susceptibility of the RBC to hemolysis. Acute hemolysis can subsequently lead on to hemoglobinuria and blockage of renal tubules due to deposition of acid hematin, causing renal injury and failure. Laboratory studies have also demonstrated that naphthalene induced production of free oxygen radicals results in lipid peroxidation and deoxyribonucleic acid damage.

### Clinical Features

The onset of signs and symptoms usually occurs 1–2 days after exposure because of the slow rate of metabolism of naphthalene to its oxidative metabolites. After ingestion, vomiting, diarrhea and

fever appear in 1–2 days, followed on the 3rd to 5th day by an acute hemolytic crisis as evidenced by pallor, mild jaundice and pigmented urine. Children may present with severe loin pain, burning sensation in the urethra and strangury. Severe toxicity may result in hepatic or renal damage, cyanosis due to methemoglobinemia, tachycardia, respiratory distress, convulsions, coma and death. Five to six days after ingestion, the hemolytic process ends and if the patient survives this stage, then recovery is rapid.

When exposed through the inhalational route, it can cause headache, nausea, vomiting, mental confusion, visual disturbances, conjunctivitis and dermatitis.

Hematological changes, occurring as early as one day after initial exposure in severe cases, lead to a Heinz-body hemolytic anemia with fragmented cells, spherocytosis in peripheral smear and a sharp fall in hemoglobin, often with concurrent leukocytosis. Reticulocytosis follows with subsequent gradual restoration of the normal blood values except in the most severe cases.

### Management

Close monitoring, in anticipation of complications, is essential for at least a week following exposure. Induction of emesis is not recommended. Treatment is mainly supportive. Cathartics like magnesium sulfate and activated charcoal can be tried. It is advisable to avoid milk or fatty foods for at least 2–3 hours postexposure because of the high fat solubility. Alkaline diuresis is usually done to prevent deposition of acid hematin crystals in cases with hemolysis. Child may require transfusions of packed RBCs because of the sudden rapid fall in hemoglobin.

Clinical suspicion of methemoglobinemia should arise when there is cyanosis that does not respond to high-flow oxygen with no obvious cardiorespiratory causes. Pulse oximetry may become unreliable in the setting of methemoglobinemia. A co-oximeter type of blood gas analyzer is needed to directly measure the oxygen saturation and methemoglobin (metHb) levels. Standard treatment includes the use of methylene blue (indicated when metHb  $> 30\%$ ) and exchange transfusion. Methylene blue increases the rate of conversion of metHb to Hb by accepting an electron [in the presence of nicotinamide adenine dinucleotide phosphate and metHb reductase], to form leukomethylene blue, which can then donate this electron to reduce metHb. The use of NAC as a direct reducing agent in treating methemoglobinemia is still being investigated.

### Eucalyptus Oil or Essential Oil Poisoning

Eucalyptus and neem oils have been used as a traditional remedy for a variety of common ailments, mostly involving respiratory tract. It is also used as an antiseptic, repellent, and as an agent for fragrance and flavoring. Most prevalent is the standard cineole based oil of eucalyptus (minimum 70% cineole). Other constituents include pinene, limonene, beta citronellol, citral and geraniol.

The safe adult dosage has been estimated to be 0.06–0.2 mL. Death has occurred even after ingestion of 4–5 mL, and is usual after 30 mL.

### Clinical Features

It acts as a local irritant causing burning sensation in mouth and throat, abdominal pain and vomiting. Inhalation can cause bronchospasm leading to tachypnea and wheezing, however respiratory depression occurs in severe intoxication. The exact mechanism causing CNS features is not yet known; it causes CNS depression manifested by diminution or loss of reflexes, depressed consciousness progressing to coma. Convulsions or tonic posturing may be a prominent manifestation in children, although it is rarely reported in adults. Ataxia and pulmonary involvement has been reported.



## Management

Management is primarily supportive. Attempts to induce vomiting should be avoided because of risk of aspiration. Gastric lavage may be performed, preferably after insertion of a cuffed endotracheal tube in the presence of CNS depression. Tonic posturing or seizures usually respond to intermittent diazepam. Mechanically ventilated patients may initially require higher pressures because of aspiration pneumonitis. There are isolated case reports of use of naloxone as an antidote and use of hemodialysis in eucalyptus poisoning.

## Neem Oil Poisoning

*Neem* is endemic in Indian subcontinent. Extract from its seed (*margosa* oil) has been found to have antifertility, antihyperglycemic, anti-inflammatory, antiulcer, antimicrobial, estrogenic, immune and insect repellent effects. Neem oil, as a traditional medical remedy, is used as antibacterial, antifungal, insect repellent, and treatment of skin diseases. The oil is a mixture of many steroids, triglycerides and terpenoids along with minimal amount of aflatoxins. It contains active ingredients like azadirachtin, nimbin, picrin, and sialin. The exact toxic dose is not known, but fatality has been reported even with ingestion of a few drops of neem oil and common with ingestion of 15–20 mL.

Azadirachtin, a complex tetranortriterpenoid, is implicated in causing the effects seen in neem oil poisoning. Azadirachtin manifests its toxicity possibly by interfering with mitochondrial bioenergetics, resulting in inhibition of the generation of the electrochemical proton gradient (primary form of energy generated in mitochondria) leading to cellular hypoxia.

## Clinical Features

Children manifest with vomiting and lethargy around 30 min to 1 hour following ingestion of neem oil. They have progressively worsening sensorium, seizures and metabolic acidosis. Hepatic toxicity as evident from an elevation in transaminases and a Reye syndrome like presentation has also been described. They can have sudden deterioration with fatality in the first 12–24 hours.

## Management

There is no specific antidote available, and gastric lavage is not recommended for neem oil poisoning. The management is primarily symptomatic and outcome is good in the absence of neurological manifestations. Neurological sequelae like vision loss and choreoathetoid movements have been reported.

## Camphorated Oils

Camphorated oils and derivatives of camphor act as CNS stimulants and also cause local irritation. Camphorated oil contains 20% camphor, while VICKS VapoRub, a commonly used remedy contains 4.3% camphor, 6% eucalyptus oil and 4% menthol. Camphor ingestion may manifest with poor sensorium and seizures, usually within 20–30 min after ingestion. Children present with burning sensation in mouth, abdominal pain and vomiting within 5–10 min of ingestion. The symptoms peak at around 90 min, and spontaneously resolve with supportive care.

Decongestant capsules use for common cold remedies usually have a mixture of essential oils. Accidental ingestion can produce irritation of the oropharynx, nausea, vomiting, and diarrhea. The predominant systemic effect, though rare, is CNS depression.

Nasal instillation can result in severe respiratory distress and even respiratory arrest has been reported.

## PREVENTION OF COMMON HOUSEHOLD POISONING

The risk mitigation strategies included new packaging requirements and precautionary labeling to protect toddlers and children from ingestion of such toxic substances, e.g., acceptable packaging includes tear and moisture-resistant sachets, and plastic containers that allow volatilization but no direct contact with the naphthalene.

Recommendations by the American Academy of Pediatrics include storing poisonous substances always in locked cabinets, preferably out of sight and reach of children. Household products should have child-resistant packaging and should always be kept in their original containers. All unused and leftover products, especially pesticides, should be disposed of properly. Proper educational programs targeting household chemicals and their use and storage should be developed and disseminated.

### IN A NUTSHELL

1. Poisoning in the household accounts for majority of poisoning episodes in children less than 5-year-old.
2. Explorative nature of children, attractive packaging and poor storage and disposal of dangerous agents within the household are the major predisposing factors.
3. Organophosphate and carbamates are among the most common causes of life threatening poisoning in children. The life threatening early clinical features are easy to identify (cholinergic toxidrome).
4. Patients who develop intermediate syndrome after organophosphate poisoning can die suddenly if not recognized early and given ventilator support.
5. Rodenticide poisoning involving yellow phosphorus (Ratol) has high fatality rate with very little early manifestations.
6. Among the life threatening plant poisons, oleander and datura are the most common, each with characteristic constellation of symptoms.
7. Most of the household products of daily use have limited toxicity unless consumed in large doses.
8. Antidotes are available for only very few household poisonings; prompt supportive therapy is the cornerstone of treating household poisonings.

## MORE ON THIS TOPIC

Eddleston M, Ariaratnam CA, Sjöström L, Jayalath S, et al. Acute yellow oleander (*Thevetia peruviana*) poisoning: cardiac arrhythmias, electrolyte disturbances, and serum cardiac glycoside concentrations on presentation to hospital. *Heart*. 2000;83:301-6.

Eddleston M, Buckley NA, Eyer P, Dawson A. Management of acute organophosphorus pesticide poisoning. *Lancet*. 2008;371:597-607.

Karalliedde L, Baker D, Marrs TC. Organophosphate-induced intermediate syndrome: aetiology and relationships with myopathy. *Toxicol Rev*. 2006;25:1-14.

Riordan M, Rylance G, Berry K. Poisoning in children 4: household products, plants, and mushrooms. *Arch Dis Child*. 2002;87:403-6.

## Chapter 9.5

# Corrosive Poisoning

Urmila Jhamb

Corrosives/caustics are a group of chemicals which cause severe injury to the tissue on contact by a chemical reaction. These are widely used for various purposes at home (especially cleaning) and in industry in both crystalline and liquid form. Corrosive substances may be acids, alkalis (most dangerous), oxidants and heavy metal salts. Corrosive ingestion in children is mostly accidental unlike adults where it is more often suicidal. Children are curious by nature and accidental ingestion of corrosives is due to their easy availability in and around the houses. Children less than 5 years are most commonly involved. Storage of acids in mineral water bottles or other household containers increases the risk as it can be mistaken for a drinkable fluid. Lack of supervision of children and poor living conditions in addition increase the hazard of ingestion of corrosives.

## EPIDEMIOLOGY

Corrosive ingestion may account for 0.3–0.9% of pediatric admissions. Death rates may range from 0% to 13% although later on esophageal strictures (OS) can form in 5–50% depending on severity of corrosive injury. The accidental corrosive poisoning is on the decline in high-income countries but it is quite significant in developing countries. A study from India compared the trends in childhood poisonings from 1993 to 2008 and it was found that the corrosives ingestion as percentage of all poisonings had been fluctuating between 4.3% and 12.3%. Some recent studies (2011–2013) reported this percentage as 7.6% (Chandigarh) to as high as 24.9% (Delhi). In India, there is poor regulation of sale of corrosive substances and they are freely available in households. Corrosive ingestion was reported to be the commonest among nondrug poisonings from Turkey, second most common after kerosene from Delhi and next after kerosene and organophosphorus from Chandigarh.

## ETIOLOGY

Common corrosives causing poisoning are listed in **Table 1**. The most common corrosive poisoning is variable in different countries. Studies from USA, Denmark, Israel, UK, Peru, Spain, Australia, Saudi Arabia, Turkey and Pakistan reported alkalis as the most frequently ingested corrosives. Majority of these are sodium hypochlorite or disinfectants and cleaning solutions containing sodium hydroxide. However, in India there is strikingly different scenario with acid ingestion occurring in majority of cases. Acids are often used as toilet cleaners in Indian homes.

## PATHOPHYSIOLOGY

Acids precipitate protein and cause coagulation necrosis. In this process, hydrogen ( $H^+$ ) ions desiccate epithelial cells producing an eschar. This leads to edema, erythema, mucosal sloughing, ulceration and necrosis of tissues. Alkalis cause liquefaction necrosis. This process includes dissolution of protein, collagen destruction, saponification of fat, cell membrane emulsification, submucosal vascular thrombosis (few hours after ingestion) and cell death.

Inflammatory response and development of granulation tissue continue in the next several days after corrosive ingestion. Because of these changes, esophagogastroduodenoscopy between the 5th and the 15th day after corrosive ingestion is not recommended.

**Table 1** Common substances causing corrosive ingestion

Acids	Alkalis
Sulfuric acid in car batteries	Caustic soda, i.e., sodium hydroxide (in household cleaners, laundry detergents and drain cleaners)
Hydrochloric acid for toilet cleaning (also in Lysol)	Sodium metasilicate or disilicates (in dishwasher powder)
Detergents containing sodium phosphate	Clinitest tablets (used to check urine sugar) have sodium hydroxide (also have copper sulfate, citric acid and sodium carbonate)
Nitric acid as metal cleaner	Potassium hydroxide (industrial paint strippers)
Phenol and boric acid as disinfectant	Ammonia in household cleaners (ammonium hydroxide)
Hydrofluoric acid as swimming pool cleaner and rust remover	Phenol
Oxalic acid as rust removers	Potassium permanganate
Vinegar (acetic acid)	Disc batteries (contain 45% solution of potassium hydroxide or sodium hydroxide; if lodged in esophagus can leak and perforate)
Formic acid used in the rubber tanning industry	Oxidizing agents
Aqua regia or Goldsmith's solvent is a 3:1 mixture of hydrochloric acid and nitric acid	Sodium hypochlorite (household bleach) is alkaline oxidizing corrosive
	Hydrogen peroxide in hair dyes
	Heavy metals
	Zinc chloride
	Mercury chloride

Consequently, there is little collagen deposition until the second week after ingestion. After 3 weeks, tissue fibrosis occurs during healing and causes narrowing of esophageal and/or stomach lumen forming strictures (**Table 2**).

Factors that determine the corrosive potential are concentration (industrial use products are more concentrated and more corrosive while hand use products are less corrosive), physical form (solids cause deep but localized injury in oral cavity while liquids cause extensive injury in esophagus and stomach), amount ingested, duration of contact, pH of agent (pH <2 and >12 are more corrosive), presence or absence of food in stomach.

Alkalis are usually colorless, tasteless, odorless and more viscous. Therefore, these are ingested in larger amount. The combination of their viscous nature and the process of liquefaction keep them in mucosal contact for a longer time and therefore, lye produces deeper (transmural) injuries. Acids are ingested in smaller quantity because of their pungent odor and bad taste.

**Table 2** Consequences of caustic injury

Necrosis	Within seconds of exposure to caustic agent
Ulceration and perforation	Within 24–72 hours of exposure
Fibrosis	Occurs by 14–21 days of exposure
Stricture	After weeks to years of exposure
Carcinoma formation	After decades of alkali exposure

They are rapidly swallowed and thus, may cause more gastric than esophageal injury.

Many studies have however reported that the esophageal injuries are common even with acid poisoning. The coagulum formed in acid ingestion prevents its transmural spread and therefore full-thickness or perialimentary injury is less common. Both acids and alkalis cause fibrosis, cicatrization and stricture formation.

## CLINICAL PRESENTATION

Children present with burns around and in the oral cavity with drooling of saliva. There is pain in lips, mouth, throat, chest and abdomen. Dysphagia, nausea, vomiting, hematemesis and melena may occur. Hoarseness, dysphonia, and stridor can occur due to laryngeal edema. Respiratory distress can occur due to airway obstruction, chemical pneumonitis or pulmonary edema.

Gastrointestinal (GI) perforation is an uncommon but major complication of corrosive ingestion seen in 6–7% cases. This usually occurs in the first 48 hours but can be delayed up to 14th day. Chest pain and presence of mediastinal air may point to esophageal perforation. The major clinical findings of gastric perforation are abdominal pain, tenderness and distension with radiologic evidence of pneumoperitoneum.

## TREATMENT

### Immediate Management after Ingestion

Immediately mouth should be rinsed (skin or eyes if involved should be flushed) and any remaining corrosive should be removed. If the child is having difficulty in breathing, child should be allowed to be in position of comfort. Efficacy of milk or water for diluting/neutralizing corrosive has not been confirmed by many controlled studies. Milk must be given within the first hour to be effective and this may compromise the urgent endoscopy. Other neutralizing agents are mild vinegar, lemon or orange juice for alkali and milk, eggs or antacids for acids. Some authors feel that the neutralization reaction produces heat which can cause further injuries of upper GI tract. Sodium bicarbonate produces carbon dioxide increasing the risk of perforation and is not recommended for neutralization of acids. Thus, no neutralizing substance, water or milk has any proven benefit.

### Early Treatment in Hospital

#### Initial Stabilization

If there is history of minimal corrosive ingestion and no oropharyngeal burns on examination, then the patient requires only observation in the emergency room. If there is respiratory distress along with stridor or hoarseness of voice then the patient requires admission in intensive care unit. Urgent endotracheal intubation should be done as airway edema may rapidly progress over minutes to hours. Supraglottic edema causing acute upper airway obstruction may require tracheostomy. Delay in prophylactic airway protection may make subsequent attempts at intubation or bag mask ventilation difficult or impossible. There is no clear role for systemic steroids or adrenaline nebulization in decreasing airway edema and reducing the need for endotracheal intubation (there are some reports of response to adrenaline nebulization and this may be tried for a brief period but intubation should not be delayed for long if there is no response). Acute circulatory compromise may occur due to hypovolemia because of hemorrhage, vomiting and third-space sequestration. Hemodynamic correction can be done by replacement with crystalloid fluids.

## Decontamination

Gastric lavage and induced vomiting are contraindicated because esophagus is re-exposed to regurgitated corrosive causing additional injuries. Activated charcoal does not bind to corrosives. False passage and esophageal perforation can occur by blind placement of a nasogastric tube. However, if a child reaches the hospital with a nasogastric tube already inserted, stomach contents may be aspirated. Exceptions to general rules of decontamination are zinc chloride and mercury chloride poisoning because both cause systemic toxicity.

### Diagnostic/Prognostic Upper Gastrointestinal Endoscopy

Mostly it is agreed that since severity of oropharyngeal injuries is not a reliable indicator for esophageal or gastric injuries, upper GI endoscopy should be performed early by 12–24 hours (but can be safely performed up to first 72–96 hours). This should be avoided from 4th to 14th day because of the healing process occurring intensively during this period and there is risk of perforation. Third-degree hypopharyngeal burns are an absolute contraindication for endoscopy. Other relative contraindications are respiratory distress, hemodynamic compromise, peritonitis and mediastinitis (suspected perforation) as well as mild ingestion (asymptomatic patients with normal oral/upper airway examination).

Children with first-degree injuries may be initially given liquids and within 24–48 hours a regular diet is allowed (**Table 3**). They may be followed up on an outpatient basis. In patients with IIB and III degree of damage, food particles can exacerbate the inflammation by entering the granulocytes of the esophageal wall. In these cases, *esophageal rest* is recommended and the child may be fed by gastrostomy or jejunostomy tube. In those who can swallow their saliva by 48 hours, intake of milk/nutritional liquids is recommended by some authors and surgical gastrostomy to be reserved for children who are unable to swallow liquids or saliva. Patients with second- or third-degree burns may need a barium swallow or repeat endoscopy after 3 weeks. First-degree injury rarely causes stricture. Second-degree injury infrequently causes and third-degree injury often causes strictures. Most frequent sites of esophageal stenosis are the cricopharynx, at the level of the aortic arch or bifurcation of trachea and the lower esophageal sphincter. The stomach and duodenum are usually spared but pyloric or antral stenosis can occur.

Some clinicians believe that asymptomatic patients may not be unnecessarily subjected to endoscopy. Uygun et al found that DROOL Scores (**Table 4**) were significantly lower (more severe) in patients with subsequent OS than those without. A DROOL Score less than and equal to 4 was a significant predictor of esophageal stenosis (100% sensitivity, 96% specificity, 85% positive and 100% negative predictive values). The authors also believed that endoscopy assesses only the gastroesophageal mucosa, whereas esophageal muscle layer burns and necrosis leading to esophageal stenosis (OS) are not visualized. Similarly, Bicakci et al reported 350 cases of corrosive ingestion in which enteral feeding was discontinued for 24 hours and after that those who did not tolerate enteral feeding were started on parenteral feeding. Early esophagoscopy or gastrostomy was not done in any patient. In patients with persistent dysphagia, contrast study of upper GI tract was performed within 3 weeks after injury. If there was OS, a dilatation program was initiated. Five percent patients

**Table 3** Severity of esophageal injuries caused by corrosives on upper gastrointestinal endoscopy (classification by Zargar\*)

Grade of injury	Description of injury
0	Normal mucosa
I	Superficial mucosal edema and erythema
II	Mucosal and submucosal ulcerations
IIA	Superficial ulcers, erosions, blisters, exudates hemorrhage
IIB	Deep discrete or circumferential lesions
III	Transmural ulcerations with necrosis
IIIA	Focal deep gray or brownish-black ulcers
IIIB	Focal deep gray or brownish-black ulcers
IV	Perforation

\*There are some other classifications available with minor differences.

**Table 4** The DROOL Score for caustic ingestion

Component of acronym	Signs and symptoms	Score 0	Score 1	Score 2
Drooling	Drooling of saliva	≥12 hours	<12 hours	No
Reluctance	Reluctance to eat or dysphagia or food intolerance	≥24 hours	<24 hours	No
Oropharynx	Oral and oropharyngeal burns	Severe lesions*	Edema, hyperemia	No
Others	Number of other signs and symptoms, e.g., persistent fever, hematemesis, abdominal tenderness, retrosternal pain and dyspnea	≥2	1	No
Leukocytosis	Total leukocyte count (/mm <sup>3</sup> )	≥20,000	<20,000	No

\*Friability, hemorrhage, erosion, blisters, whitish membrane, exudates, ulcers and necrosis.

required dilatation and in all patients, the symptoms were completely relieved. A median of five dilatation sessions (1–19 dilatations) were required. Kiriştioglu et al suggested that there is no need for endoscopy in liquid household bleach ingestion until there is persistent drooling as this agent is mild corrosive and they found hardly any strictures in these patients. Therefore, the type of corrosive ingested is also important. Hair straighteners and relaxers containing calcium or lithium hydroxide are highly alkaline but they rarely cause severe injury.

It is, therefore, suggested that in resource limited settings in developing countries, patients may be fed liquids as soon as they can swallow saliva. Those who cannot swallow may be subjected to gastrostomy or jejunostomy. Patients with persistent dysphagia may be subjected to endoscopy at 10–14 days or barium swallow is done at 3 weeks for detection and dilatation of stricture.

There is no role of steroids in first-degree burns as these heal well with no stricture formation. Some authors recommend steroids within 48 hours in grade II injury (especially IIB as IIA injury infrequently causes strictures). Steroids are

contraindicated in third-degree burns because of a higher risk of developing perforations. Various protocols, e.g., dexamethasone (1 mg/kg/day for 3 days and gradually weaned at 10 days) or prednisolone (2 mg/kg/day intravenous till patient starts taking orally and then 1–2.5 mg/kg/day orally for 3 weeks and then tapered) or methylprednisolone (2 mg/kg/day for 2–3 weeks and then tapered) or high-dose methylprednisolone (1 g/1.73 m<sup>2</sup>/day for 6–15 days) have been tried. In most studies, they have not found to prevent stricture formation. A review of 14 studies by Oakes showed no measurable benefit of the use of systemic steroids.

Tissue destruction from caustic injury increases the risk of infection by enteric organisms. Antibiotics are not recommended prophylactically in corrosive poisoning until there is evidence of infection but are recommended in cases with GI perforation. Gastroenterologists routinely recommend proton-pump inhibitors and H<sub>2</sub>-blockers in corrosive ingestion.

An approach to management of corrosive ingestions in children is shown in **Flow chart 1**.

### Long-term Treatment

The most common late complication is OS or gastric stenosis. These may appear from 3 weeks to 3 months after corrosive ingestion and sometimes even after 1 year. Isolated corrosive pyloric stenosis without esophageal involvement is an uncommon phenomenon but can occur sometimes (reported in 5% cases in one study). The most severe gastric injuries occur in antrum or pylorus where the corrosive remains for a long time. Gastric obstruction is suggested by weight loss and feeling of full stomach, nausea or vomiting.

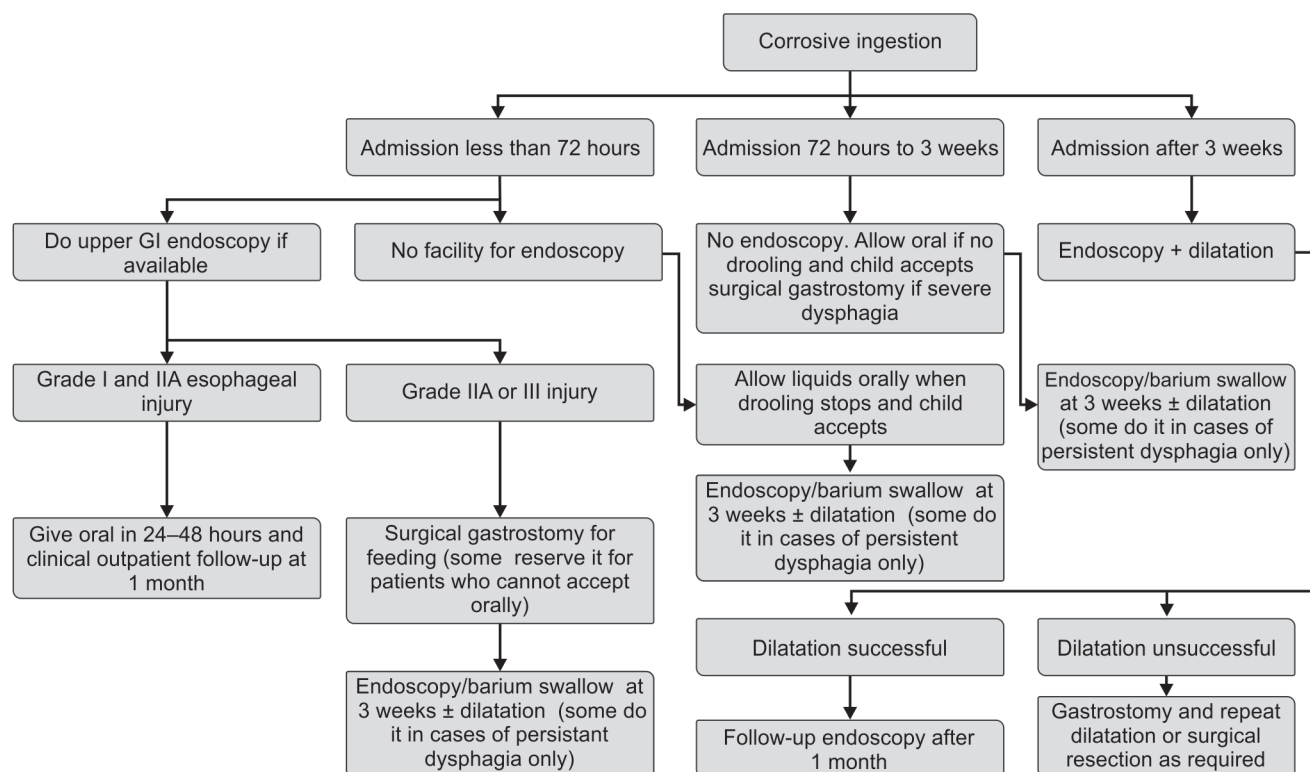
Esophageal and stomach cancer may occur decades later (25–50 years). Only few cases of postcorrosive carcinoma are reported from India. Lye ingestion has been associated in almost all cases of postcorrosive carcinoma reported in the world literature. It may be possible that in India, low incidence of esophageal malignancy may be due to overwhelmingly common ingested corrosive being acid.

Corrosive OS may be managed by endoscopic dilatation or by surgical resection. Dilatation by rigid Savary bougies (much more common and several Indian centers have reported good results) or balloon dilatation at regular intervals can be carried out. Dilatation is done till a lumen size of 15 mm or the size of thumb of child is achieved and there is no dysphagia. Subsequently, whenever dysphagia recurs dilatation is repeated. Average duration of stricture resolution has been reported to be 15–16 months by dilatation with bougies/balloon. Recurrent strictures can occur.

In patients with esophageal injuries of grade IIB and III, special intraluminal stents (made of silicone rubber or polyflex) may be placed under endoscopic guidance to prevent or treat esophageal stenosis. However, the efficacy is less than 50%, with a high migration rate (25%). Moreover, cost and experience are other factors to be considered.

Application of mitomycin (variable concentrations used in literature, e.g., cotton soaked in mitomycin 0.4 mg/mL solution for 5 minutes or 1 mg/mL for 2 minutes) at the stricture site after dilatation has been found to improve results of dilatation and require less sessions of dilatation. Mitomycin inhibits DNA-dependent RNA synthesis which reduces fibroblastic proliferation in submucosa and gives the mucosa enough time to creep and cover the stricture site, which prevents restenosis.



**Flow chart 1** Suggested management of corrosive ingestions in children

Though nasogastric tube placement may ensure patency of the esophageal lumen, the tube itself can contribute to the development of long strictures and routine use is not uniformly recommended. It may form a nidus for infection and worsen gastroesophageal reflux, causing delay in mucosal healing. There is a potential risk of esophageal or gastric perforation by insertion of nasogastric tube in acute phase. However, enteral nutrition through a nasogastric tube has been demonstrated to be as effective as jejunostomy feeding in maintaining nutrition in such patients, with a similar rate of stricture development. Positioning a nasogastric tube has another advantage of providing a lumen for dilatation, in case a tight stricture develops. Therefore, after caustic injuries the placement of a nasogastric tube may be considered, but the decision should be made with caution and done on a case-by-case basis.

### Surgery

Surgery is indicated if dilatation fails or there is complication after endoscopic dilatation such as perforation. If there is complete stenosis, fistula formation or location/length of the stricture is such that endoscopic management is impossible then surgery is the only alternative. Broadly, surgical management consists of either esophageal bypass (esophagus left in situ) or esophageal resection and replacement with a conduit. If children are admitted when the stricture is already well established, dilatations are more difficult and followed by a significantly higher recurrence rate than early procedures and more future need for esophageal replacement.

The American Society of Gastrointestinal Endoscopy recommends surveillance of patients 15–20 years after corrosive ingestion, endoscopic examination every 3 years and low threshold for evaluation of dysphagia.

### Psychosocial Management

At the time of injury, there is often a sense of guilt/blame and anxiety over the child's survival and future morbidity. The medical team managing the child needs to support the child's parents and caregivers. Long-term profound psychosocial impact of disfiguring corrosive injuries on the child has been documented. Children may develop behavioral or educational problems such as delinquency and school avoidance. These need to tackle whenever detected.

### PREVENTION

Corrosive agents need to be stored out of reach in a locked, child-resistant cupboard. Limit the concentration of such materials and make their containers childproof. Children less than 5 years need to be supervised at all times. There is need for legislation to regulate sale of concentrated corrosives.

### MORE ON THIS TOPIC

Bicakci U, Tander B, Deveci G, et al. Minimally invasive management of children with caustic ingestion: less pain for patient. *Pediatr Surg Int*. 2010;26:251-5.

Chibishev A, Simonovska N, Shikole A. Post-corrosive injuries of upper gastrointestinal tract. *Contributions, Sec. Biol Med Sci*. 2010;31:297-316.

- Contini S, Scarpignato C. Caustic injury of the upper gastrointestinal tract: a comprehensive review. *World J Gastroenterol*. 2013;19:3918-30.
- Contini S, Swarray-Deen A, Scarpignato C. Esophageal corrosive injuries in children: a forgotten social and health challenge in developing countries. *Bull World Health Organ*. 2009;87:950-4.
- Ghosh VB, Jhamb U, Singhal R, Krishnan R. Common childhood poisonings and their outcome in a tertiary care center in Delhi. *Indian J Pediatr*. 2013;80:516-8.
- Lakshmi CP, Vijayahari R, Kate V, Ananthakrishnan N. A hospital-based epidemiological study of corrosive alimentary injuries with particular reference to the Indian experience. *The Natl Med J India*. 2013;26:31-6.
- Naik RRR, Vadivelan M. Corrosive poisoning. *Indian J Clin Practice*. 2012;23:131-4.
- Ozdemir R, Bayrakci B, Tekşam O, et al. Thirty-three-year experience on childhood poisoning. *Turk J Pediatr*. 2012;54:251-9.
- Pelclová D, Navrátil T. Do corticosteroids prevent esophageal stricture after corrosive ingestion? *Toxicol Rev*. 2005;24:125-9.
- Temiz A, Oguzkurt P, Ezer SS, et al. Predictability of outcome of caustic ingestion by esophagogastroduodenoscopy in children. *World J Gastroenterol*. 2012;18:1098-103.
- Uygun I, Aydogdu B, Okur MH, et al. Clinico-epidemiological study of caustic substance ingestion accidents in children in Anatolia: the DROOL score as a new prognostic tool. *Acta Chir Belg*. 2012;112:346-54.
- Weigert A, Black A. Caustic ingestion in children. Continuing education in Anaesthesia. *Crit Care Pain*. 2005;5:5-8.
- Zhang C, Zhou X, Yu L, et al. Endoscopic therapy in the treatment of caustic esophageal stricture: a retrospective case series study. *Dig Endosc*. 2013;25:490-5.

## IN A NUTSHELL

1. Corrosive substances may be acids, alkalis (most dangerous), oxidants and heavy metal salts. Ingestion in children is mostly accidental at home.
2. In India majority of ingestions are due to acid unlike most other countries where alkali ingestion is more common.
3. Acids cause coagulation necrosis and alkalis cause liquefaction necrosis.
4. Acids tend to be ingested in smaller amounts as they have pungent odor and unpleasant taste, are swallowed rapidly after ingestion and may cause more gastric injury than esophageal.
5. Alkaline agents are usually colorless, tasteless and odorless and are therefore ingested in larger amount. Due to viscous nature and liquefaction necrosis they remain in mucosal contact for a long period of time and produce deeper injuries.
6. Efficacy of milk and water or other neutralizing substances as an antidote has not been confirmed.
7. Gastric lavage, induced vomiting are contraindicated. Activated charcoal does not bind to corrosives.
8. Endoscopy if available is performed early to detect the degree of injury to esophagus and stomach. Feeding can be started when patient can swallow saliva.
9. The most common late complications are esophageal and gastric strictures/stenosis. Steroids do not offer any benefit in prevention of stricture formation.
10. Treatment for OS is by dilatation at regular intervals by bougies (mostly) or balloon. Surgical management is indicated if there is failure of dilatation.

## Chapter 9.6 Snakebite

S Mahadevan, R Ramesh Kumar

Approximately 5 lakhs envenomings and 20,000 deaths occur each year due to snakebite worldwide. The maximum affliction of envenoming of more than 100,000 per year has been reported in South Asia, Southeast Asia and sub-Saharan Africa region. In the South East Asian region, India still contributes to highest snakebite related mortality. In tropical region like India, most of the deaths in snakebite are due to the late referral of victim to the hospital where anti-snake venom (ASV) is available for definitive management. Apart from late referral of victim factors contributing to high deaths are: (1) lack of community awareness about occupational hazards (2) not adopting the simple preventive measures (3) use of harmful first aid practices such as tight tourniquets, cutting and suction of snakebite site and (4) lack of confidence of primary care physician to administer ASV at peripheral setting in the fear of anaphylaxis of ASV. The *National representative snakebite mortality survey of India* found that snakebite related deaths remained an underestimated and underreported cause of accidental deaths. Occurred more commonly in the rural setting, in males than females and peaked at age group of 15–29 years and during the monsoon months of June to September. In India annual snakebite deaths were highest in Uttar Pradesh, Andhra Pradesh and Bihar.

### POISONOUS SNAKE SPECIES IN INDIA

All snakebites are not venomous. Venomous snakes are distributed widely in almost all countries situated in the western hemisphere from latitudes of 50°N to 50°S and in the eastern hemisphere from latitudes of 65°N (Scandinavia) to 50°S. Sea snakes are mainly distributed in the Indian Ocean and Pacific Ocean from latitudes of 30°N to 30°S. On land, venomous snakes have been found in

altitudes 4,000 m and higher in the Americas and Himalayas from sea level, and sea snakes can travel up to depths of 100 m and more in the oceans. In India, more than 330 species of snakes are found of which more than 60 species are venomous. However, only four snake species, namely common krait (*Bungarus caeruleus*), common cobra (*Naja naja*), saw-scaled viper (*Echis carinatus*) and Russell's viper (*Daboia russelii*) are being considered for most of the medically significant venomous snakebites in India (Figs 1A to D). However, this practice of considering only these four poisonous snakes has led to nonidentification of other unnoticed poisonous snake species contributing to more deaths. The discovery of the hump-nosed pit viper (*Hypnale hypnale*) causing life-threatening symptoms is an example of this situation. The ASV manufacturers produce antivenom only against these four major snake species due to this nonrecognition. In India, particular species are distributed in particular region: central Asian cobra (*Naja oxiana*) in the far north-west, greater black krait (*B. niger*) in the far north-east, monocellate cobra (*N. kaouthia*) in the north-east, hump nosed pit-viper (*Hypnale hypnale*) in the south-west coast and Wall's and Sind krait (*B. walli* and *B. sindanus*) in the east and west part of India, may be responsible for additional fatality due to snakebite envenomation. In order to entirely identify all the medically significant snake species in India, we need to shed the old order of *The Big Four*.

### PATHOPHYSIOLOGY

Snake venom is a complex mixture of various compounds; the venom of any given snake species might contain 100 and more different types of toxic and nontoxic proteins and peptides, and also contain nonprotein, carbohydrates, lipids, amines and various small molecules. Ninety percent of venom constituents are pharmacologically active peptides and proteins, which are responsible for almost all of its biological effects and clinical manifestations. The venom composition is exclusive to each species only, i.e., *species-specific*—e.g., neurotoxins in the venom of elapids, and cytotoxic and anticoagulant/procoagulant substances



**Figures 1A to D** The *Big Four* highly venomous snake in India. (A) Common cobra (*Naja naja*); (B) Russell viper (*Daboia russelii*); (C) Saw-scaled viper (*Echis carinatus*); (D) Common krait (*Bungarus caeruleus*)



in the venom of vipers and colubrids. The amount of venom injected is not associated to the number of bites or the size of the snake, or it is fangs.

Cytotoxic enzymes like phospholipases A2, metalloproteinases cause edema, blister and tissue necrosis at the bite site of a venomous snake through activation of proinflammatory pathways. Further, these enzymes support the release of other inflammatory mediators like bradykinin, prostaglandin, cytokines and sympathomimetic amines, which induce pain at the bite site. Peptides present in the venom cause hypotension via inhibition of angiotensin-converting enzyme (ACE). Safarotoxins and endothelins may cause the myocardial ischemia and cardiac arrhythmias as these toxins are potent coronary artery vasoconstrictors.

Neurotoxins cause muscle paralysis by acting on neuromuscular transmission either at presynaptic or postsynaptic levels. However, neurotoxins usually do not enter into the central nervous system via the blood-brain barrier. Phospholipase A2 complexes such as  $\beta$ -neurotoxins—taipoxin, paradoxin, trimucrotoxin, viperotoxin, pseudocerastes, textilotoxin, and crotoxin cause the inhibition of acetylcholine release from the presynaptic vesicles. Since these toxins affect formation of new acetylcholine vesicles at presynaptic terminal, these inhibitions are likely to be irreversible. Neurotoxins such as  $\alpha$ -neurotoxins are three-finger protein

complexes that act at postsynaptic level and have a curare-like action. Moreover, these types of toxins usually cause reversible blockage of acetylcholine receptors at postsynaptic terminal. Iridotoxin remains the best-characterized example of  $\alpha$ -neurotoxin. Complex neuromuscular transmission obstruction may occur as some venom composition comprise of both  $\alpha$ - and  $\beta$ -neurotoxins.

Metalloproteinases, via activation of factor X and serine proteases, act as potent activators of prothrombin. The snake venom C-type lectins and some three-finger toxins may promote or inhibit platelet aggregation due to its anticoagulant or procoagulant activity. Due to certain surprising effects like anti-inflammatory, immunomodulatory and antitumor of snake venom, it is under experiment for use as likely healing agents for various diseases. Patients suffering from acute ischemic stroke have been treated for years with toxin *ancrod*, a serine protease derived from the venom of Malayan pit viper due to its defibrinogenating properties. **Table 1** summarizes the mechanisms of action of snake venom proteins and peptides.

## CLINICAL FEATURES

### Systemic Features

Envenomed patients may experience arterial hypotension and shock, due to venom-induced systemic vasodilation and

**Table 1** Snake venom proteins and peptides: Mechanisms of action

Type of protein/Peptide	Example of toxin	Snake species	Mechanism of action
Acetylcholinesterase	—	<i>Elapidae</i>	Destruction of acetylcholine resulting in paralysis of muscles
Anticholinesterase	Fasciculins	<i>Dendroaspis spp</i>	Depolarizing neuromuscular block resulting in paralysis (dendrotoxins)
Calcium dependent-type galactose-binding lectins	Rhodocytin	<i>Viperidae, Elapidae</i>	Mainly affects the platelet
Cysteine-rich secretory proteins	—	<i>Elapidae, Viperidae</i>	Inhibition of the smooth muscle
Cysteine proteinase inhibitors	Cystatin	<i>Viperidae, Elapidae</i>	Inhibit metalloproteinases
Cobra venom factor, complement C3	Cobra venom factor	<i>Elapidae, Viperidae</i>	Local tissue damage
Disintegrin and metalloproteinase (ADAM)	Hemorrhagins (atrolysins, jararhagin); procoagulants (fibrolase, ecarin, Russell's viper venom factor-X activator)	<i>Viperidae, Elapidae</i>	Endothelial damage, bleeding, necrosis
Endothelins	Sarafotoxins	<i>Atractaspis spp</i>	Hypertension, effects on myocardial muscle
Factor-V, factor-X activators	—	<i>Viperidae, Australasian Elapidae</i>	Venom induced consumption coagulopathy (VICC)
Kallikrein (kininogenase) serine proteases	—	<i>Viperidae</i>	Hypotension
Kunitz-type proteinase inhibitors	Dendrotoxins	<i>Elapidae</i>	Inhibition of circulating serine proteases resulting in depolarizing neuromuscular block
L-amino oxidase	—	All	Programmed cell death (Apoptosis)
Natriuretic peptides	—	<i>Elapidae</i> : atrial-type and brain-type; <i>Viperidae</i> : C-type	Hypotension
Nerve growth factor	—	Many	Not known
Phospholipases A2	$\beta$ bungarotoxins	<i>Bungarus spp</i> (many phospholipases A2 in venoms of most snakes)	Presynaptic inhibition resulting in paralysis and destruction of nerve terminals, myotoxicity, hemolysis, inflammation, necrosis, platelet effects
Vascular endothelial growth factor (VEGF)	VEGF-homologous potent hypotensive factor	<i>Viperidae</i>	Endothelial damage, increased permeability resulting in third space loss, edema, hypotension



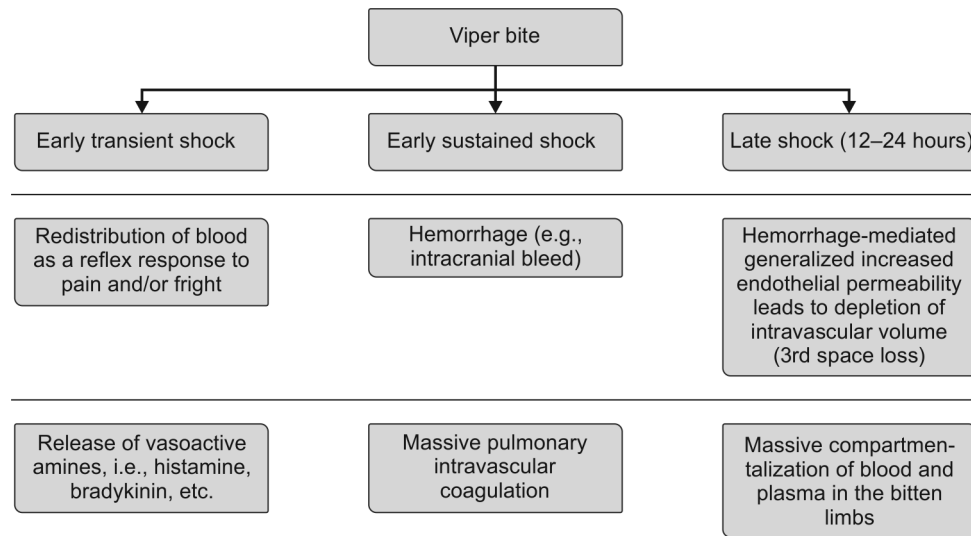
capillary leakage alone or along with a combination of acute bleeding induced hypovolemia. The clinical course of a viper bite may produce three kinds of shock (**Flow chart 1**). Severe envenomation may result to acute renal insufficiency as a result of hypovolemic shock due to vasodilation or bleeding, coagulopathy, rhabdomyolysis and direct nephrotoxicity of venom causing acute tubular necrosis. *Hemorrhagins* present in Russell's viper venom may cause acute hypopituitarism due to the hemorrhagic destruction of the pituitary. Viper and colubrids envenomation may produce clinical features of both thrombotic and hemorrhagic complications. The toxins in the venom may alter the coagulation pathway and the platelets function by different mechanisms, indicating the underlying basis for the clinical occurrence of thrombosis and hemorrhages in different parts of the human body.

muscles. Recovery of paralysis usually starts in the reverse order, and around 2 days is the median time taken for onset of recovery from respiratory failure. The subsequent pattern of involvement of descending paralysis is difficult to explain neurophysiologically.

### Locked-in Syndrome in Snakebite

In LIS, patient is conscious yet unable to communicate; the pupillary reflex is absent (internal ophthalmoplegia due to autonomic dysfunction). There are three kinds of LIS: *classic*, where even if the patient retains vertical eye movements and consciousness, he is afflicted with quadriplegia and anarthria. *Incomplete* LIS is similar to the *classic* type of LIS, except for the presence of voluntary movements in addition to vertical eye movement. In *total* LIS, except for the preserved consciousness there is a total

**Flow chart 1** Different types of viper bite-induced shock



### Neurological Complications

A snakebite victim may present with various neurotoxic features ranging from early morning neuromuscular syndrome to several cranial nerve palsies. These conditions are defined by different names like *locked-in syndrome* (LIS) in snakebite, brain stem reflex suppression, peripheral LIS and early morning snakebite syndrome. Single venom may lead to severe and complex neurological damage as it can present with both anticoagulant/procoagulant and neurotoxic effects. Reversal of paralysis by anti-venom is rendered improbable due to the high-affinity binding properties of neurotoxins. A rapid improvement in neurotoxicity occurs when the implicated toxins have a postsynaptic effect, e.g., cobra envenomation. Binding of  $\alpha$ -toxin (three-finger-fold polypeptide toxin) in the venom of black-necked spitting cobra, to the acetylcholine receptor has been shown to be reversible. The common krait is a nocturnally active snake with a painless bite; so many patients with neurological manifestations present to the emergency without history of snakebite.

Onset of paralysis after snake envenomation, i.e., the *time lag* is usually around 4–12 hours. The earliest clinical manifestation of paralysis is usually drooping of the upper eyelid (ptosis) followed by external ophthalmoplegia. The usual progression of paralysis but not necessarily in the following order is the involvement of muscles of palate, jaw, tongue, larynx, neck and muscles of deglutition. A complete quadriplegia and *locked-in* state can occur when the proximal limb muscles are involved earlier than distal

loss of power, immobility and inability to communicate. The most likely causes of LIS to be considered while evaluating patients are stroke, trauma or encephalitis involving ventral pons; however, it can also be caused by extensive damage of bilateral corticobulbar and corticospinal tracts in the cerebral peduncles. LIS can also be caused by other conditions such as severe Guillain-Barré syndrome, neuromuscular junction blockade (myasthenia gravis, toxins) (**Table 2**). Duration of LIS can range from 30 hours to 6 days. Key points are summarized in **Box 1**.

Locked-in syndrome in snakebite occurs due to neuromuscular paralysis of voluntary muscles, which in turn is caused by a neuromuscular transmission blockade (krait venom acts at presynaptic level while cobra venom acts at postsynaptic level) (**Fig. 2**). Irreversible binding of the toxin to presynaptic portion makes clinical recovery slow in krait envenomation and recovery occurs only after synthesis of new neuromuscular junctions and vesicles. Physicians should recognize the condition of *LIC* while managing the patients to prevent the dangerous error of diagnosing brain death. In the case of viper envenomation neuromuscular paralysis may also occur along with prolonged bleeding tendency (**Figs 3A to D**).

### Venom-induced Consumption Coagulopathy (VICC)

A procoagulant or consumption coagulopathy is the most common coagulopathy seen in snake envenomation. The diagnosis of disseminated intravascular coagulation (DIC) is problematic in

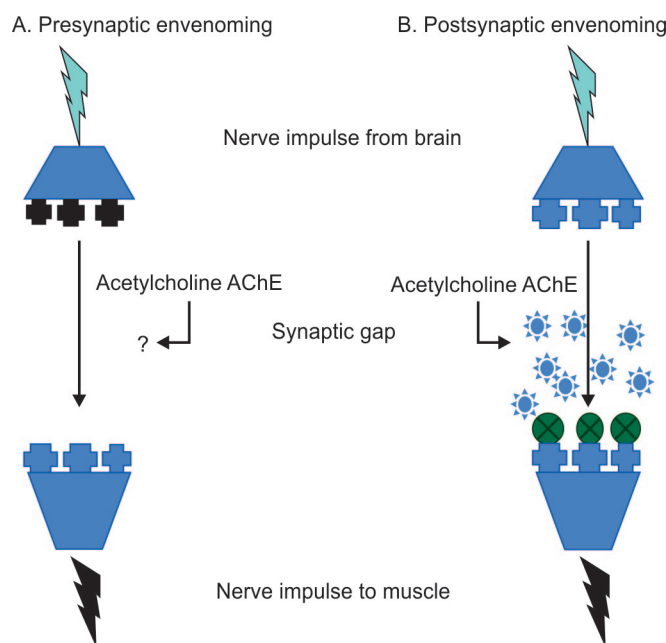
**Table 2** Differential diagnosis and causes and mechanisms of *locked-in syndrome (LIS)*

Cause	Mechanisms
Ischemic	Occlusion of the basilar artery, hypotensive or hypoxic events resulting in loss of blood supply
Hemorrhage	Hemorrhage or infiltration involving the pons
Traumatic	Contusion of brain stem, Dissection of vertebrobasilar axis system
Tumor	Involvement of ventral pons (primary or secondary tumor)
Metabolic (Na <sup>+</sup> disorders)	Central pontine myelinolysis (CPM)
Demyelination	Involving the ventral pons
Infectious	Infiltration of abscess involving the ventral pons, brain stem encephalitis (JE)

Abbreviation: JE, Japanese encephalitis

**BOX 1** Locked-in syndrome in snake envenomation

- The internal and external ophthalmoplegia can occur in snake envenomation.
- Supportive care should be continued until the effects of the venom wear off.
- In order to avoid misdiagnosis of brain death, confirmatory tests of brain death like cerebral angiography, electroencephalography, etc., should be considered.
- Treating physician should be aware of the locked-in syndrome in snakebite patients.



**Figure 2** Pre- and postsynaptic envenoming. Krait venom is also, like a cobra, strictly neurotoxic, it has no hemotoxic effect. Unlike the cobra, its venom enters the system and makes its way to the brain side of the neuromuscular junction. There a constituent element of the venom Phospholipase A2 destroys the synaptic vesicles. It is, therefore, primarily presynaptic in nature. This is the reason that krait victims take longer to recover. The body must grow more vesicles to replace the ones that have been destroyed. This results in an inability to produce acetylcholine and thus the signal from the brain cannot be transmitted across the synaptic gap. The diaphragm is unable to contract and the victim suffers respiratory failure



**Figures 3A to D** Neuroparalysis due to viper bite envenomation. (A) Local swelling; (B) Ptosis; (C) Prolonged 20-WBCT; and (D) Neck muscle weakness

snake envenomation because features of DIC such as an elevated D-dimer, prolonged prothrombin time, and low fibrinogen are always present in VICC, and thrombocytopenia is often related to VICC, as well. Few significant features of DIC, such as evidence of systemic microthrombi formation and end-organ failure are not characteristics of VICC. Patients with VICC may appear to be asymptomatic without any systemic features. The natural course of VICC differs from DIC with respect to rapid onset of coagulopathy within hours of the snake envenomation and resolution by 24–48 hours. VICC can either resolve spontaneously or after antivenom therapy over 24–48 hours.

The pathogenesis of activation of coagulation is different in VICC from DIC. In the case of DIC, activation of the coagulation leading to the formation of thrombin and is mediated by the tissue factor/factor VIIa pathway, which is not balanced by anticoagulant system due to impairment in the major anticoagulant pathways. In addition, there may be suppression of the fibrinolytic system leading to impairment of the fibrin removal in contrast to VICC, wherein these series of events does not occur. In VICC, the activation of coagulation is usually due to the effect of one of the procoagulant toxin present in the snake venom at one point of the pathway in the coagulation and not via the activation of tissue factor/factor VIIa pathway. Depending on the action of the toxin on the pathway, the resultant coagulopathy clinically can range from mild, partial or complete consumption of fibrinogen alone seen with thrombin-like-enzymes in vipers venom, to more severe coagulopathy, seen with prothrombin activators present in elapids venom, factor X activators in Russell's viper venom that the cause severe depletion of fibrinogen, factor V, factor VIII and activation of factor X respectively.

Venom-induced consumption coagulopathy differs from DIC in the following aspects: there is no microvascular thrombosis, no obvious fibrin formation and resultant end-organ damage or organ failure. Complication in VICC is usually due to bleeding, whereas DIC is characterized by classic fibrin formations, microvascular thrombosis that result in end-organ failures, as well as bleeding complications. Metalloproteinase prothrombin activators found in snake venom activate the coagulation pathway and concurrently cause injury to the blood vessel, resulting in the risk of bleeding manifestation in VICC.

The current available consensus guideline criteria for diagnosis of DIC if applied to VICC will often match most of the criteria and suggest overt DIC in a given patient. However, VICC

is clearly different based on the current understanding of the pathophysiology of activation of coagulation, the time course, and the prognosis. These are the main reason for the long-time belief that snakebite can cause DIC. Therefore, it is important that the terminology *VICC* be used to clarify the clinical syndrome requiring different treatment approaches.

Coagulopathy seen in snake envenomation is usually due to the direct effect of toxins present in snake venom. Using specific antivenom to remove these toxins should allow the coagulopathy to return to normal homeostasis. Nevertheless, the antivenom can neither repair the complications caused by coagulopathy like end organ failure nor can it stop any secondary phenomena activated during coagulopathy like hyperfibrinolysis. Hence, it is essential to administer the appropriate antivenom as early as possible in sufficient quantity, once coagulopathy is detected, and any further supplementary doses of antivenom if the clinical condition warrants the same. It is of equal importance to avoid other therapies like heparin, warfarin, fresh frozen plasma (FFP), cryoprecipitate that may further worsen the condition of coagulopathy. Heparin will not *switch off* the pathologic process of *VICC*, so it is of no help, rather it may induce its degree of pathologic changes in the clotting process. The addition of FFP or cryoprecipitate may only complicate things, especially with procoagulant unless the antivenom has removed all the venom.

### Snakebite Induced Thrombotic Microangiopathy (TMA)

Clinical syndromes of thrombotic microangiopathy have been reported in patients with snake envenomation and are characterized by thrombocytopenia, acute renal failure and hematological abnormality suggestive of microangiopathic hemolytic anemia. The exact mechanism of snakebite associated TMA remains unclear and proper definition of this condition is still not available. The TMA appears to occur in conjunction with *VICC* of not only certain snake species, but also in several snake species including vipers and elapids. Though features are consistent with TMA, it progresses despite normalization of coagulopathy, suggesting a different but related process in the pathogenesis. The presence of overlapping clinical features in *VICC* and TMA in snake envenoming is the likely reason for the mistaken idea that snake envenomation is the cause of DIC.

The treatment of snake envenomation associated TMA remains controversial. Recommendations for the administration of FFP, cryoprecipitate and plasmapheresis remain unproven and

are associated with worsening clinical condition. In most of the patients improved with supportive care and in many cases it is not recognized as such.

### Acute Kidney Injury

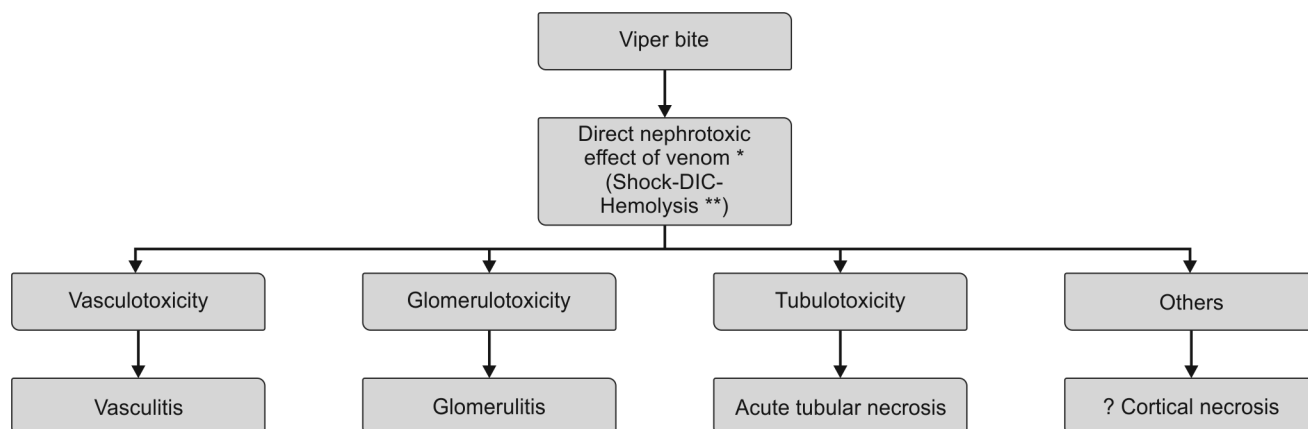
In many cases of envenomation due to various snake species, renal involvement has been reported. However, the most severe type, acute renal failure, is mainly seen in viper envenomation (**Flow chart 2**). In India, this is usually seen in most common viper species of Russell's viper and the Saw-scaled viper envenomation. The frequency of snake envenomation associated acute renal failure has been reported as 3–32% in India, 1.2% in Thailand, and as high as 40% in Myanmar. A proposed mechanism of renal injury is venom-induced cellular injury through enzymes, polypeptide and different cytokines. Myotoxic or hemotoxic snakes cause renal failure and are responsible for the following complications—rhabdomyolysis, intravascular hemolysis, DIC or bleeding.

Renal failure can occur as early as an hour to as late as days after envenomation, with evidence of the rapid rise in blood urea and serum creatinine. Nonoliguric renal failure is not uncommon and can persist for an average duration of up to 3 weeks. The histopathology of snakebite associated renal failure consists of predominantly acute tubular necrosis (ATN) in 73% and acute interstitial nephritis (AIN) in 5–15% of patients while reported changes in glomerulus pathology are rare. Metalloproteases and phospholipase A2 may be responsible for degeneration and necrosis of tubular epithelial cells and interstitial edema and cellular infiltration. Immune-mediated mechanisms play a diminutive role in the pathogenesis of renal failure. However, in Russell's viper envenomation, diffuse AIN disproportionate to tubular cell degeneration has rarely been reported as a mechanism of renal failure. Though many factors can contribute to the development of AIN, direct toxicity of snake venom has been postulated in the development of the interstitial inflammation via production of cytokines and adhesion molecules.

The exact role of direct nephrotoxicity by snake venom remains unclear, but hypersensitivity reaction to the venom or antivenom protein has rarely been found to cause the acute renal failure. The conclusion that antivenom protein is the cause of renal failure needs to be proven. The histopathological finding of AIN is correlated with poor prognosis for development chronic kidney disease (CKD) during long-term follow-up.

Independent risk factors associated with renal failure and dialysis requirement are, delayed administration of an adequate

**Flow chart 2** Mechanisms of viper bite-induced renal failure



\* Major contributing factor in the pathogenesis of viper bite-induced renal failure.

\*\* Contributing factor in only few cases. Shock may be a key predisposing factor in the cortical necrosis.



dose of ASV, presence of cellulitis, and bite during the winter months, low platelet count, bleeding, intravascular hemolysis and hypotension at presentation. Management of snakebite induced renal failure is primarily of supportive care along with timely administration of ASV. Rather than being concentrated in referral hospitals, ASV should be made available in all emergency and primary health centers near local communities.

### Compartment Syndrome

Envenomation of a limb can lead to cutaneous necrosis, compartment syndrome and even necrotizing fasciitis. Compartment syndrome in snakebite is uncommon and it usually affects the upper limb. The principal local effect of venom is edema, which occurs within 2 hours after a bite and intensifies during the following 3 days. Swelling and vasoconstriction lead to ischemia and compromise the vitality of the limb. The six symptoms/signs that point towards compartment syndrome are pain on passive stretching, disproportionate pain, pulselessness, pallor, paresthesia and paralysis. However, presence of arterial pulses does not exclude intracompartmental ischemia. The most reliable test in suspected cases is to measure intracompartmental pressure directly through a cannula introduced into the compartment and connected to a pressure transducer or manometer. McQueen and Court-Brow consider that a difference of 30 mm Hg between diastolic and compartment pressure is the threshold of fasciotomy. Early treatment with antivenom remains the best way of preventing irreversible muscle damage.

### MANAGEMENT

The steps involved in the management of snake envenomation victims are: (1) First aid treatment practice(s) (2) Transport of the victim to a nearby health-care facility (3) Rapid clinical assessment and resuscitation of the victim (4) Detailed clinical assessment and identification of snake species (5) Diagnosis and investigations or laboratory tests (6) ASV administration (7) Observing and documenting the response to ASV (8) Decision regarding follow-up dose(s) of ASV (9) Additional supportive care (10) Treatment of bite area (11) Recovery (12) Management of chronic complications if any. Immediate treatment of snakebite in the field consists of safe identification of the snake species whenever possible and early transports of patients to the nearest health-care facility with ASV administration. Risk factors for poor outcome are listed in **Box 2**.

#### BOX 2 Risk factors for poor outcome (death or major disability)

- Age (younger the age: adjusted OR 0.85; 95% CI 0.7–0.9)\*
- Walking for > 1 km after the bite (adjusted OR 57; 95% CI 4.2–78.2)\*
- Hemoglobin ≤ 10 g/dL at admission (adjusted OR 6.2; 95% CI 2–18.2)\*
- Species of snake (cobra)
- Vomiting

\*Independent risk factors for poor outcome

### First Aid

The first aid treatment aims to (1) to delay systemic absorption of venom (2) to preserve life and prevent complications before medical care is given (3) to control distressing or dangerous early symptoms of envenoming (4) arrange the transport of the patient where medical care is available including administration of ASV (5) to do *NO HARM*. First-aid treatment in children can be performed by anyone else who is present and able.

*Unhelpful first-aid treatment* Traditional healers undertake the immediate treatment of snakebite in most of the developing countries. These traditional, accessible, available and affordable first-aid methods are mostly useless and dangerous. The various

healing methods include: efforts to suck the venom out of the wound, tying tourniquets (tight bands) around the limb, making local incisions or pricks/punctures (tattooing) at the site of the bite or in the bitten limb, use of (black) snake stones, topical instillation or application of chemicals, herbs or ice packs, electric shock (**Fig. 4**). Traditional treatments by local people should not be allowed to do harm or delay medical treatment. Traditional treatment distorts the clinical picture and delays presentation, and can trigger an infection, bleeding, gangrene, and other complications including death.

### Reliable Technique: Pressure Immobilization Method

Snakebite victims' first choice of first aid is resort to tying tight bands (tourniquets) around their limbs. The tourniquets are ineffective in retarding venom flow. There is also the risk of ischemic damage to the victim due to an increase in the necrotic action of the venom. In the eventual release of the tourniquet, there is a danger of neurotoxic blockage and clotting. Early transport to medical care facility is advisable and harmful traditional treatments should be ignored. In the late 1970s the Pressure Immobilization Method (PIM) was developed in Australia as a reliable technique to prevent venom flow into the system (**Figs 5A to E**).

#### Pressure Immobilization Method

Until possibility of a bite by a neurotoxic elapid eliminated, bandaging the bitten limb at a pressure of about 50–70 mm Hg and immobilizing it with a splint (pressure immobilization) or pressure pad is required at the bite site in a similar way as is done for a sprain. PIM obstructs the lymphatic and venous drainage, which in turn delays absorption of large molecular weight neurotoxins into the system, without the dangerous use of tight tourniquets. The clinical efficiency of these methods is yet to be sufficiently examined. In a simulated environment emergency room physicians and lay people failed to apply the method correctly as the required bandage pressure varied between lower and upper limbs. The technique also required complete immobilization. Walking for more than 10 min invalidated the effect of the bandage, even if it was applied in the correct range of pressure.

### Do it R.I.G.H.T.

Both PIM and tourniquets require the use of equipment affecting the feasibility in developing countries. Moreover, in a primary care setting, practical application of pressure immobilization has been difficult to teach; these are not recommended for use in the National Protocol for Management of snakebite in children. As per the recommendations by National Protocol, the first aid treatment is based around the mnemonic: *Do it R.I.G.H.T* (**Box 3**). Ideally, tight bands, bandages and ligatures if applied, should not be released until the patient has reached the hospital, where resuscitation facilities and ASV are available. Investigations of other methods like the early administration of ASV, early transport of the victim to the health-care facility in rural setting by volunteer motorcyclists, and education of paramedics and ambulance crews about basic life support are potential areas of future study.

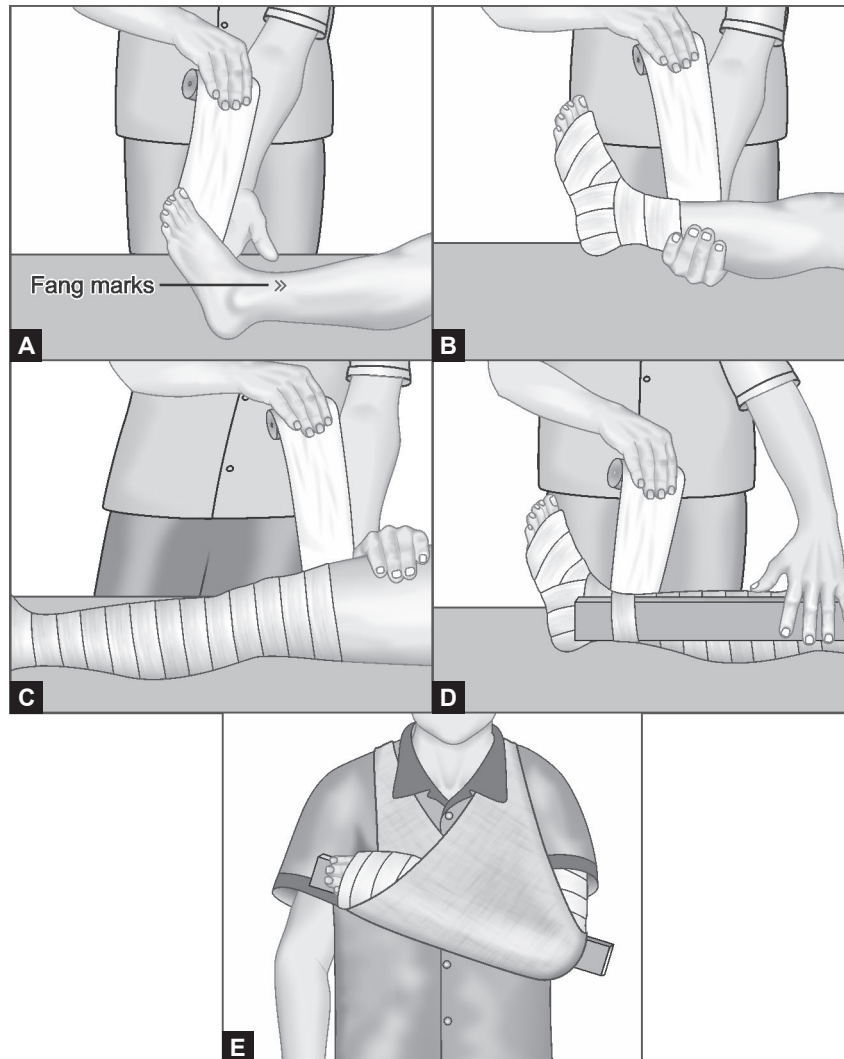
### Identifying the Species of Envenoming Snakes

The usual reports of unidentified snakebites tend to ignore the vast interspecies diversity of snake venom actions. Attempts should be made to discourage the capture or killing of the snakes responsible for the bite. It is both dangerous and ecologically destructive. The captive snake can be wrongly identified, leading to unsuitable treatment. Herpetologists have been known to make serious errors with respect to recognition of snake species. It is also unreliable





**Figure 4** Inapplicable first aid treatments. *DO NO HARM* during first aid



**Figures 5A to E** Pressure immobilization method. (A to C) Commencing distal to bite the site, apply the bandage as tightly as binding a sprained ankle, enveloping the bite site and extending to above major joint; (D and E) Apply splint to prevent movement of a limb, thereby preventing muscle use and lymphatic flow

**BOX 3 Do it R.I.G.H.T.**

- *R.* = Reassure the patient  
*Rationale:* Seventy percent of snakebites are from nonvenomous species. Only 50% of snakebites by venomous species really envenomate the patient.
- *I.* = Immobilize the patient as is done for a fractured limb  
*Rationale:* We can carry children. Bandages or cloth should be used to hold the splints in place, and not to block blood supply or apply pressure. Use of tight ligatures to apply any kind of compression, is dangerous and they do not work!
- *G.H.* = Get to Hospital immediately  
*Rationale:* There is *NO PROVEN* benefit in the treatment of snakebite with the use of traditional remedies.
- *T.* = The doctor should be briefed about any systemic symptoms such as ptosis that manifest on the way to hospital.  
*Rationale:* To prepare the treatment plan.

to try to identify the species following descriptions by victims or their escorts or from photos of snakes. A more reliable method in snakebite identification is to differentiate the various *clinical syndromes* of snake envenoming by a detailed analysis of a series of clinical signs and symptoms (**Flow chart 3**).

### Diagnosis and Testing

Bite marks do not help in ascertaining if the snake was venomous or nonvenomous. Venomous snake species have multiple sets of fangs, and nonvenomous snake species can leave puncture marks from enlarged teeth, which appear to be fang-like. Based on the presence or absence thereof, the following features formed the basis of *snake envenomation diagnosis*: snake bite history, bite marks, local manifestations—swelling and pain at the bite site, or systemic manifestations—features of neurotoxicity or spontaneous bleeding and/or if the dead snake was brought in for identification.

#### 20-minute Whole Blood Clotting Test (20-WBCT)

It is an informative and useful bedside standard test for coagulopathy in the management of snake envenomation. This vitally needs a *new, clean, and dry test tube* and requires 2 mL of fresh venous blood, which is then left untouched for about 20 min, before being gently tilted once. In the case of hypofibrinogenemia (*incoagulable blood*), the blood is still liquid (unclotted) and runs out. Incoagulable blood is an undisputed diagnostic of a viper bite in India and certainly removes any doubt of an elapid bite. The wall of the test tube or vessel may not stimulate clotting of the blood

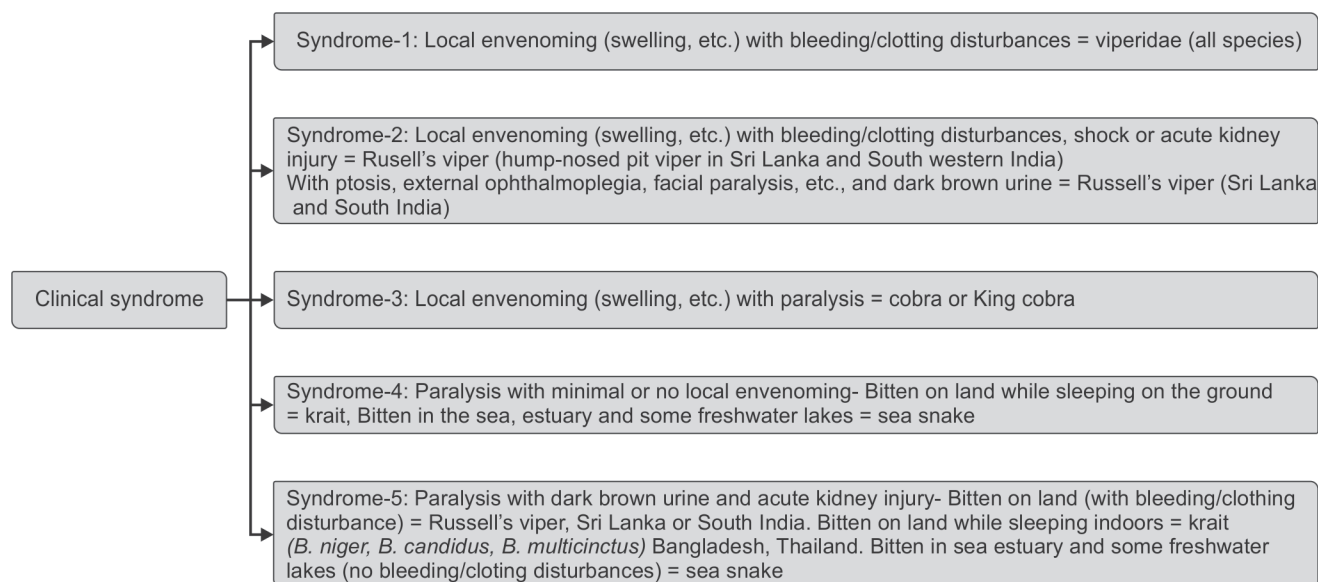
sample (surface activation of factor XI—Hageman factor), if it is not made of ordinary glass or detergent has been used as a cleansing agent, and hence, the test will be invalid. In the case of doubt, it is best to redo the test in duplicate, along with *control* element (e.g., a blood sample of a healthy relative).

### Other Tests

**Hematological abnormalities** Hemoconcentration (a transient increase of hemoglobin (Hb) is a result of a generalized surge in capillary permeability (e.g., in Russell's viper bite). Often, decreased Hb levels result from blood loss or intravascular hemolysis if it is a case of Indian and Sri Lankan Russell's viper bite. Snake bite victims of vipers and Australian elapids may show a decrease in platelet count. Early neutrophil leukocytosis reflects evidence of systemic envenoming by any species. In the case of microangiopathic hemolysis, fragmented red cells (helmet cell, schistocytes) are seen on blood film. Gross hemoglobinemia or myoglobinemia results in a pinkish or brownish plasma/serum.

**Biochemical abnormalities** In case of severe local tissue damage or, generalized muscle damage in particular (sea snake, South Indian and Sri Lankan Russell's viper bites), elevated levels of muscle enzymes (creatine kinase, aldolase) and aminotransferases are found. Massive blood extravasation leads to elevated bilirubin. Snake envenomation by a Russell's viper, hump-nosed viper and sea snake causes acute renal failure with raised levels of creatinine, potassium, and urea or blood urea nitrogen. Early hyperkalemia follows extensive rhabdomyolysis in sea snakebites.

**Flow chart 3** Approach of snakebite patients based on clinical syndrome



## Antisnake Venom

This method of envenoming treatment was first introduced in Saigon in the 1890s by Albert Calmette at the Institute Pasteur and was widely accepted in clinical practice without formal clinical trials. A mule or donkey or horse (equine) or sheep (ovine) is immunized with the venom of one or more snake species. Immunoglobulin [usually pepsin-refined Fab2 fragments of whole IgG] purified from the plasma of these animals is used to obtain antivenom. Antivenom raised against a specific snake species is called *Specific* antivenom. Hence, it contains specific antibodies to neutralize the venom of that particular snake or its closely related species (para-specific neutralization).

**Antisnake venom administration criteria** Antisnake venom treatment should be administered as soon as the following symptoms present:

- The 20-WBCT suggesting a coagulopathy, symptoms of spontaneous bleeding or neurological impairment such as ptosis. Even when symptoms have persisted for several days or more in the case of hemostatic abnormalities, ASV may reverse systemic envenoming. If symptoms of coagulopathy persist, it is appropriate to give ASV.
- Local symptoms such as rapid swelling across a joint including half the bitten limb even in the absence of a tourniquet. When the swelling persists 1 hour after the removal of the tourniquet, it should be attributed to venom release rather as an effect of the tourniquet
- Persistent abdominal pain and vomiting.

Whether local administration of ASV can prevent local tissue necrosis remains uncertain. There is limited evidence available to confirm that for ASV to be useful it is required to be administered in the initial hours after the bite; however, once there is an indication, treatment with ASV should not be delayed.

**Antisnake venom doses and administration** A frequent topic of debate has been the initial dose of ASV to be administered to a patient. The first bite of a Russell's viper can inject an average of 63 mg (SD 7 mg) of venom. Taking into account the average dose of injected venom, the initial dose has been calculated to neutralize its effect. This method aims to cover the majority of victims with the initial dose. 6 mg of Russell's viper venom can be neutralized by a single vial of polyvalent ASV; therefore, both children and adults require an initial dose of 8–10 vials. If the range of venom injected falls between 5 mg and 147 mg, it requires a maximum ASV dose of around 25 vials. Suitable levels of ASV in children (higher level—because of body mass, lower level—to prevent adverse reaction) are yet to be ascertained.

Reconstituted ASV is diluted in 5–10 mL/kg bodyweight of normal saline or 5% dextrose (5D) or Ringer lactate (RL) solution and should be administered over 1 hour at a constant rate with hemodynamic monitoring. The degree of severe systemic hypersensitivity reactions is not affected by the slow (over 120 min) or rapid (over 20 min) infusion of ASV. Administering each dose over a long period has no benefit, while prolonging the time before ASV can neutralize the venom proves to be counter-intuitive.

**Adverse reactions to antisnake venom** The primary reasons for not administering ASV in peripheral hospitals/dispensary are the adverse reactions to ASV (pyrogenic or anaphylactic). Most primary care doctors are reluctant to treat snakebite victims; due

to possible life-threatening reactions. Doctors should not shy away from treating snakebite victims as early treatment with appropriate drugs can overcome these reactions. Positive outcomes can be realized with early intervention against these actions.

Antisnake venom should be discontinued and adrenaline 0.01 mg/kg body weight intramuscular should be given if any of following *signs* appears: nausea, vomiting, diarrhea, urticaria, itching, and fever, shaking chills, abdominal cramps, tachycardia, hypotension, bronchospasm and angioedema. In addition, 2 mg/kg of hydrocortisone IV and a dose of intravenous antihistaminic drug should be administered to provide protection against anaphylactic reactions. After being given ASV, usually more than 10% of patients develop a reaction. It can occur within a few hours (called as an early reaction) or even after 5 days or more (called as the late reaction). After sufficient recovery of the patient, a slow restart (10–15 min) of ASV can be made under close observation of the patient. Typical drip rate can be resumed later. ASV test dose does not have any role in predicting anaphylactic or late serum reaction and may presensitize the patient to the protein.

## Anticholinesterase Drugs

Patients with neurotoxic envenoming, specifically cobra bites can experience a potentially useful yet variable effect from anticholinesterase drugs. Every patient with neurotoxic envenoming should be considered for a trial of anticholinesterase. However, this should not delay ASV treatment. Atropine sulphate (50 µg/kg) is administered through an intravenous injection followed by 0.04 mg/kg of neostigmine bromide by an intramuscular injection. Even though the short-acting edrophonium chloride (Tensilon) is suitable for this test, its nonavailability is a limiting factor; a dose of 0.25 mg/kg through a slow intravenous injection is used to administer the drug. The patient is observed for signs of improved neuromuscular transmission over the next 10–20 min (edrophonium) or 30–60 min (neostigmine). Ventilator capacity (peak flow, FEV-1 or maximum expiratory pressure) may improve and ptosis may withdraw. Patients with a positive response can be continued on 0.01–0.04 mg/kg dose of neostigmine, every 2–4 hours for 24 hours, by intravenous, intramuscular, or subcutaneous injection along with atropine to inhibit muscarinic side effects.

## Repeat Doses of ASV

In antihemostatic bites, after the initial dose (over 1 hour) has been administered, no further ASV is required for the next 6 hours. The liver requires the time to restore the clotting factors. The following factors are considered for a repeat dose of ASV (1) Persistence or recurrence of bleeding (after 1–2 hours) or blood incoagulability (after 6 hours) (2) Reappearing or deteriorating cardiovascular or neurotoxic signs after 1–2 hours.

## Supportive Care

Antisnake venom treatment can be relied upon to neutralize the free circulating venom, prevent further progress of envenoming and allow for recovery. Nevertheless, these processes do take time, and envenomed patient may require further life support systems such as assisted ventilation, treatment of shock, and renal dialysis until the afflicted tissues and organs have sufficient recovery time.

### IN A NUTSHELL

1. Snake envenomations are an important cause of mortality, particularly in rural areas.
2. The important venomous snakes in India are common cobra (*Naja naja*), Russell's viper (*Daboia russelii*), saw-scaled viper (*Echis carinatus*) and common krait (*Bungarus caeruleus*).
3. The composition of the venom is species-specific, i.e., neurotoxins predominate in the venom of elapids, while cytotoxic and anticoagulant/procoagulant substances are found in the venom of vipers and colubrids.
4. Neurotoxic features of snakebite vary from early morning neuromuscular paralysis to several cranial nerve palsies. In addition, there may be brain stem reflex suppression and LIS.
5. The most common coagulopathy associated with snake envenoming is a procoagulant or consumption coagulopathy; usual manifestation is spontaneous bleeding.
6. Initiation of appropriate first aid is important; at the same time harmful practices should be discouraged.
7. In India, ASV is polyvalent antivenom effective against *Naja naja*, *Bungarus caeruleus*, *Daboia russelii* and *Echis carinatus*.
8. Antisnake venom should be given only to patients in whom its benefits are considered likely to exceed its risks.
9. The dose of antivenom is same for children and adults; children need relatively higher doses for their body size.
10. Patients with neurotoxic envenoming, specifically cobra bites may benefit from anticholinesterase drugs such as neostigmine.

### MORE ON THIS TOPIC

- Del Brutto OH, Del Brutto VJ. Neurological complications of venomous snake bites: a review. *Acta Neurol Scand*. 2012;125:363-72.
- Kasturiratne A, Wickremasinghe AR, de Silva N, et al. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. *PLoS Med*. 2008;5:e218.
- Koh DC, Armugam A, Jeyaseelan K. Snake venom components and their applications in biomedicine. *Cell Mol Life Sci*. 2006;63:3030-41.
- Mohapatra B, Warrell DA, Suraweera W, et al. Snakebite mortality in India: a nationally representative mortality survey. *PLoS Negl Trop Dis*. 2011;5:e1018.
- Nakagawa TA, Ashwal S, Mathur M, et al. Clinical report—Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. *Pediatrics*. 2011;128:e720-40.
- Sankar J, Nabeel R, Sankar MJ, et al. Factors affecting outcome in children with snake envenomation: a prospective observational study. *Arch Dis Child*. 2013;98:596-601.
- Sitprija V. Animal toxins and the kidney. *Nat Clin Pract Nephrol*. 2008;4:616-27.
- Smith E, Delargy M. Locked-in syndrome. *BMJ*. 2005;330:406-9.
- Warrell DA. Snake bite. *Lancet*. 2010;375:77-88.
- White J. Snake venoms and coagulopathy. *Toxicon*. 2005;45: 951-67.



## Chapter 9.7

# Scorpion Sting

S Mahadevan, R Ramesh Kumar

Scorpion sting envenomation in children is a life-threatening medical emergency. Children are at a higher risk of severe envenomation and death due to myocardial involvement, pulmonary edema, and neurological complications as compared to adults.

## EPIDEMIOLOGY

Worldwide, more than 1.2 million scorpion stings and 30,000 deaths are reported annually. In India, Saudi Arabia and South Africa, the reported case fatality rate of children hospitalized with scorpion sting ranges from 3% to 22%. Over 1,050 species of scorpions are known to exist worldwide. Approximately 50 species of scorpions are venomous and are responsible for clinical presentation in humans. These venomous species are included in the genera of *Centruroides*, *Buthus*, *Androctonus*, *Parabuthus*, *Leiurus*, *Mesobuthus*, *Tityus* and *Hemiscorpius*. In India, out of the 86 scorpion species, the only poisonous scorpions of any medical importance are *Hottentotta tamulus* and *Palamnaeus swammerdami*. *Hottentotta tamulus* (also named as *Mesobuthus tamulus*), the Indian red scorpion (also called as Eastern Indian scorpion), is responsible for most deaths, most of which are preventable with appropriate treatment (Figs 1A and B).

## DISTRIBUTION AND HABITAT

In India, scorpions are usually found to habitat dry, warm regions, with a primary species concentrated in coastal and rural parts with rich red soil. The scorpions usually inhabit dark sheltered places such as crevices in the walls, under rocks, bricks and logs, in dry paddy husks, under loose tree barks, behind furniture and inside clothing and shoes. They are nocturnal in habit, remaining hidden in the daytime and emerging at night to feed; this explains why maximum human stings are reported during the night.

In the summer, there is a drastic increase in scorpion stings. Scorpion stings are primarily a result of accidental encounters. If trapped or roughly handled, scorpions are likely to use their stings. Envenomation in scorpion sting does not always happen as a scorpion can control its ejaculation. Hence, a sting can be partial, total, or nonexistent.

## PATHOPHYSIOLOGY

### Composition of the Scorpion Venom

Scorpion venom is a heterogeneous mixture of short neurotoxic peptides with significant variation between different species. The neurotoxins are *species-specific* as well as *target-specific*—each one targeting the ion channels of a particular kind of animal—some are more effective against insects, some lethal to molluscs and yet others may target mammalian nerve cells. The venom also contains histamine, histamine-releasing factor, serotonin, hyaluronidase, certain enzymes, enzyme inhibitors, salts, peptides, nucleotides and free amino acids. Venom is usually deposited in the skin, deep into the subcutaneous tissue; absorption is complete in around 7–8 hours while 70% venom concentration in blood is reached within 15 minutes.

### Effect of the Venom Toxins on Autonomic Function

The venom alters voltage-dependent ion channels. The sodium channel is affected by beta (of *Centruroides* spp) and alpha (of *Buthus* spp) toxins. The toxins *tityus* and scyllatoxin, and charybdotoxin of *Leiurus* species act mainly on potassium channels. The toxin inhibits the inactivation of the ion channels and result in persistent neuronal excitation and an autonomic storm. The effects of the toxins on the calcium and potassium channels may be less important in humans.

The alpha toxins stimulate the release of epinephrine, norepinephrine, and vasoactive peptides such as endothelin and neuropeptide Y; these are responsible for the development of myocardial dysfunction, hypertension, pulmonary edema, tachycardia and cool extremities. In addition, hyperkalemia, free fatty acids, hyperglycemia, and free radicals accumulation injurious to myocardium occur. The venom of an Indian red scorpion causes acute myocarditis, cardiac sarcolemmal defects, and depletion of glycogen content of heart, and liver and skeletal muscles. Electron microscope studies have shown contraction band necrosis with ruptured and hypercontraction sarcomeres due to the excessive catecholamine similar to the one seen in the pheochromocytoma. The effect on the parasympathetic function may contribute the respiratory impairment; though as compared to the sympathetic effects, these are less prominent.

Increase in leukocyte count within an hour of sting and rise in renin, angiotensin II, cardiac enzyme, platelet activating factors, cytokines, serum potassium, hyperglycemia, urine and serum catecholamine, serum amylase and reduction in insulin level may occur.



**Figures 1A and B** Scorpions are arachnids belonging to the Phylum: Arthropoda; Class: Arachnida and Order: Scorpionidae. (A) Indian red scorpion (*Mesobuthus tamulus*); (B) Black scorpion (*Palamneus gravimanus*)

## Effects of the Venom on Other Organs

Scorpion sting envenomation can cause changes in coagulation profile and may lead to acute disseminated intravascular coagulation (DIC). Seizures and encephalopathy in some children are observed due to the neurotoxicity. The central nervous system (CNS) manifestations may be due to acute rise in blood pressure due to sympathetic stimulation, rupture of unprotected perforating arteries, intracerebral hemorrhage and cerebral infarction due to DIC. It has been proposed that the coagulopathy also contributes to acute lung injury and increased alveolocapillary membrane permeability.

Local inflammation is unusual in Indian red scorpion envenomation. The Iranian yellow scorpion (*Buthus compsobuthus* and *Hemiscorpius lepturus*) invokes varied skin reactions, namely, edema, erythema, severe necrosis and lymphangitis. This phenomenon could be attributed to the polypeptide variations of different venom. Victims of yellow scorpion sting may show signs of severe hemolysis and secondary renal failure. Venom of scorpion species *Tityus trinitatis* in Trinidad causes acute pancreatitis through the intrapancreatic conversion of trypsinogen to trypsin.

Envenomation caused by scorpion species *Tityus serrulatus* triggers a systemic inflammatory response like syndrome with an increase in levels of interleukin-6, IL-1a and interferon-gamma. In scorpion-envenomed children, there is a correlation between cytokines levels and clinical severity.

## CLINICAL MANIFESTATIONS

The varied clinical effects of envenomation depend upon scorpion species, amount of injected venom and lethal dose of the venom. Species-specific variations in clinical manifestations of scorpion envenomation in different parts of the world are given in **Table 1**. In the case of multiple stings by the same scorpion, severity is greater in the first victim as compared to the following victims. The scorpions' size and age, season of the sting and the time between sting and hospitalization contribute to the severity of envenoming.

The clinical features following envenomation by the Indian red scorpion are predominantly due to autonomic excitation that adversely affects the cardiovascular system. The picture may range from mild sympathetic stimulation of the heart to life-threatening complications such as myocarditis and pulmonary edema. Children due to their low bodyweight show a high severity of symptoms and develop more rapid progression. Envenomation can be graded into four categories based on the clinical manifestations during hospitalization and severity (**Table 2**).

### Local Manifestations

Following a sting, the patient experiences an unbearable radiating pain from sting site usually the toes and fingers. In children, there is the sudden onset of inconsolable, incessant crying. There is mild sweating, rise in blood pressure and transient bradycardia due to pain (**Table 3**).

### Systemic Manifestations

Systemic features following scorpion sting are due to autonomic storm—a massive release of catecholamines from the adrenergic and cholinergic neurons and the adrenal medulla into the circulation. There is an initial transient cholinergic phase that merges imperceptibly into a more sustained adrenergic phase (**Tables 4 and 5; Flow chart 1**).

Myocardial injury may be heralded by onset of excessive vomiting and palmoplantar sweating. Clinical indicators of myocardial involvement include marked tachycardia, S3 gallop rhythm, other rhythm disturbances, cold extremities and a fall in blood pressure. Early stages may be missed clinically, but for the electrocardiogram (ECG) variations like tall T waves and

**Table 1** Species-specific variations in clinical manifestations of scorpion envenomation in different parts of the world

Region	Important species	Dominant clinical picture
India	<i>Hottentotta tamulus</i> <i>Palamneus swammerdami</i>	Cardiovascular
Israel	<i>Buthus occitanus</i>	Cardiovascular
Brazil	<i>Tityus serrulatus</i> <i>Tityus bahiensis</i>	Cardiovascular
Mexico	<i>Centruroides</i>	Cardiovascular
Saudi Arabia	<i>Centruroides limpidus</i> <i>Centruroides noxius</i> <i>Centruroides suffusus</i>	Cardiovascular
Iran	<i>Hemiscorpius lepturus</i> <i>Mesobuthus eupeus</i> <i>Odontobuthus doriae</i>	Tissue necrosis Hemolysis Renal failure
South Africa	<i>Androctonus crassicauda</i>	Neurological
USA	<i>Centruroides exilicauda</i>	Neurological
Trinidad	<i>Tityus trinitatis</i>	Acute pancreatitis

**Table 2** Grading of scorpion sting envenomation at the time of arrival to the hospital

Grade	Clinical description
Grade 1	Local manifestation: Severe, <i>excruciating local pain</i> at the sting site radiating along the corresponding dermatomes, mild local edema with sweating at the sting site, <i>without systemic involvement</i>
Grade 2	Autonomic storm: Signs and symptoms of <i>autonomic storm</i> characterized by acetylcholine excess or parasympathetic stimulation (vomiting, profuse sweating from all over body, <i>ropy salivation</i> , bradycardia, premature ventricular contraction, hypotension, <i>priapism in boys</i> ) and sympathetic stimulation (hypertension with blood pressure more than the normal limits for the age, tachycardia with heart rate more than the normal limits for the age, cold extremities, transient systolic murmur)
Grade 3	Cold extremities, tachycardia, hypotension or hypertension with <i>pulmonary edema</i> (respiratory rate more than the normal upper limit for the age, basal crepitations or crackles in lungs)
Grade 4	Tachycardia, hypotension with or without pulmonary edema with warm extremities ( <i>warm shock</i> )

ST segment elevation. Mild envenoming cases show symptoms of severe vasoconstriction and hypertension. Predominant left ventricular dysfunction along with normal systemic vascular resistance can cause severe hypotension or pulmonary edema. Irreversible vasodilatation and myocardial dysfunction cause warm shock with or without pulmonary edema. Reduced left ventricular compliance, and an increase in impedance to left ventricular emptying cause the myocardial dysfunction, and pulmonary edema.

### Pulmonary Edema

Within 30 minutes of the sting, pulmonary edema develops with severe hypertension; development after 36 hours of sting can be seen with hypotension and tachycardia. It is clinically characterized by acute onset of cold extremities, sudden onset of intractable cough, dyspnea, tachycardia, systolic murmur, gallop, bilateral crepitations and low volume, fast thready pulse. In a few cases, it develops later, after an initial phase of apparent recovery. In the initial stages, pulmonary edema may be subclinical and detectable only with a chest X-ray. A sudden onset of massive

**Table 3** Local manifestation of scorpion sting

1. Mechanism	Serotonin, bradykinin and substance-P present in the scorpion venom have been implicated as causative agents of the pain
2. TAP sign	Sudden tap at and around the site of sting induces severe pain and withdrawal. It is a diagnostic sign of scorpion sting and is not usually reported by most the patients
3. Clinical importance	<ul style="list-style-type: none"> <li>Severe pain at the sting site without evidence of systemic involvement indicative of <i>benign or dry sting</i></li> <li>Whenever local pain was severe, there was often no further progression of symptoms</li> <li>There is little or no reaction at sting site. Presence of edema and signs of inflammation at the sting site blunt the sodium channel blocker action of Lidocaine administration</li> <li>Because of vasoconstriction due to release of catecholamine, pain conduction may be blunted, and it is tolerable or mild in nature. It will mask the clinical severity and presentation</li> </ul>
4. Prognostic importance	Reappearance of severe pain along with clinical improvement of peripheral circulation indicative of recovery of sting envenomation

**Table 4** Systemic manifestations of scorpion sting—due to cholinergic stimulation

Symptoms and signs	Clinical manifestation and implication
Vomiting	<ul style="list-style-type: none"> <li>Mechanism: Vomiting is due to serotonin content of venom</li> <li>Transient projectile usually vomiting due to autonomic storm</li> <li>Often seen in envenomation of <i>Mesobuthus tamulus</i> (India), <i>Androctonus crassicauda</i> and <i>Leiurus quinquestriatus</i> (Saudi Arabia, Israel), <i>Tityus serrulatus</i> (Brazil), <i>Centruroides</i> (Mexico)</li> </ul>
Cholinergic stimulation	<ul style="list-style-type: none"> <li>Manifests as increased sweating, excessive salivation, increased bronchial secretions, priapism and bradycardia</li> <li>Appear within 1–2 hours and can last for up to 6–13 hours</li> </ul>
Profuse sweating	<ul style="list-style-type: none"> <li>Sweat literally flows all over the body; it is often called as skin diarrhea</li> <li>It can persist for 3–17 hours</li> </ul>
Salivation	<ul style="list-style-type: none"> <li>Stimulation of the bronchial mucosa will result in thick ropy salivation</li> <li>It is often difficult to expectorate in children</li> <li>Can occur soon after sting and it can persist for 2–4 hours</li> <li>Excessive salivation and bronchial secretion are major contributing factors for respiratory failure</li> </ul>
Priapism	<ul style="list-style-type: none"> <li>Priapism seen in almost all male children of all age group and 20% of adult's patients envenomed by scorpions of Buthidae family except Hemiscorpion</li> <li>Priapism is the diagnostic of venomous scorpion sting</li> <li>Its absence or disappearance did not correlate the outcome</li> <li>It can persist for 5–16 hours</li> </ul>

Vomiting, profuse sweating, salivation, priapism are diagnostic of cardiac premonitory signs of scorpion sting envenomation and suggestive of circulating unbound venom in the body, can be accessible to scorpion antivenom therapy

pulmonary edema with central cyanosis, intractable cough with continuous expectoration of blood-stained froth from mouth and nostril may occur.

## Other Reported Complications

### Neurological Complications

The venom of the bark scorpion (*Centruroides exilicauda*), found in parts of the US is highly neurotoxic. *Mesobuthus tamulus* may cause focal neurological presentation including hemiparesis, hemorrhagic or thrombotic stroke. Hypoxia caused by pulmonary edema and cardiovascular failure also contributes to neurologic complications. There is a poor outcome in patients presenting with coma, convulsions, hyperthermia or brain edema.

### Acute Pancreatitis

In India, acute pancreatitis due to scorpion sting envenomation in children is a rare clinical presentation. There is 80% incidence of acute pancreatitis due to envenoming by *Tityus serrulatus* in Trinidad. In Israel, envenomation by *Leiurus quinquestriatus* in children instigates agitation, abdominal pain, discomfort and vomiting, with raised plasma immunoreactive cationic trypsin.

### Cause of Mortality

Due to lethal ventricular arrhythmias, death may occur within 30 minutes of sting. Delayed hospitalization due to poor transport, seeking traditional remedies, and lack of experience in the treatment of scorpion bites contribute to the high fatality due to scorpion sting. Excessive fluid administration may cause or worsen myocardial dysfunction. The oxygen demand of the myocardium and the necrotizing effects of circulating catecholamines are relatively increased by steroids. The oxygen requirement and increased myocardial contraction is further enhanced by digitalis.

## INVESTIGATIONS

Cardiac markers are most useful in the detection of minor myocardial injury when individuals have nondiagnostic ECG tracings. Cardiac markers used in clinical practice are cardiac enzymes—creatinine kinase, cardiac troponin I, cardiac troponin T and myoglobin. Echocardiography, ECG and chest X-ray are useful tools for the assessment of severity of myocardial involvement (Table 6).

## MANAGEMENT

The case fatality due to scorpion sting was up to 29% during the latter half of the previous century despite various treatments comprising of lytic cocktail, propranolol, decongestive agents, and insulin-glucose drip. In recent years, there is negligible fatality due to severe scorpion envenomation because of the advent of scorpion antivenom (SAV), intensive care facilities and vasodilators.

### Pain Relief and Fluid Management

In the case of severe pain, nonsteroidal anti-inflammatory drug is used to provide long-time relief. Other measures used to relieve pain are ice packs and xylocaine (local anesthetic). To settle a restless child after a sting, midazolam or diazepam is used.

Profuse sweating and vomiting cause loss of fluid, this is very often overlooked and can cause complications in the clinical course. Efforts should be taken to correct the fluid deficit and maintain the fluid balance. Hence, oral fluids should be given whenever possible. Children showing symptoms of altered sensorium and tachypnea require parenteral fluids. Care by pediatric intensive care unit and central venous pressure monitoring become vital as fluid requirement needs to be balanced with care in children with pulmonary edema.



**Table 5** Systemic manifestations of scorpion sting—due to adrenergic stimulation

Symptoms and signs	Clinical manifestation and implication
Adrenergic stimulation	Leads to tachycardia, hypertension and peripheral circulatory failure and further to myocardial injury and pulmonary edema
Cold extremities	<ul style="list-style-type: none"> <li>Cold extremities are usually due to severe vasoconstriction in response to the circulating catecholamine and can persist for 12–26 hours</li> <li>Skin over palm and dorsum look like a <i>washer man's hand</i></li> <li>Often associated with severe cardiovascular manifestations</li> <li>Recovery is associated by improvement in skin temperature, which serves as an <i>ideal clinical monitor</i> for the lay person at a primary care setting</li> </ul>
Mydriasis	<ul style="list-style-type: none"> <li>Dilated nonreacting or poorly reacting pupils often seen in the early phase of autonomic storm associated with hypertension</li> <li>Effects are due to stimulation of <math>\alpha</math>-receptor of dilator pupillary muscles by excessive circulating catecholamine</li> </ul>
Tachycardia	<ul style="list-style-type: none"> <li>Usually appears within 4 hours of the sting and can persist for up to 24–72 hours</li> <li>It is due to direct <math>\beta</math>-adrenergic stimulation of the heart</li> <li>In most cases, the tachycardia may resolve without any further progression to complications, but when it increased in severity and associated S3 gallop, and ice-cold extremities appear; it is an indicator of myocardial injury</li> <li>Impaired left ventricular filling, reduction in cardiac output due to marked tachycardia particularly in children results in delirium and convulsion due to anoxia to the brain</li> </ul>
Hypertension	<ul style="list-style-type: none"> <li>Due to <math>\alpha</math>-receptor stimulation induced vasoconstriction and <math>\beta</math>-receptor-mediated increase in cardiac contractility</li> <li>Appears within 2 hours of sting and can last for 4–8 hours</li> <li>Hypertensive stress on the myocardium, direct myocyte toxicity and catecholamine-induced injury contribute to rhythm disturbances and left ventricular failure</li> </ul>
Hypotension	<ul style="list-style-type: none"> <li><i>Transient hypotension</i>: As a result of vomiting, profuse sweating, salivation and cardiac arrhythmias</li> <li><i>Delayed hypotension</i>: As a result of the reduction in systemic vascular resistance, hypokinetic phase, hypotensive shock indicative of a reduced left ventricular contractility</li> <li><i>After 24–48 hours of admission</i>: Asymptomatic compensated shock with bradycardia but good volume pulse with warm extremities associated with prolonged corrected QT interval is usually due to depletion of catecholamines from nerve terminals</li> <li>Venom inhibits kinase II enzyme and resulting in elevation of bradykinin, a neuromuscular agent involved in the development of pulmonary edema and hypotension</li> </ul>

**Table 6** Echocardiography, electrocardiogram and chest X-ray findings in scorpion sting envenomation

Modality	Finding and clinical significance
Echocardiographic study	<ul style="list-style-type: none"> <li>Abnormal echocardiography will appear within 12–15 hours of sting</li> <li>Findings of poor global hypokinesia with reduced ejection fraction, decreased left ventricular performance and index, trivial mitral regurgitation, abnormal diastolic filling pressure</li> <li>Systolic and diastolic frames usually show no change in diameter and flattening of the interventricular septum with no systolic thickening</li> <li>There is a good correlation between clinical improvement and return of the left ventricular function toward normal in the Indian red scorpion sting envenomation</li> <li>Serial echocardiography study is useful to follow changes in myocardial function and possibility of development of cardiomyopathy</li> <li>Return to normal within 5 days to 4 weeks</li> </ul>
Electrocardiogram	<ul style="list-style-type: none"> <li>All patients with systemic involvement usually show abnormal ECG</li> <li>Abnormal ECG suggestive of myocardial injury without clinical feature of myocardial dysfunction not uncommon</li> <li>The most frequent ECG abnormalities are RST segment and T waves</li> <li><i>In acute myocardial injury</i>: Arrowhead tented T wave look like <i>Ashoka tree</i> appearance</li> <li><i>Recovery of myocardial injury</i>: Tent-shaped look like <i>Christmas's tree</i> appearance</li> <li>Usually described patterns of ECG abnormalities are early myocardial infarction like pattern, atrial arrhythmias, non-sustained ventricular tachycardia and varies conduction defect</li> <li>Indicator of serious myocardial injury: PQRS or T wave alternans</li> <li><i>Time to normalization</i>: Prolonged corrected QT and conduction defect normalized within one week, T wave inversion can persist for up to few weeks</li> <li><i>Poor prognosis indicators</i>: Low voltage ECG complex, wide QRS complex, tachycardia, hemiblock and marked ST segment depression</li> </ul>
Chest X-ray	<p>Features suggestive of cardiogenic pulmonary edema are:</p> <ul style="list-style-type: none"> <li>Unilateral distribution or bat wing appearance of lung edema usually due to left ventricular dysfunction and localized elevation of pulmonary vascular permeability</li> <li>The patchy and peripheral distribution of lung edema with air bronchograms are usually due to increased vascular permeability</li> </ul>

## Vasodilators

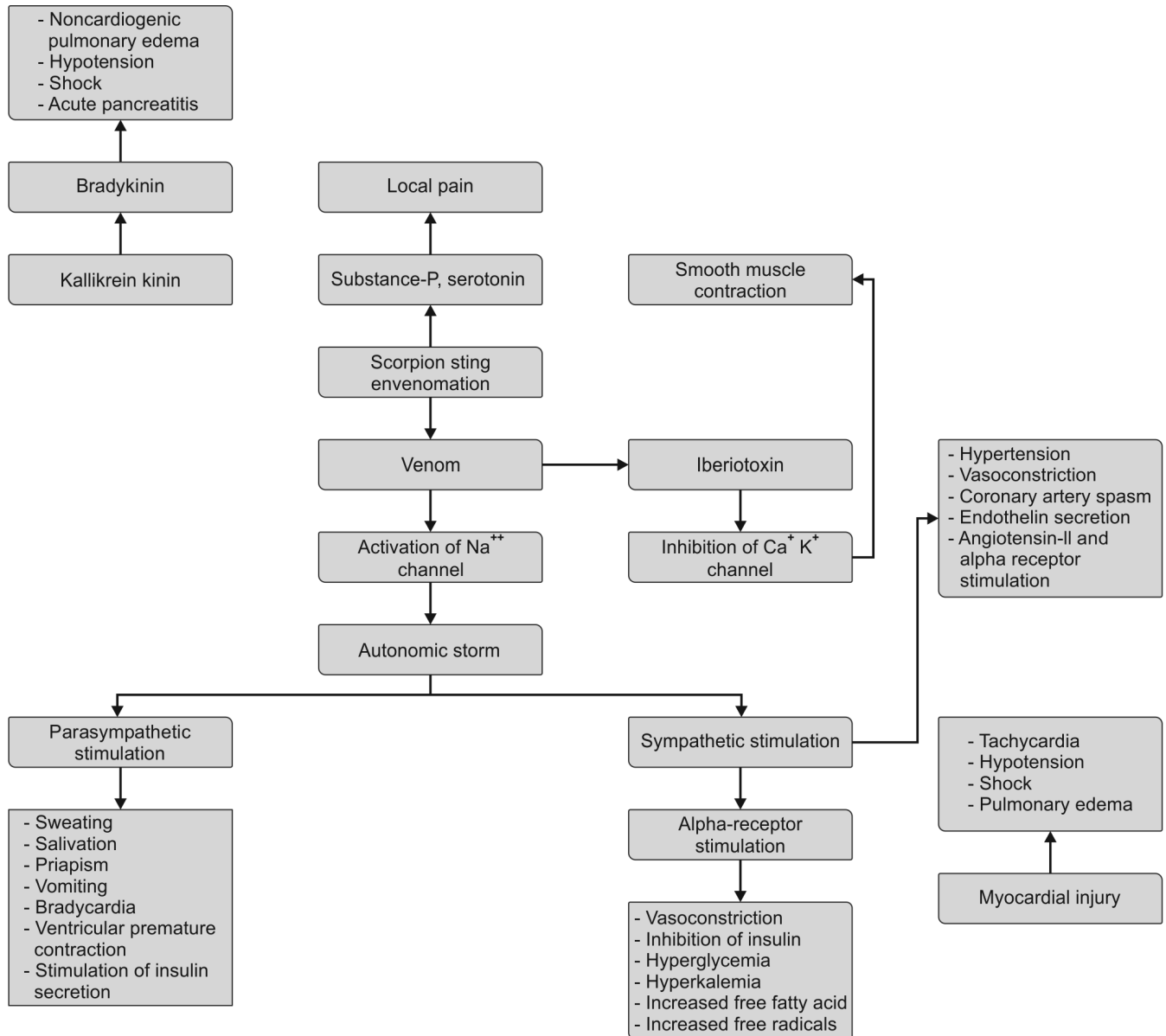
Five drugs—prazosin, chlorpromazine, dobutamine, nitroglycerine and sodium nitroprusside have been used individually or in combination in the pharmacologic support of patients with scorpion envenomation and cardiovascular manifestations.

## Prazosin

Since  $\alpha$ -receptor stimulation plays a chief role in the clinical manifestations in scorpion sting envenomation, prazosin that is a competitive postsynaptic  $\alpha_1$ -adrenoceptor is the first line of management. Prazosin subdues sympathetic effects and activates



Flow chart 2 Mechanism of scorpion sting envenomation



venom-inhibited potassium channels. It decreases the preload, afterload and blood pressure without mounting the heart rate. Vasoconstriction induced by endothelins is countered by prazosin through accumulation of cyclic guanosine monophosphate (cGMP). Prazosin is useful in the reversal of hormonal and metabolic effects of  $\alpha$ -receptors stimulation. Thus, prazosin is both a *pharmacologic and cellular antidote* to the actions of scorpion venom, with the added advantage of being cardioprotective.

It is available as an oral preparation in the form of 1 mg tablets. Owing to its photosensitivity it has to be stored in airtight containers away from light. Sustained-release tablets are not suitable in this condition. As an immediate measure, *the suggested dose of 30  $\mu\text{g/kg/dose}$*  is given to all patients showing evidence of autonomic storm. It is not to be given as prophylaxis in children when the only symptom is pain. In the case of vomiting, it can

be administered through nasogastric tube. After giving prazosin, mother should be advised not to lift the child to prevent the effects of *first dose phenomenon* due to prazosin. Oral hydration and milk feed must be encouraged. If needed, intravenous maintenance fluids should be given to correct dehydration due to excessive sweating and vomiting.

Prazosin can be given irrespective of blood pressure values provided there is no hypovolemia. However, with availability of SAV and comparative studies of dobutamine, prazosin should be avoided in those patients with borderline or hypotensive blood pressure. Close monitoring of vitals including blood pressure; pulse rate and respiration must be monitored at least every 30 minutes for 3 hours, every hour for next 6 hours and thereafter every 4 hours till improvement. Repeat dose prazosin should be considered at same dose after the 3 hours of the first dose based on clinical response

and can be given till improvement of symptoms like extremities are warm, dry and peripheral veins are easily visible. In general, no more than four doses have been required in the majority of children with scorpion sting envenomation. A major adverse effect in the use of prazosin is the occurrence of the *first dose* phenomenon, while the mechanism of action is not clear, it is seen to occur more commonly in patients who are salt and volume depleted.

### Management of Pulmonary Edema

Pulmonary edema in these children is mainly due to myocardial dysfunction. Though serious in itself, it does not necessarily mean a poor prognosis. Despite diagnostic and therapeutic advances, the management of myocardial dysfunction in the scorpion sting envenomation in children remains supportive. In children with pulmonary edema with or without hypertension, management should be directed toward relieving afterload without compromising preload. The use of diuretics to minimize or reduce fluid overload seems a reasonable measure but only when renal water excretion is impaired. Otherwise, the best way to prevent fluid overload is to maintain an adequate cardiac output. Thus dobutamine support (5–15 µg/kg/min) with vasodilatation through sodium nitroprusside (0.3–5 µg/kg/min) or nitroglycerine (0.1–1 µg/kg/min) infusion is preferred in this situation. Prazosin is to be given 1 hour before termination of sodium nitroprusside drip. If sodium nitroprusside is not available, one can use isosorbide dinitrate, 10 mg every 10 minutes sublingually as an emergency measure. Morphine, a standard therapy in pulmonary edema, should be avoided in scorpion sting, since narcotics worsen dysrhythmias in these children.

Occasionally, children with scorpion sting present with multi-organ failure. A systemic inflammatory response is presumably the cause; however, our knowledge on the pathogenesis of such a state is still incomplete. Presence of respiratory failure with or without CNS disturbances in the presence of hypertension or complicating those children with pulmonary edema should be aggressively treated with early ventilation, afterload reduction, careful sedation and acid-base correction.

### Scorpion Antivenom

Scorpion antivenom should be administered as soon as possible and through intravenous route over 30 min after reconstitution of three vials in 100 mL normal saline. In general, *Hottentotta tamulus* (*Mesobuthus tumulus*) sting envenomation causes transient parasympathetic and prolonged sympathetic stimulation. Presence of signs and symptoms of parasympathetic stimulation suggests that unbound scorpion venom is circulating in the circulation and available for neutralization by SAV. Hence, SAV can subsequently prevent the sympathetic overstimulation and its consequences like autonomic storm. Study from Mexico found that since the advent of extensive use of SAV associated with a dramatic reduction of fatality during the last decade.

Debate of efficacy of SAV as a specific antidote for scorpion sting envenomation has been resolved by recent randomized controlled trials involving the children and adults with scorpion sting proved that beneficial effects of early administration of SAV. Intravenous administration of SAV resolved the neurological manifestations within 4 hours along with a reduction of concomitant requirement of sedation with midazolam and decreased the unbound venom in the circulation. Nowadays, SAV is becoming available almost in all tropical and subtropical countries where scorpion sting envenomation is the one of the major issues. Study from Razi Institute, Iran found that a polyvalent SAV inhibits the gelatinase enzyme activity of *Hemiscorpius lepturus* species sting envenomation and is associated with a

better prognosis. In India, since 2002, SAV have been available for clinical management of scorpion sting envenomation from Haffkine Biopharma, Mumbai. The current recommended dose of SAV is single 30 mL (3 vials) dose of Haffkine Biopharma monovalent SAV diluted in 100 mL of normal saline infused intravenously over 30 min irrespective of age and weight of the patients.

### Unhelpful Treatments

Standard therapy was not clearly defined in earlier days; many therapies were in vogue without experimental justification; these should be avoided.

- **Lytic cocktail** (*Pethidine* + *Promethazine* + *Chlorpromazine*) The  $\alpha$ -blocking effect of chlorpromazine might be beneficial, but pethidine may convert sublethal dose of scorpion venom into a lethal one, and they also interfere with protective respiratory reflexes.
- **Morphine** Worsens dysrhythmias in children with scorpion sting envenomation.
- **Steroids** Moreover, steroids might enhance the necrotizing effects of excessive catecholamines on myocardium. It should not be used in the scorpion sting management.
- **Atropine** Complete abolition of parasympathetic effects may permit the domination of the overstimulated sympathetic system. Atropine potentiates tachycardia and sustains hypertension.
- **Nifedipine** Reflex tachycardia and negative inotropic effects argue against its use; despite its antihypertensive and vasodilator effect, 35% of scorpion victims developed myocardial failure and 14% acute pulmonary edema.
- **Angiotensin-converting-enzyme inhibitors** Captopril aggravates hyperkalemia and inhibits the breakdown of bradykinin, which is implicated in experimental pulmonary edema due to scorpion sting.

### PREVENTIVE MEASURES

The following preventive measures can be considered: Clear debris and trash from the areas one inhabits. Inspect boots, clothing and bedding for scorpion. Never explore into places one cannot see. Spraying 10% DDT + 0.2% pyrethrin + 2% chlorine in oil base or fuel oil + kerosene + creosote as spray in roof complexes and building foundations.

#### IN A NUTSHELL

1. Scorpion venom is a potent sympathetic stimulator.
2. Cardiac manifestations are common in Indian red scorpion envenomation.
3. Alpha-receptors stimulation plays a significant role in the evolution of myocardial dysfunction and acute pulmonary edema in victims of scorpion sting.
4. Prazosin— $\alpha$ -adrenoceptor antagonist—is cellular and pharmacological antidote to scorpion sting envenomation.
5. Time lapse between the sting and administration of prazosin and/or SAV for autonomic storm determines the outcome.
6. Scorpion antivenom is gaining widespread recognition in the management of scorpion sting envenomation.

### MORE ON THIS TOPIC

Bawaskar HS, Bawaskar PH. Efficacy and safety of scorpion antivenom plus prazosin compared with prazosin alone for venomous scorpion (*Mesobuthus tamulus*) sting: randomized open label clinical trial. *BMJ*. 2011;342:c7136.

- Bawaskar HS, Bawaskar PH. Indian red scorpion envenoming. *Indian J Pediatr.* 1998;65:383-91.
- Bawaskar HS, Bawaskar PH. Scorpion sting: update. *J Assoc Physicians India.* 2012;60:46-55.
- Bawaskar HS. Can scorpions be useful? *Lancet.* 2007;370:1664.
- Bawaskar HS. Diagnostic cardiac premonitory signs and symptoms of red scorpion sting. *Lancet.* 1982;1:552-4.
- Boyer LV, Theodorou AA, Berg RA, Mallie J, et al. Antivenom for critically ill children with neurotoxicity from scorpion stings. *N Engl J Med.* 2009;360:2090-8.
- Chippaux JP, Goyffon M. Epidemiology of scorpionism: a global appraisal. *Acta Trop.* 2008;107:71-9.
- Isbister GK, Bawaskar HS. Scorpion envenomation. *N Engl J Med.* 2014;371:457-63.
- Mahadevan S. Scorpion sting. *Indian Pediatr.* 2000;37:504-14.
- Pandi K, Krishnamurthy S, Srinivasaraghavan R, Mahadevan S. Efficacy of scorpion antivenom plus prazosin versus prazosin alone for *Mesobuthus tamulus* scorpion sting envenomation in children: a randomized controlled trial. *Arch Dis Child.* 2014;99:575-80.

# Section 10 CHILDHOOD INJURIES

**Section Editor** Rakesh Lodha

## Chapter 10.1

### Trauma: Stabilization, Triage and Transport

*Shruti Kant, Manu Madhok*

Injuries are an important cause of death and morbidity in the pediatric population. Physicians caring for children must be prepared to provide initial triage and treatment for injured children. Trauma in the pediatric population is a unique problem as children have several distinguishing anatomic, physiologic and developmental characteristics. These differences and their environment make them susceptible to injury patterns that differ from adults and can provide a diagnostic challenge. One must take these differences into consideration in the medical approach to an injured child. Having an understanding of the epidemiology, etiology, anatomic and physiologic considerations of pediatric trauma can help the physician develop a systematic approach in identifying and treating injuries in children. This chapter aims at preparing physicians for initial assessment, stabilization and transport of the injured child.

#### EPIDEMIOLOGY

Childhood injury accounts for a significant burden of disease worldwide. The World Health Organization (WHO) along with The United Nations Children's Fund estimates that across the world, over 900,000 children less than 18 years of age die annually as a result of injuries. Even in developing countries, where infectious diseases predominate, injuries are a leading cause of mortality and morbidity. While the burden of childhood injuries is not clearly known in India and other developing countries, several authors and agencies have sought to add to the epidemiological data and trends. According to the National Crime Records Bureau report of 2012, there were 22,514 accidental deaths among children less than 14 years in India.

While injuries are not gender specific, in general males tend to outnumber females with a ratio of 2:1. This is true worldwide and may be due to increased freedom afforded to males in developing countries as well as an increased tendency for risk-taking behavior among boys.

According to most authors 50-60% of injuries occur in the home setting with falls as the number one cause. Other common locations are in the street or playground. While falls are the most common cause of injury, road traffic accidents (RTAs) are the most common cause of death due to injury in children. Children most often present with blunt force trauma, although on occasion they may have penetrating trauma such as gunshot wounds or stab wounds. Head injuries and orthopedic injuries are the most common types of injuries sustained by children requiring admission to the hospital (**Box 1**).

#### ETIOLOGY

The etiology of pediatric trauma is outlined in **Box 2**. Risk factors for injury are listed in **Table 1**.

#### MODES OF INJURY

Falls are the most common cause of injuries in children. In the home setting, they can fall from stairs, ladders, furniture such as beds and sofas, parapets and rooftops. One study out of Rajasthan found that children frequently fell from the first story due to the low height of the parapets. Unlike RTAs, children with falls are less likely to have severe injuries requiring hospital admission. Most are treated in the outpatient department and discharged home.

Road traffic accidents are a leading cause of injuries and death in children. Unlike adults, the pediatric population is more likely to suffer pedestrian versus motor vehicle collisions. Victims of RTAs are more likely to suffer severe injuries, require emergency surgery, have prolonged hospital stays and have long-term disability.

Burns in children are most often scalds due to hot liquids. Other causes of burns include flame and electricity. Both genders are equally affected with a male:female ratio of approximately 1:1. A significant number of children with burns require hospitalization for treatment of their wounds.

#### BOX 1 Pediatric trauma epidemiology facts

- Annually more than 900,000 deaths occur in children under 18 years across the globe due to injuries
- Road traffic accidents are the leading cause of death due to injury
- Drowning is the third leading cause of death due to injury
- Falls are the most common cause of injury
- 50–60% injuries occur in the home setting.

#### BOX 2 Common modes of injury

- Falls
- Road traffic accidents
- Burns (flame, hot water, hot oil, etc.)
- Accidental poisoning
- Drowning.

**Table 1** Risk factors for injury

Patient factors	Parent factors	Environmental factors
Level of development	Lack of supervision	Overcrowding
Underlying medical problem	Lack of education/awareness	Poor road conditions
Lack of situational awareness	Not enforcing safety devices	Poor engineering
Not using protective equipment	Improper storage of chemicals	Low socioeconomic status
Use of intoxicating substance	Distracted driving	Natural disasters
Risk taking behavior		



Accidental poisoning by ingestion of medications or cleaning agents is another frequent cause of childhood injury. The age group most commonly affected is 1–4 years old with a male preponderance.

Drowning is the third leading cause of unintentional injury death in the world. According to the WHO low- and middle-income countries, such as India, account for 95% of drowning deaths. Children less than 5 years of age have the highest mortality rate due to drowning. Males are at a higher risk of drowning than females.

### Patient Risk Factors

Host characteristics associated with increased risk of injury include the developmental stage of the child, risky behavior, underlying medical problems, lack of awareness of surroundings and use of intoxicating substances.

### Parent Risk Factors

Parent characteristics associated with an increased risk of injury for children include lack of supervision, not enforcing use of protective equipment, such as helmets and seatbelts, lack of education/awareness of safety hazards and improper storage of household medications/cleaning agents.

### Environmental Risk Factors

These include factors such as low socioeconomic status, overcrowding, use of intoxicating substances and natural disasters such as flooding or earthquakes.

## PATHOGENESIS/PATHOPHYSIOLOGY

Several physiologic and anatomic characteristics are unique to children and should be taken into consideration when evaluating and managing a child with injuries (**Table 2**).

### Size and Shape

Children have a much smaller size and body mass. This results in transmission of a much greater amount of energy per unit body mass. Children have much less fat and subcutaneous tissue, which bring the internal organs in closer proximity to the surface. Therefore, the greater energy transmitted through the body can cause a higher incidence of multiple organ injury. Children have proportionately larger heads, which put them at higher risk for blunt head trauma. With the smaller body mass and larger head, children have a larger body surface area to volume ratio. The greater body surface area allows for added temperature loss putting this age group at increased risk for hypothermia.

**Table 2** Anatomic and pathologic considerations

<i>Size and shape</i>
<ul style="list-style-type: none"> <li>• Small size (more force transmitted)</li> <li>• Large head (increased trauma risk)</li> <li>• Less fat and subcutaneous tissue (organs closer to surface)</li> <li>• Larger body surface area (hypothermia risk)</li> </ul>
<i>Skeletal immaturity</i>
<i>Airway</i>
<ul style="list-style-type: none"> <li>• Tongue large compared to mouth</li> <li>• Larynx more anterior</li> <li>• Large occiput (passive neck flexion)</li> <li>• Short trachea</li> </ul>
<i>Circulation: Significant physiologic reserve</i>

### Skeletal Immaturity

Incomplete calcification and open growth plates make the skeleton in this age group pliable. The skeleton is able to transmit a greater amount of force internally to the organs without sustaining any bony injury or fracture. Thus, it is not uncommon to see injuries such as pulmonary contusion or cerebral contusion without rib fractures or skull fracture. The corollary to this is that fractures of certain bones, such as ribs or skull, implies transfer of a massive amount of energy and as such should alert the physician to the possibility of significant internal injuries such as traumatic brain injury, pulmonary contusion, pneumothorax, mediastinal injury, etc.

### Airway

There are several anatomic considerations which affect the management of the pediatric airway:

1. The tongue and tonsils in a child are relatively large compared to the size of the oral cavity, making visualization of the larynx and vocal cords more difficult.
2. The larynx is more anterior and cephalad, also making visualization more difficult.
3. The epiglottis can be floppy again making visualization of the cords difficult.
4. The child's large occiput causes passive flexion of the airway; particularly the posterior pharyngeal tissue has a tendency to buckle resulting in airway obstruction. This obstruction can be avoided by placing a 2 cm thick layer of padding beneath the shoulders and torso. This helps to maintain a neutral head position and opens up the airway.
5. The infant trachea is much shorter which makes it easy to intubate the right mainstem bronchus or to cause dislodgement of the endotracheal tube. In either case, this can lead to inadequate oxygenation and ventilation. Right mainstem intubation can also result in barotrauma from hyperinflation of the right lung.

### Circulation

Children generally have great physiologic reserve and can maintain a state of compensated shock with a normal blood pressure even in the face of significant hypovolemia from blood loss. It may take up to a 30% loss of blood volume before a child will manifest a drop in blood pressure. It is important for the physician to recognize the subtle signs of shock in an injured child of which tachycardia and delayed capillary refill time are the earliest signs.

## CLINICAL FEATURES

Pediatric trauma victims can have a range of clinical presentations. They may have minor injuries such as simple contusions or lacerations or present with multiple trauma. It is up to the physician to systematically determine the extent of the child's injuries. Certain clinical features can aid the medical provider in making these determinations.

### Airway

Stridor may represent partial airway obstruction due to an object or swelling from trauma. Paradoxical chest/abdominal movement may signal complete airway obstruction.

### Breathing

Tachypnea is a frequent finding in children with injuries. Tachypnea alone may be due to anxiety, blunt trauma to the chest, drowning and ingestion of a toxic substance. Decreased breath sounds can suggest pulmonary contusion, pneumothorax or hemothorax. Paradoxical chest movement can indicate flail chest.

Bradypnea can indicate significant head injury and may signal a need to secure the airway by intubating.

Pulse oximetry can also aid in assessing for respiratory compromise.

### Circulation

Children usually have a large physiologic reserve. Tachycardia is one of the earliest clinical signs of hypovolemic shock. Other subtle signs include pale or mottled skin, cool or clammy extremity skin compared with central skin, weak/thready peripheral pulses. Drop in blood pressure and altered level of consciousness are late signs of hypovolemic shock. Average systolic blood pressure in children is (90 mm Hg plus  $2 \times$  age in years). The lower limit of systolic blood pressure is (70 mm Hg plus  $2 \times$  age in years). Physicians should pay close attention to the subtle changes in circulation and institute early resuscitation.

### Abdomen

Abdominal injury can present with bruising, abdominal tenderness, guarding, rigidity, abdominal distension or blood in the rectum. Seatbelt sign across the lower abdomen can be a harbinger of hollow viscus injury and/or a Chance fracture of the lumbar vertebrae. Flank tenderness can be suggestive of renal or adrenal injury. Hematuria and blood at the urethral meatus is indicative of genitourinary injuries. Pelvic instability suggests transmission of significant forces and should alert the physician to the possibility of genitourinary injuries and other intra-abdominal injuries.

### Neurologic

Altered level of consciousness can be indicative of direct head injury, poor cerebral perfusion due to uncompensated hypovolemic shock, decreased oxygenation of the brain or hypoglycemia. Patients may present with paresis, paralysis or decreased sensation suggesting spinal cord injury.

### Head, Eyes, Ear, Nose and Throat

An irregular pupil or conjunctival hemorrhage suggests eye trauma. Leakage of cerebrospinal fluid or blood from the nares or ear canals can be suggestive of basilar skull fracture. Additional findings of skull fracture can include Battle's sign (ecchymosis behind the ears), raccoon eyes (ecchymosis around the eyes). There may be maxillofacial instability indicating fracture of the facial bones.

### Musculoskeletal

Fractures are suggested by swelling, tenderness, crepitus and/or deformity. Similarly, sprains and strains can be suggested by joint instability. A tight swollen extremity with decreased sensation, severe pain, decreased or absent pulses suggests compartment syndrome.

### DIFFERENTIAL DIAGNOSIS

When assessing an injured child, it is important that the physician avoids premature closure and thus misses possible underlying problems whether they are occult injuries or other medical problems. The differential can therefore be broad. For example, a patient presenting with altered level of consciousness with a history of a fall may have sustained intracranial injury. But it is important to consider other possible causes of altered mental status—Did the child ingest a toxin? Did the child have a seizure? Was a syncopal event due to cardiac arrhythmia or hypoglycemia the cause of the fall? Did the child sustain any injuries other than the obvious head injury?

One can help ascertain the extent of a patient's injuries and possible medical problems by eliciting a thorough history, performing a thorough exam and using diagnostic studies and imaging as indicated and after initial stabilization of the patient.

### TRIAGE

Trauma patients can have injuries that vary from a simple splinter to the victim of a RTA with multiple trauma causing significant hemodynamic or respiratory symptoms. It is the responsibility of the physician to determine the extent of the child's injuries. This can be a rather difficult process but can be achieved through triage.

Triage is a very difficult process. Triage involves the initial sorting by which a physician can quickly assess the extent and severity of a patient's injuries and determine the treatment priorities for stabilization.

Initial assessment of a trauma victim can be done in just a few seconds by assessing the airway, breathing, circulation and debilitation (ABCD). For example, an appropriate response to the question of name and recent events by the patient tells the physician that the airway, breathing and mentation are not significantly compromised. Difficulty in responding to these questions indicates compromise of A, B, C and/or D. However, this simple assessment may be difficult to make in the infant or young child, who may be too young or too anxious to respond appropriately.

Other considerations during the initial assessment are whether the patient sustained localized trauma such as an isolated extremity injury or if there is multiple trauma to different sites. This is not an easy determination to make as certain injuries can be occult, the patient may not be cooperative with attempts to examine them due to age or intoxication. Thus, this is a dynamic process and the physician must keep an open mind and perform a thorough exam. When in doubt, it is best to assume multiple trauma until proven otherwise.

### Mass Casualty Events

A mass casualty event is defined when the number of patients exceeds the capacity of the resources (personnel and facility) available. In mass casualty situations, the goal of triage is to provide care to those patients who will most benefit from the limited resources. The priority is to maximize the number of victims who survive. This means that the medical provider may need to withhold care from some patients who, under different circumstances, would have received medical care.

As you can imagine, this is a formidable and stressful process for medical providers who have to choose which patients should receive care and which ones should not. Often in these situations, the tendency is to overtriage children, thus assigning resources to children who neither need nor benefit from them. So the physician must be wary of this pitfall.

There are several mass casualty incident (MCI) triage systems available. The Simple Triage and Rapid Treatment (START) system is one of the most popular triage tools used by many countries. Other triage tools include SALT (Sort, Assess, Lifesaving intervention, Treatment/Transport), Triage Sieve, CareFlight Triage, etc. JumpSTART is a modification of the START tool, which is more suitable for children and parallels the START tool. It is currently the most widely used MCI triage tool suitable for children. Sacco triage system is a newer tool developed for children.

### STABILIZATION

The goal of management of the injured child is to minimize secondary injury as a result of the primary injury. The Advanced



**Figure 1** Layout of a trauma emergency care room

Trauma Life Support (ATLS) recommends a systematic and team approach. The approach to management involves systematically assessing the ABC's and providing interventions as indicated by clinical presentation. After each intervention it is important that the physician assess the patient's response. The clinician should not move to the next step until the first problem has been effectively dealt with. The primary survey involves evaluation of airway, breathing, circulation, disability and exposure (**Fig. 1**).

### Airway

The first step is assessment of airway patency. A crying or verbal child indicates a patent airway. If the patient has signs of airway obstruction as described in the clinical features section, it must be addressed immediately. There are several interventions a physician can perform to establish an open airway. Ensure the patient is placed with head in the neutral position (the child's midface should be parallel to the surface they are laying on). Performing the jaw thrust maneuver can further open the airway. Consider possibility of cervical spine injury and avoid excessive motion of the neck. Ideally the cervical spine should be immobilized with a semi-rigid collar or with sandbags. If the child still has signs of airway obstruction, the physician will need to establish a definitive airway. Physicians should be alert to the fact that in the case of burn victims a definitive airway should be established at the earliest sign of developing obstruction.

### Breathing

The physician should note tracheal position, assess for jugular distension, equal chest rise and breath sounds. If there is a suspicion of tension pneumothorax or massive hemothorax, a chest tube should be placed, after confirming the same. In the case of significant respiratory compromise with poor oxygenation and/or ventilation due to flail chest or pulmonary contusion, endotracheal intubation should be undertaken as indicated.

### Circulation

Important clinical aids to assessing the circulatory status include heart rate, pulses in all extremities, capillary refill time, level of consciousness and skin color. If patient has signs of hypovolemic shock, the physician should immediately institute fluid resuscitative measures with isotonic fluid and blood transfusion as needed. Hemorrhage is the most common cause of shock in trauma victims. It is imperative that the physician identifies the source of bleeding and achieves hemostasis. External bleeding is easily identified and best controlled by direct pressure. In cases of massive external hemorrhage not controlled by direct pressure, a temporary tourniquet may be applied. Identification of internal bleeding can be more of a challenge. There are several areas of the body where a child can have significant blood loss before overt clinical signs are visible such as abdomen/pelvis, retroperitoneum and thigh. Management of internal hemorrhage may require surgical intervention.



## Neurologic Evaluation

A quick neurologic assessment can be obtained by using the Glasgow Coma Scale or the alert, voice, pain, unresponsiveness (AVPU) method to assess mental status. Depressed level of consciousness can be due to direct trauma, decreased oxygenation and/or perfusion and should prompt reassessment of the patients ABC's. The goal of management in traumatic brain injury is prevention of secondary injury to the brain by maintaining appropriate perfusion and oxygenation of the brain as well as a euglycemic state.

## Exposure

The patient should be completely undressed for several reasons: This facilitates a complete evaluation; prevents hypothermia—if the clothes are wet, they can cause cooling and aids in removal of toxic exposures if the clothes are saturated. Once patient evaluation is complete, they should be covered with blankets to prevent hypothermia. After the primary survey and stabilization is achieved, a complete head to toe exam should be done to identify all injuries. This is also the time when laboratory and imaging studies can be obtained as clinically indicated to aid in diagnosis and further management (**Table 3**).

## TRANSPORT

On occasion it may be necessary to transport an injured patient for more definitive care. A patient should be transferred if their medical or surgical needs exceed or may exceed the capabilities of the current facility. Transport should occur in a timely manner once the patient has been stabilized to the extent possible given resources and physician capability. Transfer should not be delayed for diagnostic testing (laboratory or imaging) which will not change the need for transfer. For example, if the patient is stable but needs to be observed for a splenic laceration and possible ongoing hemorrhage that may need surgical intervention, this observation should be done at a facility where there is a surgical team and operating theater immediately available. During transport there should be ongoing monitoring of vital signs and support of the cardiopulmonary system.

## OUTCOMES/PROGNOSTIC FACTORS

Globally, approximately 950,000 deaths occur each year in children under 18 years. Nearly 95% of these deaths occur in low- and middle-income countries. In India, injury is the second leading cause of death in the 5-14 years age group and the fourth leading cause of death for children less than 15 years. Due to the lack of a national trauma registry, limited data is available on trauma outcomes and prognostic factors in India. Several authors have conducted studies to determine the utility of trauma prediction scores such as the Revised Trauma Score (RTS), Injury Severity Score (ISS) and the Trauma and Injury Severity Score system,

which combines the RTS, ISS and age to determine the probability of survival.

It has been reported that the trauma mortality rate in developing countries is significantly higher than developed countries. One of the chief causes for this is the lack of prehospital care, which causes a time lag to definitive care and misses the *golden hour* for instituting lifesaving therapies.

The compelling need for an organized trauma system has been well established in the literature. Considerable efforts should be made to develop a national trauma registry, organized prehospital care, a medical transportation network and regional trauma centers.

## PREVENTION

Primary injury prevention should be a goal for all physicians who provide care to children. Just as we have made strides in preventing infectious diseases through immunizations and clean healthful practices so we should focus our efforts on preventing childhood injury. We need to understand the scope of the problem, risk factors associated and some of the barriers to prevention efforts, which are unique to India and similar developing countries. There is a paucity of epidemiological information related to injuries in India. Earnest efforts should be made to establish a reliable surveillance system to accurately define the burden of disease.

Injury prevention requires a multipronged approach and should include collaborative efforts between various sectors such as media (education), engineering (safety devices, safer roads), policy makers (legislature) and law enforcement. These efforts should be continued on national, state, regional and community levels.

### IN A NUTSHELL

1. Most injuries occur in the home setting with falls as the number one cause. Other common locations are in the street or playground.
2. Road traffic accidents are the most common cause of death due to injury in children.
3. Burns in children are most often scalds due to hot liquids. Other causes of burns include flame and electricity.
4. Accidental poisoning by ingestion of medications or cleaning agents is another frequent cause of childhood injury. The age group most commonly affected is the 1–4 years old with a male preponderance.
5. Drowning is the third leading cause of unintentional injury death in the world. Low- and middle-income countries accounts for 95% of drowning deaths. Children less than 5 years have the highest mortality rate due to drowning.
6. Triage involves the initial sorting by which a physician can quickly assess the extent and severity of a patient's injuries and determine the treatment priorities for stabilization. It is the responsibility of the physician to determine the extent of the child's injuries.
7. The goal of management of the injured child is to minimize secondary injury as a result of the primary injury. The ATLS recommends a systematic and team approach by assessing the ABC's and providing interventions as indicated by clinical presentation.

**Table 3** Common laboratory and imaging studies

Laboratory studies	Imaging studies
Complete blood count	Chest radiography
Comprehensive metabolic panel	Pelvic X-ray
Amylase/lipase	Computed tomography (CT) head
Coagulation profile	CT cervical spine
Type and screen/cross	CT chest
	CT abdomen/pelvis
	Extremity radiographs

## MORE ON THIS TOPIC

American College of Surgeons Committee on Trauma. Initial Assessment and Management. In: Advanced Trauma Life Support Course Manual. 9<sup>th</sup> ed. 2012.



- Deshmukh VU, Ketkar MN, Bharucha EK. Analysis of trauma outcome using the TRISS method at a tertiary care centre in Pune. *Indian J Surg.* 2012;74:440-4.
- Gururaj G. Injuries in India: A national perspective. NCMH Background Papers—Burden of Disease in India. Ministry of Health and Family Welfare, Government of India. 2005.
- Jenkins JL, McCarthy ML, Sauer LM, et al. Mass-casualty triage: time for an evidence-based approach. *Prehosp Disaster Med.* 2008;23:3-8.
- Lee LK, Fleisher GR. An approach to the injured child. In: Fleisher GR, Ludwig S. *Textbook of Pediatric Emergency Medicine.* 6<sup>th</sup> ed. USA: Lippincott Williams and Wilkins; 2010.
- National Crime Records Bureau. Accidental deaths and suicide in India—Annual Report, 2012.
- Peden M, Oyegbite K, Ozanne-Smith J, et al. *World Report on Child Injury Prevention.* Geneva: World Health Organization; 2009.
- Sharma M, Lahoti BK, Khandelwal G, et al. Epidemiological trends of pediatric trauma: A single-center study of 791 patients. *J Indian Assoc Pediatr Surg.* 2011;16:88-92.
- Singh J, Gupta G, Garg R, Gupta A. Evaluation of trauma and prediction of outcome using TRISS method. *J Emerg Trauma Shock.* 2011;4:446-9.

## Chapter 10.2

# Drowning/Submersion Injuries

Arun Bansal

Drowning is defined as “a process resulting in primary respiratory impairment from submersion/immersion in a liquid medium.” Term *drowning* should be used regardless of the outcome. It also specifically recommended that terms, such as *near-drowning*, *silent drowning*, *wet drowning*, *secondary drowning*, *passive drowning*, and *dry drowning* be abandoned. Uniform way of reporting a drowning event is by Utstein template of reporting. This allows standardization of the event and comparison.

## INCIDENCE

Drowning is an important cause of death all over the world. As per the World Health Organization (WHO), 0.7% of all deaths worldwide or more than 500,000 deaths each year are due to unintentional drowning. Toddlers and adolescents are common age groups among children who are more vulnerable. Drowning is a leading cause of death worldwide among boys 5–14 years of age. In young children, drowning event occurs more at home. Infants drown in bathtubs most frequently. Most of the events occur due to lack of adult supervision. Toddlers usually drown in swimming pools. Adolescents are more adventurous, thus, drowning events are more common in natural bodies of water. Intoxication may also play a role. Certain pre-existing medical problems may lead to increased chances of drowning, like in a child with seizures, arrhythmias, long QT syndrome, etc. Main risk factors for drowning are age less than 14 years, male sex, alcohol abuse, low income, poor education, rural residency, risky behavior, and lack of supervision.

## PATHOPHYSIOLOGY

The primary physiologic effects of drowning are due to hypoxic-ischemic and reperfusion injuries. Long-term neurologic sequelae of drowning occur almost exclusively among patients who have drowning-associated asphyxial cardiac arrests. Patients who do not experience cardiac arrests rarely have significant sequelae. Drowning-associated asphyxia is caused by laryngospasm, apnea, or pulmonary aspiration of water. This leads to hypercarbia, hypoxia, and acidosis and decreases myocardial contractility, elevate pulmonary artery and systemic vascular resistance, and produce cardiac arrhythmias.

Lung injury causes abnormal surfactant function and increased capillary endothelial permeability which leads to increased poor lung compliance, intrapulmonary shunting, ventilation or perfusion mismatch, and atelectasis which cause further hypoxemia and hypercarbia. When severe enough, this process may lead to acute respiratory distress syndrome (ARDS). As against earlier beliefs, lung injury is similar in fresh water and saltwater drowning.

The most devastating consequence of drowning and the most frequent cause of death is hypoxic-ischemic injury to the brain. The degree of central nervous system injury is related to the duration of untreated cardiac arrest, the effectiveness of initial cardiopulmonary resuscitation (CPR), and secondary cerebral injuries after resuscitation (e.g., further hypoxic episodes, inadequate cerebral blood flow, cerebral edema, and

hyperthermia). The whole drowning process, from submersion to cardiac arrest, can occur in seconds to few minutes, but sometimes in hypothermia or in ice water, the process can last for an hour.

## CLINICAL FEATURES AND MANAGEMENT

The *golden period* in the management of drowning victims is before the patient reaches hospital. Immediate rescue from water and prompt initiation of basic life support are critical for good outcomes. Time is the most important element, therefore bystander CPR is of utmost value. Unfortunately, only less than a third of the drowning victims get bystander CPR.

## Resuscitation

Hypoxic-ischemic injury during drowning results in myocardial dysfunction, which manifest clinically as shock. If left untreated, it can lead to complete cardiac arrest. Either in shock or cardiac arrest, victim may be unresponsive, apneic, and with no pulse. Prompt CPR with rescue breathing and effective chest compressions can be lifesaving. Even some bystander CPR is better than no resuscitation. Heimlich maneuver or other attempts to clear the airway of water not only are ineffective, but frequently are detrimental by inducing emesis and aspiration of gastric contents. After opening the airway with the head tilt-chin lift maneuver, two mouth-to-mouth rescue breaths should be provided. Single rescuers should provide two rescue breaths before each cycle of 30 chest compressions (please refer to Chapters on BLS, Resuscitation for the details).

Common arrhythmias noticed are bradycardia, asystole or ventricular fibrillation. Early ECG recording is therefore essential. The victim should be treated at a place where adequate facilities are available. Victim should undergo detailed evaluation and treatment upon arrival at the hospital. Focus should be rapid cardiopulmonary assessment, evidence of shock, hypothermia and associated trauma as well as for signs of neurologic and pulmonary injury.

The drowning victim may have variable symptoms ranging from no sequelae to cardiac arrest. CPR should be continued until return of spontaneous circulation or until resuscitation is futile. There are no predictors of normal neurological outcome. Good outcomes have been noticed even after 1 hour of drowning, extreme hypothermia or acidosis. Due to this, it is recommended that all victims receive aggressive care for the first 24 hours until the prognosis can be better determined.

## Cardiovascular Effects

Patients may be in shock, even after initial resuscitation. Shock could be decompensated or compensated, manifesting with tachycardia, abnormal perfusion, decreased urine output, acidosis or encephalopathy. Shock is usually because of decreased myocardial contractility following hypoxemia and acidosis. Intravascular hypovolemia due to fluid shift also contribute to decreased cardiac output. Management of shock is like any other case with shock. Patient may require fluids and inotropes.

## Hypothermia

Many reports are available in adults as well as in children about good recoveries following icy water drowning. Many factors play a role to decide about inducing hypothermia in a drowned victim. Mild hypothermia may be useful in some cases. Studies in adults suggest improved outcome with mild hypothermia in drowning victims with cardiac arrest and ventricular fibrillation. Similar

case reports are also available in children who had prolonged submersion in icy cold water. In spite of lack of evidence, mild hypothermia (32–34°C) may be a good option in children who are comatose but hemodynamically stable. This may be continued for up to 24 hours. Rewarming should be done in children with severe hypothermia (< 28°C) and in moderate hypothermia (28–32°C) with cardiovascular instability.

Rewarming is of two types, namely:

1. *Passive rewarming* This is usually done at the scene. Protect the patient from wind and cold and remove wet clothes.
2. *Active warming*
  - a. *External rewarming* This is performed with heaters or warm air, but it can lead to vasodilatation and cardiovascular instability.
  - b. *Internal rewarming* It is the gold standard, especially in children with cardiac arrest or hemodynamic instability. In the developed world, it is achieved commonly with cardiopulmonary bypass or extracorporeal life support. In developing countries, body cavity lavage (peritoneal, bladder, pleural, gastric) are alternative methods.

An important thing to note while rewarming is to prevent hyperthermia. Hypothermia reduces the electrical and metabolic activity of the brain. The rate of cerebral oxygen consumption is reduced by 5% for reduction of 1°C in temperature.

## Trauma

Accidental injuries are common in drowning while diving, boat accidents or other motor vehicle accidents. Thorough examination need to be done to look for any traumatic injuries including, brain, spine, intra-abdominal. CT scan, if needed, should be done after stabilization.

## Hypoxia-Ischemia

Hypoxic-ischemic injuries are most common in drowning patients as brain is the most susceptible organ to hypoxia. Children who are neurologically normal at admission are likely to be normal. However, children who are comatose or have altered sensorium, serial examination in the next 24–48 hours is important to predict outcome. Children, who return to normal neurological examination within 24 hours, usually have good outcome. Only factor proven to be of benefit for good outcome is on site CPR or immediate resuscitation and mild hypothermia. No benefit is seen with various medical therapies like, drugs, management of raised intracranial pressure (ICP) or its monitoring. Focus should be to prevent secondary insult like, hypoxia, hypercarbia, seizures, or hypo-/hyperglycemia.

## Pulmonary Involvement

Drowning victims may require mechanical ventilation, if they have respiratory distress. Target should be to achieve normocarbia, and normal oxygenation. Hypercarbia can be dangerous in these children as it can lead to rebound raised ICP due to increase in cerebral blood flow. Child requires continuous monitoring initially as the pathology is progressive and ventilator requirement may increase. Both, atelectasis and over-distension is detrimental. These children are usually ventilated with conventional modes of ventilation but, newer modes including high frequency ventilation may be needed as per requirement. Chest X-ray is needed in these cases to detect pulmonary involvement. Pneumonia should be suspected if there is clinical evidence along with bacteriological and

radiological evidence. But, prophylactic antibiotics have no role and are best avoided.

Pulmonary injury following drowning can lead to ARDS. It can be due to direct injury to lungs because of drowning or indirect due to pneumonia, sepsis, etc. ARDS may develop over hours or days. Diagnosis of ARDS is made as in any other ARDS case. The course of ARDS is also similar in these cases, exudative phase, fibrosing stage and resolving phase. Treatment of ARDS is also same like in any other ARDS.

## Other Organ Involvement

Significant hypoxia or cardiac arrest may cause damage to other organs or may lead to multiorgan dysfunction. Other organs to be affected are kidneys and liver. These organs may show manifestations up to 72 hours. Renal injury may present in the form of oliguria/anuria, increased renal functions or acute tubular necrosis. Presentation of liver damage may be in the form of increased liver enzymes, bilirubin, or abnormal liver synthetic functions.

Children who have significant organ involvement should be managed in Pediatric ICU. However, mildly symptomatic or asymptomatic children can be discharged after initial observation in emergency. Children with Glasgow coma scale (GCS) more than 13, normal oxygenation, normal renal and hepatic functions, and normal examination by 12 hours can be discharged and need not require admission.

## PROGNOSIS

No single factor can guide the need of resuscitation in drowning victims. Duration of drowning has been associated with outcome. However, prolong submersion in icy water has shown good outcome. Moreover, it is difficult to tell exact duration of submersion. Hence, all children should receive aggressive resuscitation at admission.

Similarly, no clinical or laboratory parameter at admission is available to predict good neurological outcome. Studies on this are lacking and need further investigation.

In children who return to spontaneous circulation, outcome improves over a period of time. Children who show significant motor improvement in first 24 hours are the ones who had no or mild neurosequelae at discharge. Children who remain comatose or have nonpurposeful motor movements show severe disability at discharge. Apart from neurodisability, children with lung injury may have chronic pulmonary disability like reactive airway disease or chronic lung disease.

## PREVENTION

Incidence of drowning incidence has declined in the last three decades, mainly due to better preventive efforts. Still, lot more is required, as more than two-thirds of the events are still preventable. Optimal preventive efforts differ as per age group. Infants and young children should enter the pool always under adult supervision. In spite of that, lapses may occur. Most childhood drowning are usually silent and the supervisor may not hear any splashing or struggle. Therefore, multiple barriers of prevention are recommended. Fencing of pool with a proper latch has shown to decrease the drowning incidence by 50–80%. Adolescents should be educated about water safety and risk of intoxication while swimming or when near any water body. Swimming lessons cannot make a child *drown-proof* under all conditions.

### IN A NUTSHELL

1. Childhood drowning is a common cause of mortality and morbidity.
2. Terms like near drowning, dry drowning, passive drowning, and dry drowning are not used nowadays.
3. Important factors which lead to drowning are age (toddlers and adolescents), lack of supervision, adventurous behavior, and use of intoxicating substances.
4. Preventive strategies are more important than post drowning care.
5. Main pathophysiology after drowning is pulmonary aspiration and hypoxic ischemic injury to brain.
6. Bystander CPR is the most important factor for good outcome and should be initiated as soon as possible.
7. Duration of submersion and hypothermia are the other important factors which can affect the outcome.
8. Mild hypothermia can be protective, but hyperthermia should be avoided.
9. Pulmonary involvement may vary from mild pneumonia to severe ARDS.
10. Pulmonary edema encountered in children after drowning is due to acute respiratory distress syndrome and not from fluid overload. It should be treated with positive end-expiratory pressure and not diuretics.

### MORE ON THIS TOPIC

- Austin S, Macintosh I. Management of drowning in children. *Pediatr Child Health*. 2013;23:397-401.
- Burford AE, Ryan LM, Stone BJ, et al. Drowning and near-drowning in children and adolescents. *Pediatric Emerg Care*. 2005;21:610-17.
- Byard RW. Drowning in children – an ongoing problem. *J Pediatr Intensive Care*. 2012;1:3-4.
- Meyer RJ, Theodorou AA, Berg RA. Childhood Drowning. *Pediatr Rev*. 2006;27:163-9.
- Szpilman D, Bierens JJL, Handley AJ. Drowning. *N Engl J Med*. 2012;366:2102-10.
- Vahatalo R, Lunetta P, Olkkola KT, Suominen PK. Drowning in children: Utstein style reporting and outcome. *Acta Anaesthesiol Scand*. 2014;58:604-10.
- Zuckerbraun NS, Saladino RA. Pediatric drowning: current management strategies for immediate care. *Clin Ped Emerg Med*. 2005;6:49-56.



## Chapter 10.3

# Animal Related Injuries

Arun Kumar Baranwal

Animal-related injuries pose a major public health problem in children worldwide, especially in South Asia. Predominant rural population and agriculture-based economy are the major contributory factors. Changing social, demographic and economic scenario led to increase in its importance and has altered profile of such injuries. Animal-related injuries constitute 6–12% of all injuries in community-based studies from India. Numerous animals have potential to inflict injuries in children, the most important being caused by dogs, monkeys, cattle and wild animals. About 48,000 occupational fatalities were estimated to occur in India during 2006 in the farm sector alone. However, with over 1.1 crore cattle farmers and suboptimal health and safety infrastructure, the actual number of cattle-related injury associated fatalities can only be speculated. There is no empirical pediatric data on animal-related injuries in South Asian countries. Health impacts of animal-related injuries are dependent on type and health of inflicting animal, size and health of the victim, availability and appropriateness of accessible health-care infrastructure. These have significant economic impact as well in terms of cost of travel, treatment, vaccination, loss of wages and school absences, etc.

## EPIDEMIOLOGY

Animal-related injuries may be broadly classified as *small-animal bite injuries* and *large-animal-related injuries*. The causative animal and the spectrum of injuries are dependent on the kind of animal cohabitating with the human population. Living in close contact with domestic animals and often not far from wild ones is common in South Asia. India alone is estimated to house about 25 million dogs, mostly stray ones in rural and urban habitations (**Fig. 1**). An estimated 17.4 million small-animal bites occur in India every year. In a multicentric study from six cities of India over 18 months, dog bites were commonest (92%, mostly stray ones), followed by bites by monkey (3.2%), cat (1.8%), fox (0.4%) among 1,357 fresh bite injuries. Half of them were in children (age, 2–18 years), and mostly unprovoked (64.3%) and by stray animals (64.7%). Boys were attacked more often than girls (2.5:1). Another study revealed seasonal pattern of dog bite, the peak incidence being 10 weeks



**Figure 1** Cohabitation of stray dogs is common in South Asian urban and rural residential areas

following the peak stray-dog breeding period, due to maternal protective behavior of the stray dogs. In a community based study from Delhi, overall incidence of small-animal bites was 8/1000 population/year. Incidence for minor and major injuries was 2.5/1000 and 5.3/1000 respectively.

Monkey bites are the second most common small-animal bite in South Asia, which assumes significance as monkeys are supposed to be regular carriers of rabies virus. Cat bites also constitute a significant number in Indian studies on small-animal bites. Other animals inflicting bites are mongoose (in rural areas), camels (in Rajasthan and Haryana), black bear (in Himalayan territories), large cats (tigers, lions, leopards) (in wild and in various bioreserves), wild dogs, hyenas, wolves, crocodiles and other reptiles.

Cattle-farming is an important economic activity in South Asia, which is mainly based on subsistence farming with average herd size of just five animals. It leads to children being at risk of *large-animal*-related injuries due to their close social and occupational associations with them in villages and rural towns. An US study revealed that moving or herding the cattle was the most common task being performed at the time of injury. The same is likely to be true in South Asia as well, as buffalo-back riding by children is a common scene here (**Fig. 2**). Estimating the number of *at risk* children and the extent of cattle-related injuries is difficult due to lack of reporting system, occupational health facilities and safety infrastructure, despite harboring the largest number of cattle in the world. In an US based survey, half of the cattle-related injuries occurred in children less than 10 years, which is due to engaging them at younger age in agricultural work, lack of knowledge and experience of hazards associated with cattle.

An increasing incidence of wild animal-related injuries has been reported from Himalayan and sub-Himalayan regions causing mortality and serious morbidity. Intrusion of the forest, deforestation, low socioeconomic status and living near forest are the contributory factors. Many times these injuries are inflicted in forests and bioreserves or sanctuaries. Again, it is difficult to estimate the magnitude of the problem as most injuries do not come to medical attention at all.

## MECHANISMS OF INJURY AND CLINICAL FEATURES

*Small-animal bites* range from benign to serious life-threatening injuries. Dog bites include abrasions, lacerations, piercing wounds, avulsion of tissues and/or crush injury. Cat bites and rat bites are usually piercing wounds, the former often penetrate to deep tissues. For the purpose of post-exposure rabies prophylaxis, the animal bites have been categorized as given in **Table 1**. Lower extremities are involved in about half of the cases, and almost two-thirds of those patients who needed post-exposure prophylaxis had Category III bites. The risk of injury to the head, face and neck is greater in children (**Fig. 3**) compared to adults leading to increased severity, necessity for medical treatment and fatalities.

*Cattle-related injuries* can be classified based on mechanism of injury (blunt trauma versus penetrating trauma) and the injured body parts (trunk, face, extremities). Most injuries appear to be blunt trauma due to kicking or crushing type injuries, however penetrating injuries from cattle horns are also common. Horn-related injuries have a distinct pattern based on child's activity at the time of injury. Fall from back of slowly moving buffalo usually cause limb injuries, involving mostly lacerations, contusions and fractures.

*Blunt injuries* are due to high energy impact with severe crushing tissue damage, and are more common in children. These are mostly caused by kicks, other mechanisms being pushed, trapped between the animal and wall or a gate, butting and trampling. Force generated is usually sufficient to cause multiple fractures,



**Figure 2** Practice of buffalo-back riding among young children while moving or herding cattle is a common scene in Indian villages

including the skull and maxillofacial fractures, leg wounds or serious thoracoabdominal injuries involving vertebrae and ribs. Abdominal injuries are associated with intestinal contusions, visceral ruptures and even eviscerations. Fatalities are more common with the blunt injuries compared to the penetrating injuries. The less severe non-fatal injuries like fractures of extremities are more frequent than these life-threatening injuries. In an US survey on the farm animal-related nonfatal injuries among children, scrapes and abrasions were commonest (26%) injuries, followed by cuts and lacerations (18%), fractures (17%), and contusions (15%). Head and hand were the most commonly affected body parts. Corneal injuries may be caused by cattle tails or ears.

*Goring*, i.e., stabbing with horns lead to penetrating injuries, mostly affecting abdomen followed by perineum, neck and head. Mechanism involves multiple forces; initially horn penetrates usually in an upward trajectory and victim gets lifted upwards. Following this, a forceful turning of the animal's head creates rotational forces. These forces cause complex and destructive tracts with considerable visceral injury, even with seemingly small external wound. In a retrospective study of bull horn injuries among adults from Vellore (India), 61% of injuries occurred to perineum or abdomen, and wounds were directed obliquely upwards. Injuries to femoral vessels, external and internal genitalia, anus and rectum are also seen depending on the site of entry wound.

*Wild large-animal-related injuries* have a combination of cutting, penetrating and crushing wounds. These are contaminated significantly from claws and teeth of the animal. Fall of large animal on child's body along with attack with its limbs can lead to deep lacerations, penetrating and blunt injuries to skull, face, neck and trunk. Victims may have complex fractures of limbs (with/without injuries to tendons and nerves), facial bones, skull and ribs. Comminuted fractures of first and second cervical vertebrae with spinal cord injuries, trauma to major neck vessels and pharynx may complicate the problem. Camel bites are seen to be associated with maxillofacial fractures. The elephant-related injuries are peculiar due to strength of impact and larger area of body involved. These injuries usually occur in far-flung forests with considerable delay in notification, rescue of the patient and definitive care. Without urgent management, risk of disfigurement, functional loss and death is very common.

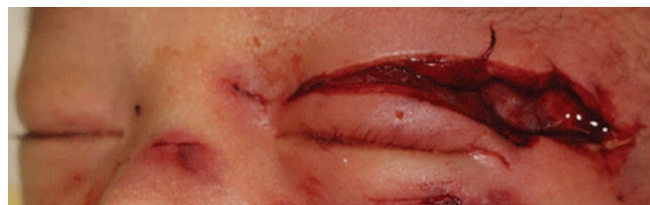
## APPROACH TO DIAGNOSIS

Management of the victim of animal-related injuries involves detail history and physical examination. A careful attention to the

**Table 1** WHO categories of bite injuries for the purpose of rabies prophylaxis

Categories	Description
Category I	Touching and feeding animals, licks on intact skin
Category II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding
Category III	Single or multiple transdermal bites or scratches; licks on broken skin; contamination of mucous membrane with saliva from licks; contacts with bats

Source: World Health Organization. Rabies. 2013. Available from: <http://www.who.int/mediacentre/factsheets/fs099/en/>. Accessed on May 01, 2014.



**Figure 3** Deep upper lid wound from monkey bite

circumstances surrounding the injury, e.g., type of animal (small or large; domestic or wild), provoked or unprovoked attack, place of attack, mechanism of injury (blunt, penetrating, tearing or crushing) will be clinically relevant. Time elapsed since the injury has lot of bearing on the surgical management of the wound. An unprovoked dog bite is likely to be from a rabid one. Information on drug allergies and immunization status of the child (tetanus) and animal (rabies) will be useful in treatment planning.

Type, size, location and depth of the wound should be carefully examined. Wounds should also be evaluated for presence of the contaminating material, status of underlying structures and range of motion if a limb is injured. Injury severity score or trauma and injury severity score may be used to measure injury severity in cases of large-animal-related injuries. Extent and severity of tissue destruction and risk of infection are of paramount importance in deciding the management decisions and prognosis. High index of suspicion should always be there for serious underlying bone or soft-tissue injury.

A detailed diagram of injury should be made in the patient's medical record for prognosis, follow-up and medicolegal issues. Radiographs of skull, cervical spine, chest, abdomen and extremities should be obtained as clinically indicated. It will help in detecting foreign material as well. Victims of large-animal-related injuries should undergo detail radiological survey to detect fractures. Patients with injuries to face and/or head have high likelihood of fracture and/or penetrating injury of the skull. A computed tomography may help in formulating a comprehensive management plan.

## COMPLICATIONS

Rabies is the most significant complication of animal bite injuries; it can also occur with direct contact of saliva with mucosa or fresh skin wounds (refer to chapter on rabies in Section 31, Viral Diseases). In fact, India has maximum human rabies cases in the world, and estimated to contribute about 20,000 fatalities per year, which is likely to be a gross underestimation for lack of organized system of rabies surveillance. Although all age groups are susceptible, it is most common in children less than 15 years of age. Infection is the most common complication of dog bites. Decision to do microbial studies of bite wounds depends



on the time elapsed since bite, depth of wound, presence of contamination and clinical evidence of infection. As infection rate for bite wounds presenting to health-care facilities within 8 hours is small (2.5–20%), it need not to be cultured unless wounds are deep, extensive, contaminated, and/or there are early signs of infection, or patient is immunocompromised. Infection rate in monkey bite and cat bite wounds is high ( $\approx 50\%$ ) even in cases receiving early medical attention, these wounds should always be cultured. All small-animal bite wounds presenting after 8 hours should always be cultured. Large-animal-related penetrating injuries and wild animal bites may involve resistance from the victim, which drives mud, grass and other contaminating material into the wounds. Infection rate is dependent on multiple factors including timeliness of and level of access to health-care and socioeconomics. Risk for infection is more with crush injuries, deep puncture wounds, and wounds to the hand. Thus, these wounds should always be cultured.

Tetanus is an important consideration in all animal-related injuries, especially in large-animal-related ones due to heavy contamination, more so in the agricultural setting. It assumes significant importance due to poor coverage of and lack of awareness about the 10-year booster immunization against tetanus.

## MANAGEMENT

Management of the animal-related injuries involves different strategies for *small-animal* bites and *large-animal*-related injuries.

### Management of Small-Animal Bites

Prompt treatment of all bites and abrasions is of the utmost importance. The purpose is to remove as much rabies virus (if there is any) as possible from the site of inoculation before it gets absorbed on nerve endings. Wound management is of maximal value when applied immediately after bite (within minutes if possible); however it must be done even after several hours or days of the bite. Immediate wound treatment is shown to reduce potential of rabies by about 80% in experimental studies. The wound management comprises of following:

**Wound toileting** Immediate flushing and washing the wounds, abrasions and the adjoining areas with plenty of soap and water, preferably under a running tap for at least 15 min. If soap is not available, simple flushing of wounds with plenty of water may be enough. In case of punctured wounds, catheters should be used to irrigate wounds.

**Chemical treatment** After toileting whatever residual virus remains in the wounds should be inactivated by irrigation with Savlon, Dettol, povidone iodine, tincture, or alcohol (70%).

**Suturing** Primary suturing should be avoided to prevent additional trauma which may help spread rabies virus into deeper tissues. If suturing is necessary, it should be done 24–48 hours later, applying minimum possible stitches, under cover of local rabies immunoglobulin infiltration. Topical antibiotics and antitetanus measures should be ensured if indicated.

**Systemic antibiotics** All Category II and III bite injuries from dogs, monkeys, cats and rats need systemic antibiotics regardless of evidence of infection. A varied mix of aerobic and anaerobic bacteria colonizes oral cavity of the biting animal, and thus most bite wound infections are polymicrobial. Oral versus parenteral route may be guided by the severity of wound, presence and degree of local infection and/or systemic toxicity, and immunocompetence of the victim. Co-amoxiclav may be preferred for empirical oral treatment. Azithromycin may be an alternative for penicillin sensitive patients, as it is effective against

both aerobic and anaerobic bacteria. Erythromycin, clindamycin and co-trimoxazole are not useful in small-animal bites for lack of relevant antimicrobial coverage.

**General management** Patients with bites on the limbs should be asked to keep it elevated for about a day or two, or until edema has subsided. Wounds of the hand should be immobilized in functional position for about 3–5 days. All bite victims need follow-up for re-evaluation of the wounds within 2–3 days.

### Management of Large-Animal-related Injuries

Management approach for victims of large-animal-related injuries is similar to that of victims of road traffic injuries. Life support measures, detailed examination, multispecialty consultation, coordinated planning and relevant surgical procedures need to be instituted at the earliest in time critical manner to minimize morbidity and mortality. Following are the principles of the management:

**Resuscitation and stabilization** A high degree of suspicion to have major and multiple traumas is required. The initial primary goal is meticulous resuscitation and optimal stabilization as per the guidelines of pediatric advanced life support and advanced trauma life support. Management should be initiated at the site of attack itself with the best possible measures to stop bleeding, administer fluid and immediate transport to the nearest secondary or tertiary center as per the available health-care infrastructure. Once at hospital, primary survey of the whole body needs to be performed. Resuscitation and stabilization of trauma patients are detailed in Section 10.1, and should be followed for large-animal-related injuries as well.

**Initial wound management** After initial resuscitation, thorough attention to local wound care and exploration are required. Wounds are usually heavily contaminated, and thus appropriate material should always be obtained for culture. Management consists of cleaning and vigorous irrigation with liberal amounts of saline using a syringe. Antibiotic-containing solutions are not recommended for irrigation. Puncture wounds should gently be irrigated with a syringe and a catheter or blunt-tipped needle; however high-pressure irrigation should be avoided. Generous debridement of devitalized tissue and removal of all foreign material is the mainstay of surgical management. Fluctuant areas need to be incised and drained. The thirty-five percent of bull horn injuries reported from Vellore (India) required extensive surgical intervention. About half of the primarily closed wounds developed infection in this study, while it was seen only in 6% of the secondarily closed wounds. Thus delayed and/or partial closure of the wounds is considered as standard of care. However uncomplicated, clinically uninfected lacerations on face, head and neck, presenting within 6 hours, thoroughly irrigated and debrided, primary closure is preferable because of generous blood supply to this region. Broad spectrum antibiotics including anaerobic coverage are indicated in all penetrating wounds pending the culture results. Prophylaxis against tetanus and rabies should be given as indicated.

**Definitive surgical management** These injuries are usually complex and thus a well-coordinated multidisciplinary approach including pediatrician and/or pediatric intensivist, orthopedic surgeon, neurosurgeon, maxillofacial surgeon, ophthalmologist, plastic surgeon, microbiologist and psychiatrist. Acceptable cosmetic and functional results may be achieved and mortality may be prevented with timely and aggressive interventions. Cattle-related blunt trauma injuries frequently require thoracotomy, laparotomy and craniotomy as well as fracture management. For penetrating wounds, there should be a low threshold for evaluation of wounds under general anesthesia and laparotomy when abdomen is injured.

## PREVENTION AND PUBLIC HEALTH MEASURES

### Dog Bites

Despite dog bite is a public health problem and the major source of rabies in the South Asian countries, we do not have any comprehensive dog bite control program. Some organizations are involved in control activities in isolation however without intersectoral coordination. The most logical and cost-effective approach is swift mass immunization program for stray dogs, in the shortest possible time, of at least 70% of the entire dog population of the area (for herd immunity) combined with long-term aim of elimination of the stray dogs. However, in the meanwhile, following strategies may be employed:

- Training of health-care professionals (including doctors) about animal bite management.
- Timely and adequate management of all animal bite victims.
- Vaccination of the pet and stray animals through potent vaccines at regular intervals through active community participation.
- Creating awareness about timely and adequate postexposure management of all animal bites in the community.
- Research to identify interventions required to manage population, habitat, movement, behavior and demography of dogs.
- Dog birth control through sterilization.
- Census, licensing and obligatory registration of all domestic dogs in the community.
- Restrain of dogs in public places.
- Immediate destruction of dogs and cats bitten by rabid animals.
- To implement a proper waste management.
- To stimulate the research community to perform operational research to help policymakers focus on reducing the potential of animal bites in the community as an expected outcome.
- Young children should never be left unattended around any dog, and need to be supervised closely.
- Children need to be taught to respect animals, to avoid stray ones, and to be aware of their potential to cause injuries.

Incidence of dog bites were significantly reduced after implementation of stray dog sterilization program in Jaipur during 2003–2011, by reducing the overall population of the stray dogs as well as by reducing the maternal protective behavior resulting from the lack of puppies. An organized animal injury (and thus rabies) control program has started taking shape in Tamil Nadu, the same needs to be widened on national level.

### Monkey Bites

As for dogs, the population control may be the ideal and ultimate goal. However, following strategies may help avoid monkey attacks and bite injuries:

- Monkeys consider showing teeth as a sign of threat and aggression. Smiling at them may provoke an unnecessary attack, and thus should be avoided.
- The primary reason that children are bitten by monkeys is because they do not drop something that a monkey has grabbed. Children should be advised to let the things go as soon as a monkey grabs something, chances are they will examine it and drop it anyway.
- Children should be instructed not to offer feed to monkeys, it will attract many more and likely to attack in group.

### Cattle-related Injuries

Public awareness program based on the findings of operational research on interventions aiming to reduce cattle-related injuries and to limit its impact in the existing occupational and health-care scenarios may be helpful. Parents in farming community may be advised to consider the age, physical and mental abilities of the child while assigning a job to him or her for its safe accomplishment. Efforts to educate and create awareness among children and their parents about cattle handling skills, recognition of animal behaviors, danger signs and mechanisms to avoid them can reduce incidence of injury. Adequate supervision of children in their farm activities may avert many mishaps. Wearing protective gear while herding and moving the cattle or back-riding are other preventive measures. North American Guidelines for Children's Agricultural Tasks have been developed to help guide child safety in agricultural sector and to identify which tasks can safely be performed by children of various ages and skills. These guidelines may be worked upon for their possible adaptation in South Asian countries to prevent cattle-related injuries to children.

Many cattle-related injuries are patterned, predictable and preventable. Thus a systematic approach involving workable modifications in the child, the cattle and the environment relevant to the existing socio-economic and health-care scenarios is desirable.

#### IN A NUTSHELL

1. Animal-related injuries may be broadly classified as *small-animal bite injuries* and *large-animal-related injuries*.
2. Dog bite is the most common injury followed by those from monkeys, cattle and wild animals.
3. Rabies is the most significant complication of animal bite injuries; India contributes maximum human rabies cases in the world. Tetanus is the next most important in unimmunized children.
4. Wound management is of maximal value when applied immediately after bite (within minutes if possible); however it must be done even after several hours or days of the bite.
5. All Category II and III bite injuries from dogs, monkeys, cats, and rats need systemic antibiotics regardless of evidence of infection.
6. A comprehensive dog bite control program is the need of the hour.

#### MORE ON THIS TOPIC

- Ginsburg CM. Animal and human bites. In: Kliegman RM, Stanton BF, Schor NF, St Geme III JW, Behrman RE. Nelson Textbook of Pediatrics. 19<sup>th</sup> ed. Philadelphia: Saunders; 2011. pp. 2454-7.
- Gururaj G. Injuries in India: A national perspective. From: [http://www.nimhans.kar.nic.in/epidemiology/doc/ep\\_ft23.pdf](http://www.nimhans.kar.nic.in/epidemiology/doc/ep_ft23.pdf). Accessed September 13, 2014.
- Hemagiri K, Someshwar GM, Karinagannavar A. An epidemiological study on dog bite and its management in Bellary, Karnataka. J Commun Dis. 2012;44:15-23.
- Hendricks KJ, Adekoya N. Non-fatal animal related injuries to youth occurring on farms in the United States, 1998. Inj Prev. 2001;7:307-11.
- Ichhpujani RL, Mala C, Veena M, et al. Epidemiology of animal bites and rabies cases in India. A multicentric study. J Commun Dis. 2008;40:27-36.
- Jyoti, Goel MK, Vashisht BM, Khanna P. Pattern and burden of animal bite cases in a tertiary care hospital in Haryana. J Commun Dis. 2010;42:215-8.
- Stafford KJ. Cattle Handling Skills. 2005. From: [http://www.acc.co.nz/PRD\\_EXT\\_CSMP/groups/external\\_ip/documents/publications\\_promotion/wim2\\_065192.pdf](http://www.acc.co.nz/PRD_EXT_CSMP/groups/external_ip/documents/publications_promotion/wim2_065192.pdf). Accessed September 13, 2014.
- Tak SR, Dar GN, Halwai MA, Mir BA. Injuries from bear (Ursus thibetanus) attacks in Kashmir. Ulus Travma Acil Cerrahi Derg. 2009;15:130-4.
- Watts M, Meisel EM, Densie IK. Cattle-related trauma, injuries and deaths. Trauma. 2014;16:3-8.



## Chapter 10.4

### Pediatric Burns

K Mathangi Ramakrishnan, V Jayaraman,  
T Mathivanan, V Srinivasan

The wide age range of children makes the study of epidemiology of pediatric burns very unique. Some centers are reporting suicidal burns in adolescents. These suicides are usually due to failures in examinations and emotional involvements. An update in epidemiological survey needs to be done at least once in 5 years.

#### EPIDEMIOLOGY AND ETIOLOGY

Epidemiological data provides vital information and helps us to plan preventive strategies. The important areas to be analyzed are the total number of cases burnt, place of injury, type of residential area from where they come, seasonal variations, apart from age, percent of surface area burnt, depth and site of burns. These ultimately will help estimate accurate mortality and morbidity. **Table 1** shows the profile of Pediatric Burns at Kanchi Kamakoti CHILDS Trust hospital, Chennai over a period of 20 years. The major etiology of burns is due to flame, scalds, electrical injury, chemicals and radiation.

#### EMERGENCY ROOM MANAGEMENT OF MAJOR BURNS

Although burn injuries that cover 25% or more of the body surface area (BSA) are considered as *major burns*, any burn injury more than 10% should be treated similarly. Majority of childhood burns are evaluated and resuscitated initially in the emergency department. Mortality in burn injuries is to a large extent influenced by the initial care given in the emergency department. Burn victims rarely die due to the burn, but this can occur because of associated trauma, carbon monoxide (CO) inhalation or airway compromise.

#### Initial Steps in the Management of a Major Burn

The burn injury must not distract from a sequential assessment otherwise serious injuries can be missed easily. A methodical initial approach to burn treatment is needed regardless of the etiology of the burn and is essential to prevent mortality and includes: primary

survey; investigations; pain management; secondary survey and focused history; and safe transfer to a specialized burns facility.

#### Primary Survey—ABCDE

The primary assessment, investigation and treatment of a patient with severe burns should be a continuous and integrated process. A modified *Pediatric Advanced Life Support* is performed with particular emphasis upon airway and breathing.

**A—Airway with cervical spine precautions** It is important to ensure and maintain an adequate airway, taking precautions for cervical spine stabilization and to provide humidified oxygen by mask or endotracheal intubation. Fire burns often have an inhalational and airway component. If a patient's physical examination and history indicate airway injury, a thorough assessment of the airway and placement of an advanced airway if required is indicated. It is mandatory to stabilize the cervical spine if the history and clinical examination are suggestive of injury (**Box 1**).

#### BOX 1 Symptoms and signs of respiratory tract injury

- Altered consciousness
- Stridor/hoarseness/harsh cough
- Tachypnea/dyspnea
- Singed eyebrows/eyelashes
- Soot in the nostrils/sputum
- Dysphagia/deep burns of face/neck/upper chest
- Expiratory rhonchi.

Children are especially prone to airway compromise due to their narrower airway and any mucosal swelling or fluid accumulation causes a comparatively larger reduction in airway diameter. In addition, there is a high incidence of occult upper airway obstruction caused by enlarged adenoids and tonsils, laryngomalacia and reactive airways in children. Intubation is preferred before airway closure rather than in the emergency setting once the airway has been lost. Stridor is a late sign. Supraglottic airway injury is usually the result of direct thermal injury.

Bronchoscopic visualization of the airway is recommended for assessment of subglottic airway injury, directly visualizing the upper airway with a laryngoscope provides a lot of information about the nature and extent of injury. If blisters are seen in the oropharynx or oral mucosa, or the mucosa appears dry and erythematous, one should anticipate airway compromise. Edema of the airway may not be apparent until 48 hours after a burn. If the physician waits until obvious compromise, results may be

**Table 1** Profile of Pediatric Burns at Kanchi Kamakoti CHILDS Trust Hospital (September 1992–December 2013)

%BSA	Age in years		Sex		Type of burns			
	0–9	10–18	Male	Female	Scalds	Flame	Electrical	Chemical
0–10%	557	26	335	248	510	57	10	7
11–20%	197	8	95	110	176	24	4	0
21–30%	92	5	49	48	72	17	8	0
31–40%	53	8	35	25	41	11	8	0
41–50%	12	2	6	8	12	2	1	0
> 50%	8	5	6	8	7	3	3	0
Total	919	54	526	447	818	114	34	7

Abbreviation: BSA, body surface area.

catastrophic and intubation can be extremely difficult. During intubation, it is important to have various size endotracheal tubes available and anticipate a narrowed airway. However, it is important to remember that unnecessary intubation and sedation can worsen the situation, so a decision to intubate must be made carefully.

Patients in whom complete respiratory obstruction have already occurred or intubation is unsuccessful, immediate cricothyrotomy or *mini* tracheostomy is required followed by formal tracheostomy. Also the emergency care provider must remember to place a nasogastric or orogastric tube in those patients who are comatose as they tend to have gastric dilatation, which can interfere with ventilation or cause aspiration into the airway.

**B—Breathing** All burn victims should receive 100% oxygen through a nonrebreathing mask on presentation. Respiratory system injury involving the lungs and chest can occur due to an inhalation, aspiration or direct thermal, electrical or chemical injury. It is important not to rely on chest radiograph because it is often normal at initial presentation. Respiratory system involvement below the glottis can cause problems in breathing and can have any of the following manifestations:

- Lower airway edema and irritation as a result of chemicals or toxins such as smoke inhalation leading to chemical pneumonitis.
- Carbon monoxide poisoning (which cannot be detected by pulse oximetry) can occur in all patients who are victims of house or indoor fires.
- Blast lung injury or penetrating injuries causing pneumothorax can be the initial presentation.
- Circumferential burns to the chest, which can cause respiratory compromise.

**C—Circulation** The greatest amount of fluid loss is in the first 24 hours after injury and there is a shift of fluid from the intravascular to interstitial compartment in the first 12 hours, hence any fluid given during this period will rapidly leave the intravascular compartment.

- Intravenous access should be obtained immediately in intact skin. If necessary though, catheters may be placed through burned skin or intraosseous access can be used.
- The most serious complication that can occur during intraosseous administration of fluids in a burn victim is the inadvertent administration of fluid into the muscle compartments, leading to dangerously high pressures.
- Cardiac assessment in the burned child begins with the assessment of peripheral, followed by the central pulses. It is important to remember that full-thickness burns to extremities can cause a tourniquet effect making assessment of perfusion difficult. The color of skin and capillary refill in nonburned sites can be utilized, to assess for adequacy of perfusion.
- Vital signs may be difficult to obtain since burned extremities may impede the ability to obtain a blood pressure reading by a sphygmomanometer. In these situations arterial lines, particularly femoral lines, can be placed to monitor continuous blood pressure readings.

**D—Disability** Neurological disability is assessed using alert, voice, pain, unresponsive (AVPU) or Glasgow Coma Scale. Altered sensorium may be due to hypoxia, hypovolemia or dyselec-trolytemia and sepsis if the patient presents late to the emergency room.

**E—Exposure** This involves a detailed examination of the patient after the initial stabilization of airway, circulation and disability.

The patient should be examined from head to toe, including the back for an accurate estimate of the burnt area. Associated injuries should be identified. Care should be taken to avoid hypothermia. Photographs should be taken if possible without compromising patient care whenever possible.

### Secondary Survey

This is done after primary survey and initial stabilization of the patient and involves assessment of the burnt area and concomitant injuries. A history should be elicited—the quickest way is to get an **AMPLE** history which includes **A**llergy history, **M**edications, **P**roblems, **L**ast meal time and the **E**vent (the mechanism of the burns and treatment received so far).

### Focused History in Burns

The most accurate description of events leading to the burn injury can be taken first hand from those who accompany the child in the emergency room. It should include:

- Type of agent that caused the burn (flame, liquid, electrical, chemical)
- Risk of inhalational injuries (burns in a closed space)
- If there was any explosion
- Time of injury and contact with energy source
- Risk of concomitant injuries (e.g., fall from height)
- Time and nature of cooling, first aid and fluid resuscitation given.

### Assessment of Total Body Surface Area Burnt

This is estimated using one of the following methods. Erythema is not included in estimation of burn area.

#### The Wallace Rule of Nines (Fig. 1)

The Wallace rule of nines and palmar surface do not provide accurate estimations but provide a rapid assessment in situations where charts are not available.

#### Lund and Browder Chart (Fig. 2)

It illustrates the method for calculating the percentage of BSA affected by burns in children. This chart provides an accurate estimate of burned surface area in children and can be used if available in the emergency room also.

### Depth of Burns

Burn depth is described as superficial, partial thickness or full thickness (**Figs 3A to D**).

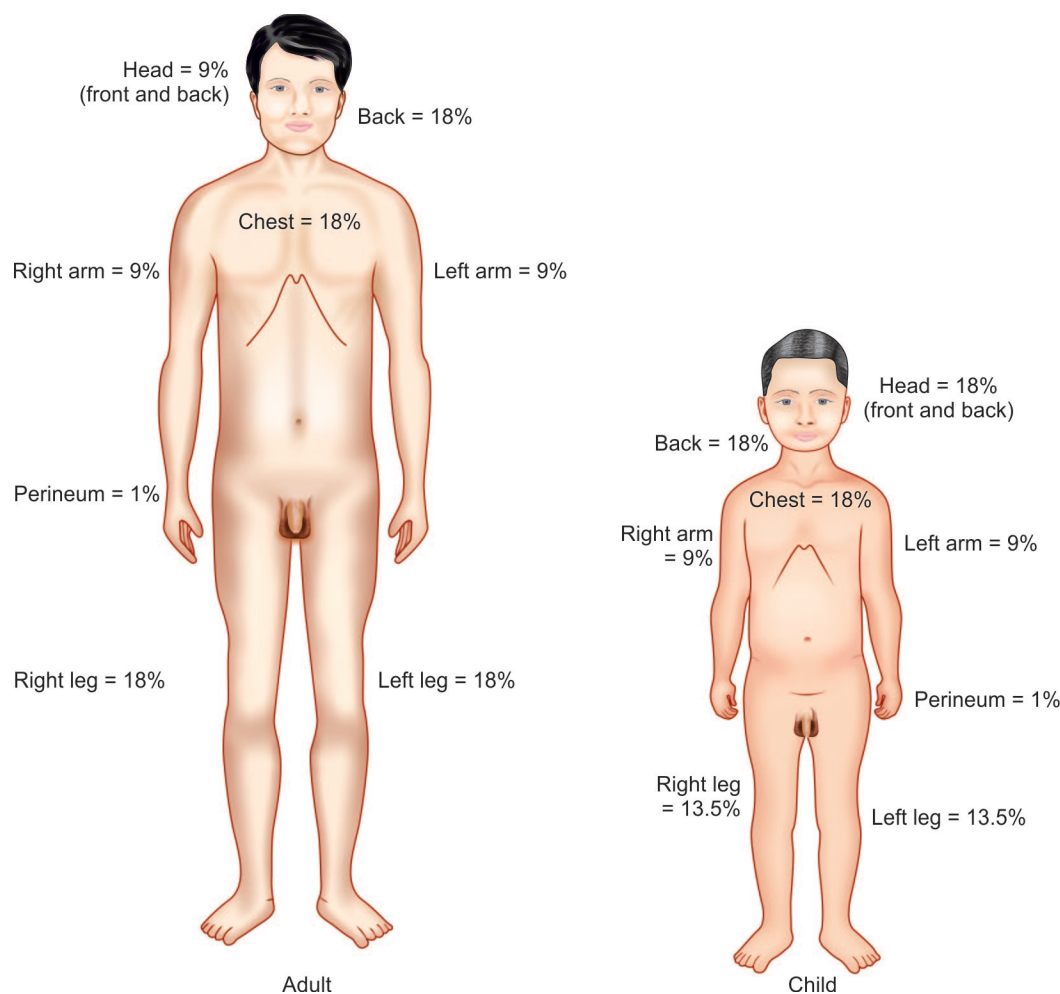
- Superficial—erythema and pain, no blisters.
- Partial thickness—red or mottled. Deep partial thickness—edematous skin with severe erythema.
- Full thickness—dry, dark appearance and leathery and may involve underlying structures including tendon, nerves, muscle, or bones.
- Deep burn needs surgical attention immediately. After escharotomy of dead tissue is done, patient's own skin or stored skin from skin bank can be used to cover the defect. This heals in 2 weeks.

Escharotomy should be done to relieve circumferential deep burns (**Figs 4A to C**).

### Fluid Resuscitation in Major Burns

#### Indications for Intravenous Fluids

- All burns of more than 15% body surface area (BSA) require intravenous fluid resuscitation to maintain adequate tissue perfusion.



**Figure 1** Wallace rule of nines

Source: Reproduced with permission from Shehan Hettiaratchy. ABC of burns. Initial management of a major burn.

- All inhalational injuries whatever the BSA require venous access to control fluid intake.
- High tension and electrical injuries need venous access for forced alkaline diuresis to avoid myoglobinuric renal damage in case of muscle injury.

### Calculation of Intravenous Fluids in Major Burns

Fluid resuscitation in the first 24 hours is based on the modified Parkland formula.

#### Parkland formula:

Total fluid requirement in 24 hours (given as Ringer lactate infusion) =  $3 \text{ mL} \times \text{total burn surface area (\%)} \times \text{body weight (kg)}$

50% given in first 8 hours

50% given in next 16 hours.

Children receive maintenance fluid in addition, at hourly rate of:

4 mL/kg for first 10 kg of body weight plus

2 mL/kg for second 10 kg of body weight plus

1 mL/kg for more than 20 kg of body weight.

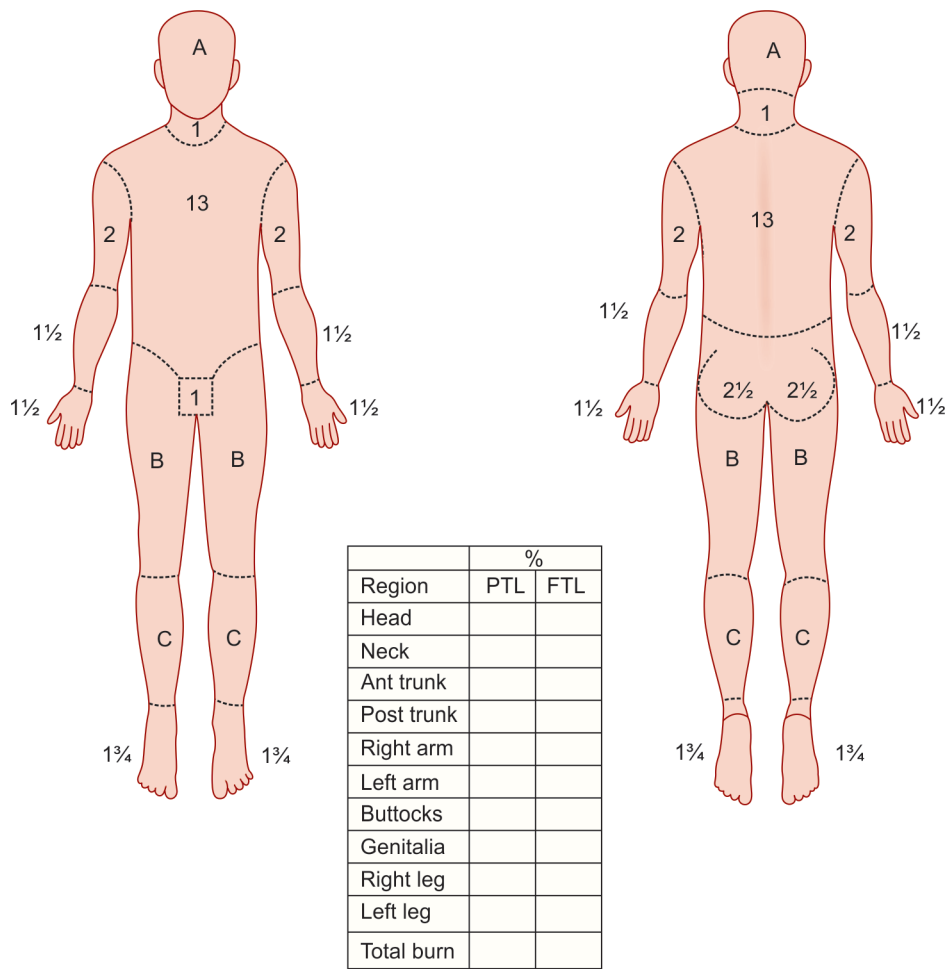
#### End point:

Urine output of 1.0 mL/kg/h in children.

The starting point for resuscitation is the time of injury and not the time of admission, hence any fluid given before admission should be deducted from the calculated requirement.

### Problems with Fluids in Children

- A burn that is 15–20% total body surface area (TBSA) can produce hypovolemic shock unless appropriately managed with crystalloid fluid replacement. Isotonic saline, most commonly lactated Ringer solution 10–20 mL/kg/h is initially infused until proper fluid replacement can be calculated. Large volumes of fluid are needed for proper resuscitation because only 20–30% of the isotonic fluid remains in the intravascular space.
- Controversy exists over the use of colloids for maintaining intravascular volume, however some resuscitation regimes use colloids if the burn is more than 85% of BSA, although it is usually administered (to replace the protein loss) after the first 8 hours as the capillary leak begins to shut down. Thus, it is necessary to appropriately calculate the extent of the burn and effectively fluid resuscitates each patient individually.
- If the patient is hypotensive, the emergency physician must be aware that it may be due to delayed presentation, cardiac dysfunction or occult blood loss and has to be managed appropriately.
- Children weighing less than 20 kg may develop hypoglycemia and should have a 5% dextrose-containing solution administered at a maintenance rate, along with the calculated volume of fluid necessary for resuscitation.



Area	Age 0	1	5	10	15	Adult
A = ½ of head	9½	8½	6½	5½	4½	3½
B = ½ of one thigh	2¾	3¼	4	4½	4½	4¾
C = ½ of one lower leg	2½	2½	2¾	3	3½	3½

**Figure 2** Lund and Browder chart for percent total body surface area burn. Be clear and accurate. Do not include erythema.

Abbreviations: PTL, partial-thickness loss; FTL, full-thickness loss.  
Source: Reproduced with permission from Shehan Hettiaratchy. ABC of burns. Initial management of a major burn.



**Figures 3A to D** Depth of burns. (A) Superficial; (B) Partial thickness; (C) Deep partial full thickness; (D) Deep burns





Figures 4A to C Escharotomy

- Catheterization and hourly measurements of urine volume are mandatory in all children with more than 10% burns.
- The color of the initial urine in patients with severe flame or high voltage electrical burns may be black, indicating hemoglobinuria or myoglobinuria, or both. This necessitates monitoring for subsequent renal dysfunction.
- It is imperative to avoid overaggressive resuscitation, particularly in small children due to the risk of pulmonary edema. This is especially important in patients who have a concomitant inhalation injury causing increased pulmonary vascular permeability.
- Because pediatric burn victims are also prone to hypothermia caused by the loss of integument, fluids administered in the emergency should preferably be warmed.

### Important Issues not to be Overlooked in an Emergent Situation

- Identifying the type of burn as thermal, chemical, electrical or radiation is essential because interventions must be appropriately tailored to the underlying cause.
- Accurate documentation of the burn location (such as ophthalmic, hand, face, inhalation, soles, or perineum) is essential for follow-up and specialist referral/consultation.
- Detailed documentation of components of the history including past medical history, medications, and allergies.
- Proper documentation from a medicolegal point is imperative and all health-care personnel are obligated to contact appropriate law enforcement and protective services if they suspect the burn was intentional.
- Intravenous antibiotics are not recommended in the initial treatment of most patients with burns, as it may increase the chance of colonization with more virulent and resistant organisms.

### INHALATION INJURY

This type of burn does not take place often in young children. During mass casualties, the people affected will include children and adolescents. Inhalation injury in burns includes: (a) thermal injury to upper airway; (b) asphyxiations in major fire accidents; and (c) smoke inhalation injury.

Amongst all these, smoke inhalation injury needs explanation. If the fire accidents occur in closed places or in a mass casualty, where there are less chances of  $O_2$  in the atmosphere due to dense smoke, smoke inhalation injury occurs. Products of combustion when plastic products or upholstery gets burnt, they emit a smoke consisting of two deadly chemical compounds namely hydrogen cyanide and CO. These obnoxious gases enter the blood stream instantaneously when the fire occurs in a closed room. CO binds to cardiac myoglobin which results in marked reduction in myocardial oxygen utilization.

Hydrogen cyanide causes tissue asphyxiations through the inhalation of intracellular cytochrome oxidase. This blocks the final step in oxidative phosphorylation and prevents mitochondrial oxygen use. Early diagnosis of the pulmonary injury is essential for survival and is primarily clinical. Primary surgery and energetic treatment with pediatric intensive care unit (PICU) is vital. As soon as the diagnosis is made, the child should be ventilated. The mortality is very high in children with inhalation burn injury.

### BURN WOUND INFECTION

#### Microbiology

Initially burn wounds are sterile but very quickly they become colonized. Subsequently, noninvasive wound infection develops and may progress into invasive sepsis. Limited infection with purulent discharge underneath a burn eschar invades the surrounding normal tissues. Bacteremia causes sepsis and ultimately damage to several organ systems. The prevalence of bacteria differs between burn units. The organisms observed at our center are summarized in **Table 2**. The types of organisms and the seasonal variation are all dictated by the location of the burn unit, city and country. In Chennai, the most prevalent microorganism was *Pseudomonas* (**Figs 5A to C**). Some cultures were found to be extended spectrum  $\beta$ -lactamase-producing types, which are difficult to treat. In spite of adequate treatment, resistant strains do develop.

**Table 2** Microorganism cultures from burn wounds

Gram-negative	<i>Pseudomonas aeruginosa</i> , <i>Klebsiella</i> , <i>E. coli</i> , <i>Acinetobacter</i> spp.
Gram-positive	<i>Staphylococcus aureus</i>
Fungus	<i>Candida</i> spp.

#### Clinical Staging of Burn Wound Infection

Regular monitoring of burn wounds allows early recognition of infection. The American Burn Association recently published criteria for the diagnosis of sepsis and wound infections. Local signs include conversion of a partial-thickness injury to full-thickness wound, worsening cellulites of surrounding normal tissues, eschar separation, and tissue necrosis. The various stages of burn wound infection include wound colonization, wound infection, invasive infection, cellulites, and necrotizing infection/fasciitis.

#### Burn Wound Colonization

Wound colonization is characterized by the presence of low concentrations of bacteria on the surface without invasion or systemic signs or symptoms of infection. Tissue biopsies obtained from colonized but not infected skin usually reveal less than  $10^5$  bacteria per gram of tissue.



**Figures 5A to C** Various manifestations of *Pseudomonas* infection. Origin is from IV line site

### Noninvasive Infection

Wound infection is associated with higher concentration of bacteria ( $> 10^5$  bacteria per gram of tissue) within the wound or wound eschar.

### Invasive sepsis

An invasive infection includes concentrations of bacteria (frequently  $> 10^5$  bacteria per gram of tissue) at an appropriate depth of the burn wound to cause supportive separation of the eschar or graft loss with involvement of unburned tissue or the presence of a systemic response consistent with sepsis.

### Sepsis

The word *sepsis* used in association with burn wounds indicates burn wound infection. An exaggeration of this status defines *severe sepsis*, which is indicative of deep invasion that can rapidly progress into septic shock and has traditionally been defined as sepsis plus multiple organ dysfunction syndrome (MODS). Systemic manifestations of sepsis are the same as those for systemic inflammatory response syndrome.

In children the transition from sepsis to severe sepsis is brisk and very difficult to identify. Following careful and rapid assessment, we have included both stages into one and children were managed aggressively whenever the early signs of wound sepsis were identified. Sepsis is a presumptive diagnosis. Antibiotics are usually started and a search for the cause of infection is initiated. Pathognomonic signs and symptoms include the following:

- Temperature more than  $39^{\circ}\text{C}$  or less than  $36.5^{\circ}\text{C}$
- *Progressive tachycardia*: In children less than 2 SD above age-specific norms
- *Progressive tachypnea*: In children more than 2 SD above age-specific norms
- *Thrombocytopenia*: In children less than 2 SD below age-specific norms
- Hyperglycemia
- Inability to continue enteral feedings more than 24 hours.

To confirm the diagnosis a documented infection must be identified from a culture, pathological tissue, or by a clinical response to antimicrobials.

### Septic Shock

Rapid systemic spread of infection will lead the child to the next phase of septic shock. The child appears very sick with high temperature and MODS, acute respiratory distress syndrome, pneumonia, and reduced urinary output necessitating PICU care. Indicated investigations include complete blood count, serum proteins, wound culture (surface swab, tissue biopsy), blood

culture, and serum procalcitonin level. Samples for culture are taken on admission, at 7 days, and at weekly intervals thereafter. In the presence of sepsis and septic shock, if blood cultures are positive, repeat cultures are done after the antibiotic regimen is completed.

### Treatment of Infectious Complications

#### Antibiotic Administration

As soon as a child with more than 10% TBSA burn is admitted, an immediate surface swab is taken for Gram stain and culture sensitivity. Prophylactic antibiotics are not given except at the extreme of ages or in case of smoke inhalation injury. Aggressive therapy is initiated whenever early signs of wound sepsis are identified. Initial choice of antibiotics is based on the Gram stain and the known sensitivity of the local microbial flora. Subsequently, antibiotic therapy is adjusted according to the culture results.

The initial antibiotic administration for children with burns and sepsis usually includes meropenem and vancomycin. Subsequently, at the conclusion of each antibiotic regimen, repeat cultures, either burn wound surface swab or blood, are done. For children in intensive care unit (ICU) for 5 weeks, surveillance for fungal infection is performed both with blood and catheter tip cultures. If fungal infection is proven, antifungal therapy is also administered.

#### PICU Management of Septic Shock in Burns

Patients are usually admitted to the PICU after a variable period of hospitalization and treatment on a regular ward. As per the approved antibiotic policy, broad-spectrum antibiotics are started immediately, aimed at treating the most common organisms prevalent in our hospital. This usually includes a  $\beta$ -lactam/ $\beta$ -lactamase inhibitor (BL-BLI) such as piperacillin/tazobactam and vancomycin. If the patient has been earlier exposed to BL-BLI combinations, a carbapenem substitute, such as meropenem, is given. In cases of prolonged hospital stay, colistin is usually added to treat *Acinetobacter baumannii*. Antifungal agents to treat *Candida* species, such as amphotericin B or an echinocandin, are also used empirically in patients who have had a prolonged hospital stay and have been exposed to multiple antibiotics. Further antimicrobial therapy is guided by the culture and sensitivity reports. Wounds are grafted only after colony counts from tissue cultures have decreased to acceptable levels. Sometimes during therapy, new microorganisms with different sensitivity patterns may develop. Moreover, a child may occasionally deteriorate despite antibiotic therapy. This could be due to immune deficiency, burn wound reaching deeper tissues such as bones and tendons, lack of proper debridement of devitalized tissues or microorganisms such as *Staphylococcus aureus* either methicillin-resistant *Staphylococcus*



*aureus* (MRSA) or methicillin sensitive forming a biofilm. A number of biofilms were detected among the MRSA infected group with recurrent infection 5 weeks after apparent recovery. For treatment of such cases, if the isolated microorganism is sensitive to more than one antibiotic, the already used antibiotic may be replaced by another one.

### Fungal Infection

If child has been in PICU with sepsis, after 3 weeks, culture is done and if found positive, antifungal treatment is continued.

## SPECIAL BURNS

### Chemical Burns (Acid, Alkali, Phosphorous, Anemia; Figs 6A to D)

These are most commonly seen to a chemical industry or as part of abuse. The chemical process continues for a longtime after the substance touches the body. Early surgical intervention is not advocated. But the vital areas (eyes) are protected with a tarsorrhaphy or soft lens to save the vision.

### Major Electric Burns (Figs 7A and B)

Major electric burns are seen in high tension electric accidents. These need immediate attention on removal of a lifeless limb. Escharotomies are done liberally, all dead tissue are removed and grafting done. These burns need ICU care.

## MANAGEMENT OF BURN WOUNDS

This varies extensively in various centers but the principle is to identify the depth of burn and extent. Then the survey in vital areas, like the face, eye and oral cavity, are performed. Airway obstructions if any is identified and details have been given earlier. Circumferential burns causing embarrassment to circulation are identified. *Nonsurgical treatment* consists of biological dressings and topical antimicrobials. *Surgical treatment* consists of primary skin grafting, secondary grafting in prolonged and infected case, reconstruction, microsurgery, and tissue expansion.

### Nonsurgical Treatment

#### Topical Antimicrobials

Superficial and superficial partial-thickness burns (**Fig. 8**) even up to 20–30% TBSA can be treated with topical antimicrobials like

silver sulfadiazine. However if any vital areas, like perineum or face, gets infected, appropriate antibiotics are given systematically after wound swab—culture and sensitivity. Circumferential burns and perineal burns would also require closed dressings.

The second degree (superficial partial-thickness burns which are circumferential must get closed dressings. Here there are a lot of topical antimicrobials used by us today. Silver sulfadiazine has been the sheet anchor for the last many years. Newer topical creams also have come in the market. The idea is to prevent infection, particularly in a closed wound, in the tropics. The dressing is changed every other day or even once a day according to soiling of the gauze.

### Collagen Dressing

Superficial and deep partial-thickness burns are treated with biologic dressings particularly collagen (**Figs 9A to E**) which is less labor-intensive and we can observe the progress of the wound daily. In certain special areas, like perineum, scrotum and groin, closed dressings may have to be used, because the membrane gets lost with dressing.

Deep partial-thickness burns need to be observed. If the area is extensive, collagen membrane can be applied (**Figs 10A to E**). But as soon as the wound healing gets delayed the membrane can be removed, excision of the burnt area and autografting should be done.

If signs of sepsis are seen, they have to be treated as per sepsis protocol mentioned earlier. If the wounds need skin grafting after infection settles, it is done as early as possible. Third-degree burns may need primary excision or tangential excision. Grafting priorities in surgical intervention are eyes, face, hands and perineum. At all cost the cornea and lens are protected with tarsorrhaphy or soft contact lens.

## Surgical Management

### Primary Surgery

In over 15% burns, all deep areas are excised and covered with autografting.

### Secondary Surgery

If the child gets into sepsis, after sepsis is cleared (blood culture negative) all the sloughed tissue can be removed and autografting is done. During surgery the child should be supported with appropriate antibiotics.



Figures 6A to D Chemical burns



Figures 7A and B Electric burns



Figure 8 Superficial and superficial partial-thickness burns

### Reconstructions

Final reconstructions like postburn contractures are released and grafted, but one has to realize that as the child grows, repeated surgeries may have to be undertaken. Microsurgical procedures may have to be done, to save the limb and function. Microsurgical free flaps also have been giving very good results in postburn contraction. *Tissue expansion* is sometimes useful for postburn scars.

### Physical Rehabilitation and Splinting

In burns, starting with respiratory physiotherapy in the early

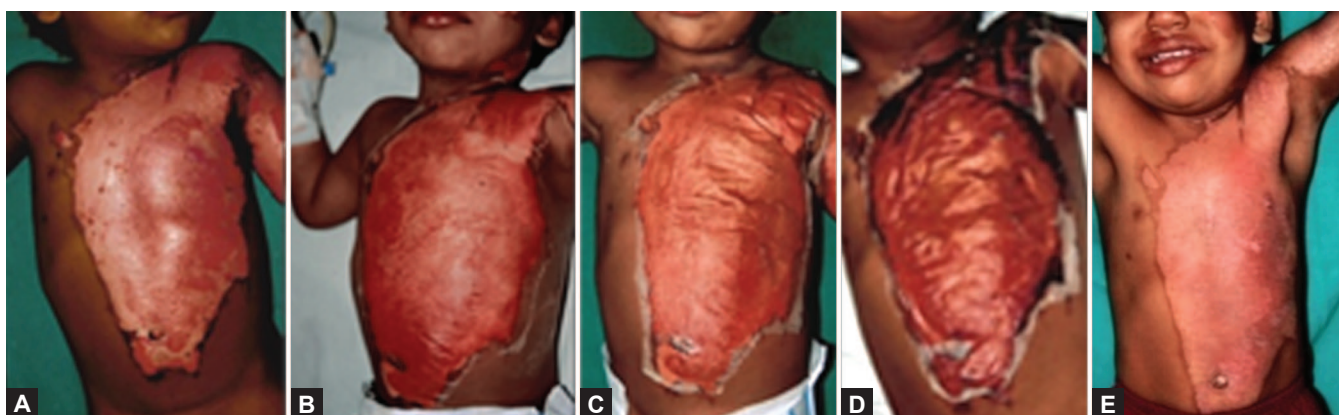
days to limb movement, and postoperative physical therapy and activated splinting also must be planned. This begins on day one of burn to the stage when child can use the part normally.

### IN A NUTSHELL

1. Although burn injuries that cover 25% or more of the BSA are considered as *major burns*, any burn injury more than 10% should be treated similarly.
2. A methodical initial approach to burn treatment includes primary survey, investigations, pain management, secondary survey and focused history, and safe transfer to a specialized burns facility.
3. Assessment of total body burnt surface area in children can be done by Lund and Browder chart.
4. All burns of more than 15% BSA require intravenous fluid resuscitation to maintain adequate tissue perfusion.
5. Regular monitoring of burn wounds is important for early recognition of infection; which needs to be treated aggressively and immediately. Prophylactic antibiotics are not indicated as a routine.
6. *Nonsurgical treatment* consists of biological dressings and topical antimicrobials. *Surgical treatment* consists of primary skin grafting, secondary grafting in prolonged and infected case, reconstruction, microsurgery, and tissue expansion.

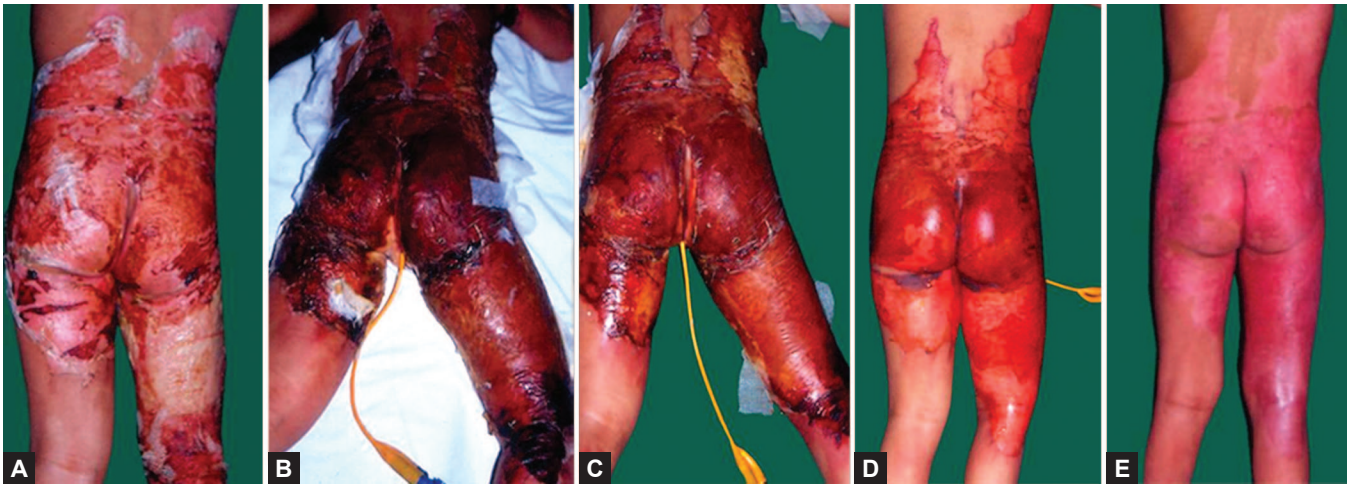
### MORE ON THIS TOPIC

- Chavez BS, Terrance S. Antibacterial agents in pediatrics. *Infect Dis Clin N Am*. 2009;23:865-77.
- Greenhalgh DG, Saffle JR, Holmes JHT, et al. American Burn Association Consensus Conference to define sepsis and infection in burns. *J Burn Care Res*. 2007;28:776-90.
- Hanumandass ML, Ramakrishnan MK. *Paediatric Burns: Total Management of the Burned Child*. Hyderabad: Paras Publishers; 2011.
- Heimbach DM, Waeckerle JF. Inhalation injuries. *Ann Emerg Med*. 1988;17:1316-20.
- Hettiaratchy S. ABC of burns: Initial management of a major burn: I—overview. *BMJ*. 2004;328:1555-7.
- Hettiaratchy S. ABC of burns: Initial management of a major burn: II—assessment and resuscitation. *BMJ*. 2004;329:101-3.
- Ramakrishnan MK, Sankar J, Venkatraman J. Infections in burn patients—experience in a tertiary care hospital. *Burns*. 2006;32:594-6.
- Reed JL, Pomerantz WJ. Emergency management of pediatric burns. *Pediatr Emerg Care*. 2005;21:118-29.
- Sinha J, Sinha S. *Handbook of Burns Management*. New Delhi: Jaypee Brothers; 1991.



Figures 9A to E Collagen dressings for superficial partial-thickness burns treated with collagen. (A) 1st day; (B) 3rd day; (C) 6th day; (D) 11th day; (E) 13th day





**Figures 10A to E** Deep partial-thickness burns treated with collagen dressing. (A) 1st day; (B) 2nd day; (C) 3rd day; (D) 9th day; (E) 13th day

## Chapter 10.5

# Cold Injuries

Manu Madhok, Shruti Kant

Cold exposure can produce various injuries in children as a result of limited adaptability to cold stress. Cold injuries can broadly be divided into localized injury to a body part or parts (peripheral cold injuries), generalized cooling of the entire body (hypothermia), or a combination of both. Early recognition and appropriate treatment is imperative for optimal outcome.

### EPIDEMIOLOGY

Frostbite is well documented in the military records and reported in countries with extremes of temperature for centuries. The earliest documented evidence of frostbite dates back to a 5,000-year-old pre-Columbian mummy discovered in the Andes. The first detailed report of multiple cold injuries was by Baron Larrey, surgeon-in-chief to Napoleon's army during the invasion of Russia in the winter of 1812–1813. The epidemiology of cold injuries is not well documented in medical literature from India and SE Asia. However, there are multiple media reports related to cold exposure every year in northern India and Himalayan range. A published case series describes 234 cases of cold injuries in a 2-year period, seen at Army Hospital in Leh, Ladakh. In United States, the Centers for Disease Control and Prevention reports that between 1979 and 2002, a total of 16,555 deaths in the United States (an average of 689 per year; range: 417–1,021) were attributed to excessive natural cold exposure, an annual death rate of 0.2 per 100,000 population. Exact incidence of cold water drowning and accidental hypothermia is unknown, but it is a low frequency event but common in childhood and boys more commonly involved than girls. The data from 1995–2004 National Hospital Ambulatory Medical Care Surveys revealed an estimate of 15,574 visits to *emergency department* related to hypothermia and other cold injuries in the United States.

### ETIOLOGY

Heat loss occurs from the body by radiation, conduction, convection, evaporation, and respiration. Children are at a higher risk for cold-related injuries and hypothermia than adults because of a smaller ratio of body mass to surface area, leading to increased heat loss; decreased ability to recognize or avoid dangerous environmental conditions; limited glycogen stores in young children to support increased heat production and the inability to increase heat production through shivering in infants. **Table 1** summarizes the risk factors for hypothermia. However, young children have an advantage of neuroprotective effect and more likely than adults to have good neurologic outcomes, despite severe or profound hypothermia. Prolonged cold exposures and temperatures below freezing point produce peripheral cold injuries. The extent of injury is proportional to the exposure and range from frostnip, to chilblains, to immersion foot, to frostbite. The infants or young children are at greater risk because of immobility and higher surface area-to-mass ratio (children) but frostbite is seen more commonly in young adults between the ages of 30 years and 49 years, most likely due to increased exposure to cold or risk-taking behavior. It is also increasing within the civilian population from participating in winter sports such as skiing, hiking, mountain and ice climbing with limited experience or inadequate preparation and protection.

**Table 1** Risk factors for hypothermia

Child-specific	Predisposing	Environmental factors
Large body surface area relative to mass leading to excessive heat loss	Underlying medical conditions, malnutrition	Extreme cold temperatures
Lack of glycogen stores and shivering capability in infants	Lack of education/awareness about appropriate clothing	Wind chill
Lack of cognitive skills for seeking shelter	Use of intoxicating substance and risk taking behavior	Wet cold conditions
Lack of supervision by caregivers	Improper storage of chemicals and not using protective equipment	Sudden weather changes

### PERIPHERAL COLD INJURIES

#### Frostnip

Frostnip is the mildest form of peripheral cold injury and involves acral areas like nose, ears, hands, and feet. Frostnip is caused by prolonged exposure to cold air in the exposed body parts like in skiers and children standing outside waiting for school bus. It presents as erythema and pain, like a first-degree burn, numbness, itching or burning sensation in hands, feet, toes, fingers, face, nose and ears. Simple warming either by pressure of a warm hand or by placing the hand in the axilla or wrapping in a warm clothing is sufficient treatment.

#### Chilblain (Perniones)

Chilblain represents a more severe form of cold injury than frostnip. It also occurs after exposure to nonfreezing temperatures and damp conditions. The etiology is idiopathic and auto-immune in some cases and precipitated by cold exposure and moisture. The surface of unprotected extremities, such as the hands, feet, and face develop capillary bed damage and show red-to-violaceous raised lesions of vasculitis. Blisters, erosions, or ulcers are sometimes seen. The lesions usually resolve spontaneously in 1–3 weeks, but they may recur in some individuals (Raynaud's phenomenon). Management involves local heat, gentle massage, and moisturizers to keep the skin supple. Nifedipine may be used to reduce the pain and speed the healing of the lesions.

#### Immersion (Trench) Foot

Immersion foot or trench foot is a disease of the sympathetic nerves and blood vessels in the feet. It is mostly seen in persons whose feet have been wet, but not freezing, for prolonged periods. The symptoms include numbness and tingling pain with itching, progressing to leg cramps and complete numbness. Initially, the skin is red, it becomes progressively pale or blotchy and then cyanotic. The progression of this cold injury has three stages. The first is a prehyperemic phase, lasting for a few hours to a few days, in which the limb is cold, slightly swollen, discolored, and possibly numb. Major pulses are barely palpable. The second, or hyperemic phase, lasts 2–6 weeks. It is characterized by bounding, pulsatile circulation in a red, swollen foot. The third, or posthyperemic, phase can last for weeks or months. The limb may be warm, with increased sensitivity to cold. The injury often produces a superficial, moist gangrene.

Management of this injury involves gentle washing and air-drying of the feet, slow rewarming, bed rest, and slight elevation

of the extremity. Improvement occurs within 24–48 hours, but may take 1–2 weeks to resolve completely. Early physical therapy is crucial. The patient should be forewarned that subsequent cold exposure will preferentially affect the previously injured area.

## FROSTBITE

Frostbite is a freezing, cold thermal injury, which occurs when tissues are exposed to temperatures below their freezing point (typically  $-0.55^{\circ}\text{C}$ , but can occur at as high as  $2^{\circ}\text{C}$  for a sustained period of time. Severity of injury depends on factors such as absolute temperature, wind chill, duration of exposure, wet or dry cold, immersion, clothing quality and patient comorbidities such as smoking, peripheral vascular disease, neuropathies, Raynaud's disease, mental health issues, alcohol and substance abuse and dementia. The risk of frostbite is correlated with ambient temperature and wind speed contributing to wind chill. This is likely when temperature (includes wind chill) drops to less than  $-20^{\circ}\text{C}$  ( $-4^{\circ}\text{F}$ ).

## Pathophysiology

The pathophysiology of frostbite can be described in four overlapping pathologic phases: prefreeze, freeze-thaw, vascular stasis, and a later ischemic phase. In the initial pre-freeze state, there is a considerable decrease in blood flow because of skin cooling and vasoconstriction. This does not involve the formation of actual ice crystals. Next, in the freeze-thaw phase, there is intra or extracellular ice crystals formation leading to protein and lipid derangement, cellular shifts of electrolytes and endothelial cell damage. The thawing process brings about ischemia-reperfusion injury and the inflammatory response. There is a release of prostaglandin F<sub>2</sub> and thromboxane A<sub>2</sub> causing platelet aggregation and vasoconstriction. After tissue thawing, in the vascular stasis phase, vasodilation and leakage from capillaries occur, causing tissue edema. Alternating freeze-thaw cycles potentiate the vascular injury and lead to ischemia. Finally, in the later ischemic phase of frostbite, there is tissue ischemia and infarction due to an inflammation response, intermittent constriction of arterioles and venules, and a continued reperfusion injury. Tissue necrosis that follows frostbite is due to either cellular injury or secondary to a vascular lesion.

## Clinical Features

The hands and feet are affected in over 90% of injuries. The injuries have been classified in grades to help with management. Commonly used classification grades frostbite injury into two types: superficial or deep. Superficial frostbite (first- and second-degree frostbite) involves the skin and subcutaneous tissues. The skin feels cold, waxy white, and does not blanch. The frozen part is numb but becomes painful and flushed with thawing. Within the first 24 hours, edema develops and blisters or bullae filled with serous fluid appear (**Fig. 1**). Deep frostbite (third- and fourth-degree frostbite) involves the deeper tissues of muscle, tendons, neurovascular structures, and bone, along with the skin and subcutaneous tissues. The frozen part is hard, numb and appears gray-blue, or mottled. It remains unchanged even after rewarming. Edema develops over next 24 hours, but bullae may not be present. They may appear later and have hemorrhagic fluid (**Fig. 2**).

## Approach to Diagnosis

Patients with frostbite frequently have associated multisystem injuries like systemic hypothermia, blunt trauma, alcohol or substance abuse, etc. The health-care providers should obtain a detailed history of exposure and comorbid conditions to determine associated injuries and appropriately treat most



**Figure 1** Frostbite superficial (second degree)

Source: Hota PK, Singh KJ. Management of cold injuries. Surgical Research Updates. 2013;1:20-25.



**Figure 2** Frostbite deep (third degree)

Source: Hota PK, Singh KJ. Management of cold injuries. Surgical Research Updates. 2013;1:20-25.

life-threatening injuries first. Accurate vital signs with core temperature determination and clear description of injury using standard anatomic terminology are important. Taking pictures of lesions help with monitoring progression and minimize tissue manipulation when multiple providers need to evaluate the injury. Imaging and laboratory tests are helpful in identifying associated injuries.

## Management

### Prehospital

The patient must be removed from cold environment. All cold and wet clothing or boots, etc., must be removed. The affected areas should be immobilized and covered with dry clothing, socks and gloves. One can attempt to warm the cold extremity by placing it in a companion's armpit or groin for 10 min but rubbing or massage should be avoided. Removal of jewelry from affected digits can be attempted. Field rewarming should only be attempted if there is no further risk of refreezing as tissue that thaws then refreezes results in more extensive injury.



## Hospital

Patient should be re-evaluated on arrival to a hospital and any associated trauma or hypothermia must be assessed and managed before frostbitten extremities are treated. Moderate or severe hypothermia should be corrected to bring core temperature above 35°C before initiating frostbite warming. Tetanus prophylaxis, aspirin, pentoxifylline and ibuprofen for antiplatelet, rheologic and prostaglandin effects, and pain control with narcotics, hydration with warm fluids should be addressed.

## Rewarming

Hot water bath at 39–42°C (102.2–107.6°F) is recommended for rewarming with attention to aseptic techniques and close monitoring of water temperature. The frostbitten tissue is removed when it appears flushed indicating return of perfusion. It may take 30–45 min. Active movement of frostbitten area is encouraged to assess tissue pliability. After cleansing of tissue and wounds, a dry dressing and splinting is recommended. Debridement of blisters is still controversial. For deep frostbite (third- and fourth-degree), antibiotic prophylaxis is recommended and hyperbaric oxygen therapy if often utilized. Imaging with angiography, magnetic resonance angiography and technetium-99 (99Tc) triple phase bone scanning help visualize vascular occlusion and demarcation of ischemic area. This is helpful in prognosis and directing surgical therapy or thrombolytic therapy. Published studies to evaluate the safety and efficacy of tissue plasminogen activator (rTPA) in the treatment of severe frostbite found that rTPA and heparin after rapid rewarming is safe and reduced predicted digit amputations, especially when initiated within 24 hours.

## Complications and Long-Term Effects

Compartment syndrome may require fasciotomy. It may take 6–12 weeks for demarcation of ischemic tissue, which may lead to amputation. Localized osteoporosis and subchondral bone loss may be seen and is of significance in children as the damage may lead to undergrowth of affected bone and development of early arthritis. Chronic regional pain is a common sequel after frostbite. The tissue after recovering from frostbite is more susceptible to subsequent freezing injury. The patients should be educated about this risk and cold sensitivity.

## HYPOTHERMIA

Hypothermia is defined as a core body temperature below 35°C (95°F). Hypothermia in children is easy to overlook but significantly impacts optimal management of underlying disease. The degree of hypothermia, defined by core temperature, influences both recognition and treatment. When reliable and precise measurement of temperature is difficult, hypothermia may be determined clinically with the use of the Swiss staging system. The definitions for staging of hypothermia are given in **Table 2**.

**Table 2** Staging of hypothermia

Degree	Temperature	Clinical findings per Swiss staging system
Mild (Hypothermia I)	Core temperature 32–35°C (90–95°F)	Impaired consciousness, shivering
Moderate (Hypothermia II)	Core temperature 28–32°C (82–90°F)	Impaired consciousness, not shivering
Severe (Hypothermia III)	Core temperature below 28°C (82°F)	Unconscious, not shivering, vital signs present
Profound (Hypothermia IV)	Core temperature below 20°C (68°F)	Unconscious, vital signs absent

## Pathophysiology

The physiologic changes in hypothermia include the following:

- Respiration progressively becomes slow, shallow, irregular, and then absent.
- Blood volume markedly decreases causing hypovolemia. This is because of vascular leak and a *cold diuresis* secondary to inhibition of antidiuretic hormone and failure of distal tubular sodium and water reabsorption.
- Cardiac output is reduced by hypovolemia, sludging of blood due to cold, decreased myocardial contractility, and bradycardia. Also, loss of vasomotor regulation causes vasodilation and lowers systemic vascular resistance. All of these factors lead to circulatory collapse.
- Hypothermia increases myocardial irritability, making ventricular fibrillation (VF) a frequent problem in severe hypothermia. Potential risk factors for VF include rough handling of patient or patient exertion, core temperature afterdrop (further cooling of the body after being removed from cold exposure), room-temperature fluids administration, direct stimulation of the myocardium (central lines, and rewarming shock).
- Other effects of hypothermia may include thrombocytopenia, coagulopathy, hyperkalemia, hypoglycemia or hyperglycemia, and metabolic acidosis or alkalosis.

## Pathological Characteristics and Clinical Features

Physiologic and pathologic changes in body correspond to the stage of hypothermia. In *mild hypothermia*, the body copes with heat loss by shivering, vasoconstriction, and an increased metabolism. Mentation and consciousness are preserved. In *moderate hypothermia*, these compensatory mechanisms begin to fail and manifested by lack of shivering, respiratory depression, decrease in metabolism, circulatory compromise, vasodilation and altered consciousness, including lethargy, confusion, and possible *paradoxical undressing* or other irrational behavior. In *severe hypothermia*, patients usually become unconscious and vital signs may or may not be present. Muscle rigidity develops. The risk of cardiac arrest increases as the core temperature drops below 32°C and increases substantially if the temperature is less than 28°C. At 28°C (82°F) the basal metabolic rate is approximately half of the normal rate and all body functions begin to fail including circulation, ventilation, and central nervous system function.

## Differential Diagnoses (Box 1)

Hypothermia may occur from environmental exposure, trauma, medical conditions, or a combination of these.

## Trauma

It is important to measure core temperature during resuscitation and efforts should be taken to prevent heat loss. Hypothermia is caused by exposure or injury, during transport and resuscitation, especially in infants and young children with larger body surface. It is often seen when environmental exposure is prolonged (e.g., motor vehicle accidents in winter with difficult extrication). Patients with traumatic brain injury or spinal cord injury are also at risk for hypothermia because of potential damage to central and autonomic thermoregulatory systems.

## Medical Conditions

Medical conditions often produce mild hypothermia. Common etiologies associated with hypothermia in children include sepsis, hypoglycemia, hyponatremia, central nervous system pathology (e.g., craniopharyngioma, absence of the corpus callosum, intracranial bleeding), endocrine disease (e.g., hypothyroidism or adrenal insufficiency), malnutrition, anorexia nervosa and burns.



**BOX 1 Differential diagnoses of hypothermia**

- *Trauma*
  - Burns
  - Drowning
  - Intracranial hemorrhage
  - Traumatic brain injury/spinal cord injury
- *Infections*
  - Sepsis
  - Meningitis/encephalitis
- *Drug overdose*
  - Ethanol
  - Barbiturates
  - Benzodiazepines
  - Clonidine
  - Antidepressants
  - Antipsychotics
- *CNS pathology*
  - Stroke
  - Brain tumors (craniopharyngioma) and congenital malformations
  - Dysautonomia
- *Metabolic/endocrine*
  - Hypoglycemia
  - Adrenal insufficiency
  - Hypothyroidism
  - Hypoparathyroidism
  - Aminoacidemia
  - Organic acidemia.

**Sepsis**

Sepsis may present as mild hypothermia, especially in young infants and older children with chronic medical conditions or immunosuppression. These patients appear sick with lethargy, hypotension, widened pulse pressure that cannot be explained by mild hypothermia.

**Drug Overdose**

Drug overdose and toxins that may cause vasodilatation and altered mental status lead to hypothermia. Overdose of ethanol, benzodiazepines, opioids, clonidine, atypical antipsychotic medications and cyclic antidepressant medications are associated with hypothermia. It is often seen in adolescents who may become disoriented or pass out after a recreational drug use in an outdoor setting and then become hypothermic.

**Approach to Diagnosis****Prehospital Care and Triage**

Prehospital providers and medical control physicians should have a high suspicion for hypothermia in children with obvious environmental exposure and in children with altered mental status or those needing critical care. Patients should be extracted from the cold environment in a horizontal position, if possible. Prehospital providers should try to minimize further heat loss, avoid excess manipulation or patient exertion during transport as it may cause mobilization of cold and acidic blood to the heart and trigger cardiac arrhythmias or instability. Key interventions include:

- Removal of wet clothing
- Gentle insulation of the patient with warm blankets or other items (sleeping bag)
- Warming of the transport vehicle
- Provision of warm intravenous (IV) fluids.

Children with moderate hypothermia need transport to a hospital with pediatric intensive care capability. The patients with severe hypothermia should undergo transport to a hospital with active rewarming or cardiopulmonary bypass facilities like Level I designated and pediatric trauma centers.

**Hospital Care**

Standard pediatric advanced life support (PALS) and advanced trauma life support (ATLS) protocols should be followed with attention to airway, breathing, circulation, disability and exposure. Administration of heated, humidified oxygen is an acceptable therapy for all hypothermic patients.

**Investigations**

No laboratory testing is required for previously healthy children with mild hypothermia from environmental exposure. However, in patients with moderate to severe hypothermia, several laboratory parameters may be altered, and the following studies should be obtained: serum glucose, serum electrolytes, lactate, complete blood count, coagulation studies, blood type and cross match (if the need for extracorporeal warming is anticipated) and blood gas analysis. Capillary samples may be unreliable for measuring acid-base balance because of poor perfusion.

**Electrocardiogram**

Hypothermic patients should have a 12 lead electrocardiogram (ECG) and then placed on a cardiac monitor during treatment. The development of ventricular fibrillation, pulseless electrical activity (PEA), or asystole are common during resuscitation during hypothermia. Hypothermia slows impulse conduction through potassium channels leading to prolongation of RR, PR, QRS, and QT intervals. There may also be elevation of the J point, producing a characteristic J or Osborn wave (**Fig. 3**). Tomaszewski originally described the J wave in 1938 as a very slow inscribed deflection between QRS complex and ST segment, however, its clinical significance was described in acidotic and hypothermic dogs by Osborn in 1953.

**Management**

The accurate measurement of core body temperature in children with hypothermia is essential to proper treatment. Successful resuscitation of the hypothermic child requires rapid attention to supportive care (airway, breathing, circulation), assessment and treatment of injury or other medical conditions, and rewarming interventions, that vary based upon core body temperature and the presence or absence of circulation.

**Airway and Breathing**

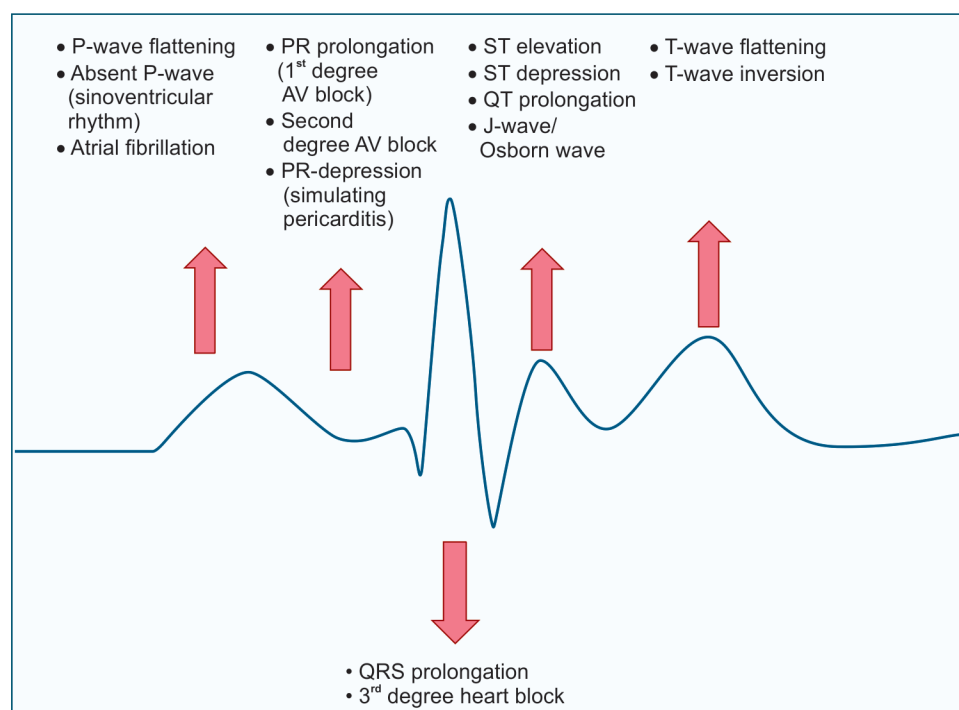
Warmed, humidified 100% oxygen [41–45°C (105.8–113°F)] via nonrebreather mask is delivered. Bag-valve-mask ventilation is reserved for children with hypoventilation and when preparing for endotracheal intubation. Endotracheal intubation is indicated in respiratory failure, uncompensated shock, or cardiac arrest.

**Circulation**

Patients with nonperfusing rhythms (asystole, PEA, VF, ventricular tachycardia without pulse) should receive chest compressions using standard rates and depths per PALS guidelines. Bedside ultrasound may be useful in assessing cardiac contractility. Sinus bradycardia, first-degree AV block, and atrial fibrillation with slow ventricular response may improve with adequate oxygenation. Cardiac pacing generally is required only if bradycardia persists despite rewarming to 32–35°C (90–95°F). The medications for bradycardia (e.g., atropine, epinephrine) may not be necessary because perfusing bradycardic rhythms usually convert to sinus rhythm with rewarming.

**Vascular Access and Intravenous Fluid Therapy**

Cold-induced vasoconstriction makes vascular access difficult, however, vascular access and aggressive volume expansion are a vital treatment for moderate and severe hypothermia. Two peripheral



**Figure 3** ECG changes in hypothermia

[Source: Chhabra L, Devadoss R, Liti B, Spodick DH. Electrocardiographic changes in hypothermia: a review. *Ther Hypothermia Temp Manag.* 2013;3:54-62.]

IV catheters (22G or bigger) should be placed for adequate access. Intraosseous needle access or central line via the femoral vein should be the next step, if peripheral access is not established.

### Warm Fluids

These patients should initially receive 20 mL/kg of heated (40–44°C) IV normal saline using high-capacity in-line warmers via rapid IV infusion methods.

### Active External Rewarming

Active external rewarming uses heating devices like radiant heat, forced hot air, warm blankets or heating pads, warm bath water, infrared heating lights or heated devices (warm packs). They should be applied to the trunk to warm the core. Active external rewarming is recommended for mild to moderate hypothermia and should be avoided for severe hypothermia.

### Active Core Rewarming

Active internal rewarming techniques are utilized for patients with moderate to severe hypothermia with core body temperature less than 30°C (86°F). This includes administration of warmed humidified oxygen, IV administration of warmed saline, peritoneal or pleural lavage and the use of extracorporeal membrane oxygenators. Left pleural lavage with heated normal saline is a preferred active internal rewarming method and is performed by placing two chest tubes in the left pleural cavity with inflow via anterior and drainage via posterior tube. Heated fluid instilled through the anterior chest tube directly warms the heart. No randomized, controlled clinical trials have been reported comparing the efficacy of these methods.

### Extracorporeal Techniques

Extracorporeal techniques include cardiac bypass and extracorporeal membrane oxygenation (ECMO) are suggested

for children with severe hypothermia and absent circulation or in patients' refractory to other techniques. Warming by cardiopulmonary bypass is the most efficient method of core heating. **Table 3** summarizes the guidelines for the management of hypothermia.

### Outcomes

Rewarming shock is a major risk of active external rewarming. Cold, acidic blood that returns to the core circulation causes a drop in temperature and pH. Rewarming shock can be life-threatening if rewarming is not accompanied by vigorous support of shock. During rewarming, significant hyperkalemia may develop especially after sustained crushing injuries.

Prediction of neurologic outcome based on physical examination in hypothermic children may be misleading. Because of the neuroprotective effects of hypothermia, the severely hypothermic child may still have good outcome. Also, prolonged intensive support (e.g., up to 5 days of ECMO) has been associated with good outcomes. Prognostic scoring systems, such as the Glasgow Coma Scale, have not proved useful for hypothermic patients, but extreme acidosis (pH < 6.6), hyperkalemia (initial K<sup>+</sup> level > 8), and lactate more than 225 mg/dL, are associated with poor outcome.

### Prevention

Hypothermia can be prevented by limiting exposure to extreme cold temperatures and using proper protection by dressing warmly and wearing layers, and changing out of wet clothes as quickly as possible. Babies and young children are more likely to get hypothermia and should wear hats and mittens in cold weather. Children should take a break to warm up while playing outside in the cold. Alcohol intoxication in adolescents is a high-risk factor for getting hypothermia. Alcohol and other chemical or drug abuse should be avoided when engaging in outdoor winter recreational

**Table 3** Management guidelines for hypothermia

<i>Prehospital</i>	<i>Hospital</i>
Quick and safe extrication	Assess patient per ATLS and ACLS guidelines
Quick assessment of ABC and initiate CPR, if needed	ABCDE and continue CPR Obtain accurate core temperature and monitor, external rewarming measures
Quick assessment of degree of hypothermia and associated injuries for appropriate transport/transfer	Warm, humidified air via patent natural airway or secure endotracheal tube
Removal of cold/wet clothing and cover with warm/dry clothing	Warm intravenous fluids via large peripheral IV or intraosseous or central access to correct for shock
Stabilize patient with minimizing tissue manipulation	Identify and correct metabolic and other medical or traumatic conditions with appropriate labs, EKG and imaging
Minimize further heat loss	Aggressive internal warming
Notification and transport to appropriate receiving facility	Consider cardiac bypass or ECMO support per institutional capability and protocols

*Abbreviations:* ATLS, advanced trauma life support; ACLS, advanced cardiac life support; ABCDE, airway, breathing, circulation, disability and exposure; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation.

activities. Secondary hypothermia in patients with sepsis and trauma can be prevented by close monitoring of body temperature, minimizing exposure and utilization of warm IV fluids and warm humidified air.

### MORE ON THIS TOPIC

- Baumgartner EA, Belson M, Rubin C, Patel M. Hypothermia and other cold-related morbidity emergency department visits: United States, 1995-2004. *Wilderness Environ Med.* 2008;19:233-7.
- Bruen KJ, Ballard JR, Morris SE, et al. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg.* 2007;142:546-51.
- Centers for Disease Control and Prevention (CDC). Hypothermia-related deaths—United States, 2003-2004. *MMWR Morb Mortal Wkly Rep.* 2005;54:173-5.
- Hallam MJ, Cubison T, Dheansa B, Imray C. Managing frostbite. *BMJ.* 2010;341:c5864.
- Handford C, Buxton P, Russell K, et al. Frostbite: a practical approach to hospital management. *Extrem Physiol Med.* 2014;3:7.
- McIntosh SE, Hamonko M, Freer L, et al. Wilderness Medical Society practice guidelines for the prevention and treatment of frostbite. *Wilderness Environ Med.* 2011;22:156-66.
- Murphy JV, Banwell PE, Roberts AH, McGrouther DA. Frostbite: pathogenesis and treatment. *J Trauma.* 2000;48:171-8.
- Twomey JA, Peltier GL, Zera RT. An open-label study to evaluate the safety and efficacy of tissue plasminogen activator in treatment of severe frostbite. *J Trauma.* 2005;59:1350-54.

### IN A NUTSHELL

1. Children are at greater risk for hypothermia because of their small body mass relative to surface area; prevention by adequate protective clothing is important.
2. In prehospital settings where obtaining an accurate core temperature measurement is difficult, the degree of hypothermia can be estimated from clinical findings.
3. The accurate measurement and monitoring of core body temperature are essential to proper diagnosis and management.
4. Patients with severe hypothermia and absent vital signs should not be considered dead until they are near normal core temperature and are unresponsive to cardiopulmonary resuscitation.
5. Because of the neuroprotective effects of hypothermia, the severely hypothermic child may still have potential for intact survival with proper resuscitation.
6. Medical conditions can result in hypothermia in children and should be considered when hypothermia is resistant to rewarming (e.g., sepsis, hypothyroidism, adrenal insufficiency).
7. Children with severe hypothermia (core temperature < 28°C) and absent circulation should be considered for extracorporeal methods like cardiac bypass or extracorporeal membrane oxygenation, if available.

# PART IV The Newborn Infant

## Section 11 NEONATAL PHYSIOLOGY AND ORGANIZATION OF CARE

Section Editor Siddarth Ramji

### Chapter 11.1

### Fetal Physiology and Growth

Deepak Chawla

Starting with a single cell fertilized ovum, an embryo develops by the process of cellular division, differentiation and maturation into a complex organism with different organ systems performing specialized functions. This rapid growth is driven by inherent genetic make-up of the fetus and is influenced by intrauterine environment, transplacental provision of nutrients and exposure of mother to various environmental agents.

After fertilization in the fallopian tube, the ovum undergoes a series of mitotic divisions to form 16-celled morula 3 days after fertilization. By the time, embryo enters the uterine cavity it has formed a cavity inside it and is now called blastocyst. Its cells are divided into an inner cell mass and an outer cells mass. Inner cell mass is called embryoblast and forms the embryo proper. Outer cell mass is called trophoblast and contributes to formation of placenta. Under effect of progesterone, uterine endometrium is in secretory phase and is ready for implantation of the embryo. During second week after fertilization, blastocyst is embedded in the uterine endometrium. Trophoblast differentiates into inner proliferating cytotrophoblast which start forming the placental villi and outer syncytiotrophoblast which invades the uterine endometrium. By end of second week, maternal blood enters the lacunar network formed by syncytiotrophoblast and uteroplacental circulation begins. Third week of development called gastrulation is characterized by formation of three germ layers: endoderm, mesoderm and ectoderm. Cephalic and caudal ends and laterality of the embryo is also established during this phase. Teratogenic influence of toxic agents such as alcohol, maternal hyperglycemia due to diabetes or intake of drugs can effect development of the germ layers leading to birth defects such as holoprosencephaly, caudal dysgenesis and situs inversus (**Table 1**).

Third to eighth week of development, known as embryonic period, is the time of organogenesis when the three germ layers give rise to different organ systems. On dorsal aspect of the embryo, neural plate is formed by ectoderm. Neural plate forms the neural folds which fuse to form the neural tube. Closure of the neural tube starts in the cervical region and proceeds in cephalic and caudal direction so that cranial end of the neural folds is closed on 25th day and caudal end is closed on the 28th day of fertilization. Cranial portion of the neural tube forms the brain vesicles and caudal portion of the neural tube forms the spinal cord. Incomplete closure of the neural tube can result in neural tube defects such as anencephaly and spina bifida. In addition to central nervous system, ectodermal germ cells give rise to peripheral nervous

system, skin and sensory epithelium of ear, nose and eyes. On ventral side of the embryo gut, tube is formed and starts increasing in length. Lateral body folds fuse to form the body cavity. Body cavity is divided into thoracic and peritoneal cavities by diaphragm which closes the pleuroperitoneal canal. Failure of closure of the ventral body folds can lead to ventral wall defects while failure of the pleuroperitoneal canal results in congenital diaphragmatic hernia (**Table 1**). Mesodermal germ layer of the embryo forms the somites which form the muscles, bone, cartilage and dermis. Heart, blood vessels, blood cells, urogenital system and spleen are also formed from the mesoderm. Endoderm germ layer gives rise to epithelial cells layers of the gastrointestinal and respiratory tracts, thyroid, parathyroid, liver and pancreas.

During embryonic period, stems cells destined to form main organ systems start dividing and different organs are recognizable by end of the 8 weeks of fertilization. On external examination head forms about half of the length of the embryo and eyes, external ears, upper and lower limbs with digits can be recognized. Due to rapid cell division embryonic period is prone to teratogenic effect of drugs, infections and radiation. Most of major congenital malformations arise in this period.

**Table 1** Abnormalities in the embryonic development

Period of gestation	Abnormality	Clinical consequences
2nd to 3rd week	Abnormal implantation of the embryo	Ectopic pregnancy
	Effect of alcohol, maternal diabetes or other teratogenic drugs on development of germ cells	Holoprosencephaly Caudal dysgenesis Renal agenesis Imperforate anus Situs inversus
3rd to 8th week	Failure of closure of neural tube on dorsal aspect of the fetus	Anencephaly Spina bifida
	Failure of closure of ventral body walls	Ectopia cordis Gastroschisis Bladder exstrophy
	Failure of closure of pleuroperitoneal canal	Congenital diaphragmatic hernia
	Cardiac looping	Dextrocardia
	Formation of cardiac septa	Atrial and ventricular septal defects
		Transposition of great vessels
		Tetralogy of Fallot
	Formation of lung bud	Tracheoesophageal fistula
	Breakdown of anal membrane	Anal atresia



Period from third to ninth month of gestation is called the fetal period. During this period, tissues undergo maturation and increase in cell size. Structure and function of different organ systems are matured. Timeline and major stages of development of the main organ systems are summarized in **Table 2**.

## FETAL NUTRITION AND ENDOCRINE FUNCTION

Fetal period is the most rapid period of growth in whole lifespan. Most rapid increase in fetal length is observed in first 3 months of the fetal period and most rapid increase in fetal weight is observed in last 2 months of the fetal period. Human placenta plays vital role in fetal growth by being the organ of transfer of nutrients from mother to fetus and by synthesizing various hormones which promote fetal growth. Placenta produces growth hormone, insulin-like growth factors (IGF) and human placental lactogen. Peptide hormones including insulin produced by mother cannot cross placenta. Insulin produced by fetus and IGFs from placenta and fetus are main growth promoting hormones of the fetus. These hormones prevent fetal protein breakdown and promote deposition of glycogen in liver and fat in adipose tissue. IGF-2 plays important role in embryonic and early fetal growth. IGF-1 is main regulator of late fetal growth. Mutations in IGF ligands or its receptors lead to intrauterine growth restriction (IUGR). Similarly, mutations resulting in insulin resistance or pancreatic agenesis also cause severe IUGR. Human placental lactogen (HPL) also coordinates transfer of nutrients from mother to the fetus. Along with increase in maternal growth hormone, it produces relative insulin resistance in mother. This results in increased circulating levels of glucose and lipids. HPL also exerts anabolic effect on fetus by increasing levels of IGF-1 and IGF-2 in fetal circulation and decreasing levels of IGF binding proteins.

Glucose is the main energy substrate for fetus and is transferred through carrier-mediated transport (glucose transport proteins (GLUT-1 and GLUT-3)). Glucose transport is driven by downward concentration gradient. If mother is hyperglycemic because of diabetes mellitus more glucose is transported to fetus. Excess glucose left after consumption for energy needs stimulates fetal insulin secretion and is deposited in fetus as glycogen and fat. Therefore babies born to mothers with uncontrolled diabetes are macrosomic and at risk of shoulder dystocia. After birth, maternal continuous glucose supply is removed and the newborn infant is dependent on the stored glycogen till feeding starts. Babies with low glycogen stores because of IUGR or inadequate mobilization of glycogen because of excess insulin secretion (infants of diabetic mothers) are at risk of hypoglycemia in this period of transition and need to be monitored for first 48–72 hour of birth.

Trophoblast plays critical role in transfer of amino acids by uptake from maternal side of placental circulation and then actively transporting them to the fetal side. This is an energy dependent process and decrease in energy substrate supply to the placenta causes decrease in fetal transfer of amino acids and therefore IUGR. This is one of mechanism of IUGR in chronic maternal hypoxia (decreased oxygen supply), maternal starvation (decreased glucose supply) and gestational hypertension (decreased uteroplacental blood circulation). Amino acids are used not only for fetal tissue synthesis but also meet the energy needs of the fetus. In third trimester, proteins are accreted at a rate of 1.5% of body weight per day.

Lipids are transferred to fetus as free fatty acids. Fetus does not use fatty acids for energy production and most of fat transferred to fetus is stored. Maximum fat storage occurs in later part of third trimester. Fat accounts for 15–20% of fetal weight at term gestation. Preterm birth and IUGR lead to decrease in subcutaneous and brown fat increasing the risk of temperature instability.

Most of fetal micronutrient accretion also occurs in the third trimester. Calcium is accreted at increasing rate as pregnancy advances to reach a peak accretion rate of 120–160 mg/kg/day in late third trimester. Calcium is transported against the concentration gradient to fetus and its level in fetus blood is regulated by parathyroid hormone (PTH). At birth when continuous supply of calcium is stopped from mother, there is surge in PTH levels to maintain the calcium levels in normal range. PTH surge may be impaired in conditions such as prematurity, maternal diabetes and birth asphyxia. In presence of these morbidities, a sick neonate on intravenous fluids may need parenteral calcium added to the fluids. Phosphorous is also transported against concentration gradient to fetus with peak accretion rate of 60–75 mg/kg/day in third trimester. Similarly, magnesium (3–5 mg/kg/day), copper (30 mg/kg/day), zinc (400 mg/kg/day) and iron (2–3 mg/kg/day) are also transferred and stored in fetus mainly in third trimester. Knowledge of rates of fetal accretion of nutrients is helpful in estimating nutritional needs of neonates born prematurely.

Thyroid hormones are essential for normal fetal growth. Maternal thyroid hormones do not play any significant role in fetal growth except in first trimester. Fetal thyroid starts functioning by about 12 weeks of gestation with appearance of thyroxine (T<sub>4</sub>), triiodothyronine (T<sub>3</sub>) and thyroid stimulating hormone (TSH) in fetal circulation. Levels of these hormones in fetus is higher than mother. Immediately after birth, there is surge in TSH levels in response to thermal stimulation of the newborn infant. In response to this T<sub>3</sub> and T<sub>4</sub> levels are increased in neonate and remain elevated for 2 weeks after birth.

## FETAL CIRCULATION AND GAS EXCHANGE

Fetus is dependent on placenta for gas exchange. Fetus receives oxygenated blood from the placenta through umbilical vein. Partial pressure of oxygen (PaO<sub>2</sub>) in umbilical venous blood is 20–40 mm Hg. More than half of this blood directly enters the inferior vena cava and rest passes through liver. In inferior vena cava, stream of blood coming from the umbilical vein and reaching the right atrium is preferentially directed through foramen ovale to the left atrium. This oxygenated blood is supplied mainly to coronary arteries, brain and upper part of the body. Less oxygenated blood coming from lower part of body in the inferior vena cava goes to the right ventricle. Pulmonary resistance is high because of lack of air in alveoli. Only 10% of right ventricular output goes to pulmonary circulation. Most of the output of the right ventricle is shunted through the ductus arteriosus to the aorta. This relatively deoxygenated blood supplies the lower part of the body and through two umbilical arteries to the placenta. Placenta is low resistance circulation and, therefore, receives largest amount (40%) of cardiac output.

Fetal tissue are able to maintain aerobic metabolism despite very low PaO<sub>2</sub> as compared to the extrauterine existence. Fetal hemoglobin (HbF) has higher oxygen binding capacity. For a given value of PaO<sub>2</sub>, HbF carries larger amount of oxygen as compared to adult hemoglobin. Higher heart rate and more red blood cell mass also ensure more oxygen delivery to the tissue each minute. Fetal oxygen demand is also lower due to lack of need of thermoregulation.

Alveoli in fetus are filled with lung fluid. This lung fluid is actively secreted by alveolar epithelium by chloride channels. Lung fluid moves up through the airways and is either swallowed or contributes to the volume of amniotic fluid. Ongoing production of lung fluid creates slight positive pressure in the alveoli and is necessary for normal lung growth. Pulmonary vasculature dilatation is dependent on presence of air in the alveoli. In absence of air, pulmonary vessels are constricted leading to high pulmonary vascular resistance.

**Table 2** Major milestones in the development of different organ systems

Time after fertilization	Cardiovascular system	Respiratory system	Gastrointestinal system	Urogenital system	Central nervous system
2 weeks	Primary heart field by heart progenitor cells				
3 weeks	Formation of heart tube		Primitive gut by folding of embryo Appearance of liver primordia	Appearance of primordial germ cells	Formation of neural plate
4 weeks	Cardiac looping	Formation of lung bud	Differentiation of esophagus Appearance of stomach Breakdown of oropharyngeal membrane	Appearance and disappearance of pronephros Appearance of mesonephros Division of cloaca starts	Neurulation
5 weeks	Beginning of formation of cardiac septa	Main stem bronchi		Appearance of metanephros	Prosencephalic and hemispheric formation
6 weeks	Arterial and venous morphogenesis	Pseudoglandular stage (Branching to form terminal bronchioles)	Gut rotation starts	Formation of urogenital ridge	Neuronal proliferation and migration
8 weeks	Formation of four-chambered heart		Breakdown of anal membrane	Disappearance of mesonephros	
10 weeks	Increase in size, maturation of different structures		Gut starts to return to abdominal cavity		
12 weeks					
16 weeks					
20 weeks					
24 weeks		Saccular stage (formation of primitive alveoli)	Increased length of small intestine		
28 weeks					
32 weeks					
36 weeks		Alveolar stage (Maturation of alveoli)		Completion of nephrogenesis	Myelination
Birth and postnatal period	Closure of foramen ovale and ductus arteriosus				

As process of parturition begins reabsorption of lung fluid starts by appearance of epithelial sodium channels in the alveolar cells. This transition from fluid secreting to fluid absorbing alveolar lining is facilitated by increase in levels of catecholamines and steroids in fetoplacental circulation with onset of labor. At birth, air enters the alveoli and pulmonary vasculature dilates leading to decrease in pulmonary vascular resistance. As umbilical cord is clamped, low resistance placental circulation is removed and systemic vascular resistance increases. This leads to functional closure of foramen ovale and change in direction of blood flow in ductus arteriosus. Perfusion of oxygen rich blood in ductus arteriosus from aorta causes constriction of the ductus leading to first functional and then anatomic closure.

## ASSESSMENT OF FETAL WELL-BEING

Intrauterine fetal death can occur in presence of maternal complications such as gestational hypertension, abruptio placenta, diabetes or intrauterine infections. Complications in intrapartum period such as cord prolapse, eclampsia, nonprogression of labor are also associated with increased risk of fetal death. Antenatal

fetal surveillance can be used to detect the effect of fetal hypoxia or ischemia on physiological variables of the fetus. If alteration in fetal physiological variables is detected, suitable intervention such as induction of labor or operative delivery can be chosen by the clinical care team.

## Fetal Heart Rate

This is commonly monitored alone or in combination with other biophysical variables. Fetal heart rate (FHR) normally shows acceleration, whenever, fetus has spontaneous body movements. In response to fetal hypoxia, this variability in fetal heart rate is decreased or lost. Nonstress test (NST) can be done to detect this normal FHR variability. NST is said to be reactive, if there are at least two accelerations that reach 15 beats/min above the baseline heart rate and each acceleration lasts for at least 15 seconds before returning to baseline. NST is said to be nonreactive, if two accelerations meeting these criteria do not occur within 40 min. A reactive NST is reassuring for fetal well-being. On the other hand, nonreactive NST can be false positive and may need further confirmation.

## Biophysical Profile (BPP)

This is another commonly used test to assess fetal well-being. It has five components including NST:

1. At least one episode of fetal breathing lasting at least 30 seconds.
2. At least three discrete body or limb movements.
3. At least one episode of active extension with return to flexion of a limb or trunk, or the opening and closing of a fetal hand.
4. Single vertical pocket of amniotic fluid measuring more than or equal to 2 cm.
5. Reactive NST.

A score of 2 is assigned to each parameter, if present and score of 0 is assigned, if absent. A total score of 8 or 10 indicates fetal well-being. Score of 6 is considered equivocal. Pregnancy can be terminated or test can be repeated in 24 hours depending on gestation. A score of 4 or less is abnormal and pregnancy needs to be terminated to decrease the risk of fetal death. Reactive NST or BPP score of 8–10 are reassuring and can be repeated after 1 week.

## Doppler Measurement of Blood Flow

Doppler blood flow measurements in umbilical artery can also be used to assess health of the fetus. With decreasing blood flow to the uteroplacental circulation blood flow during diastole in umbilical artery starts decreasing. Absence or reversal of blood flow during diastole in umbilical artery is commonly used to decide about delivery of a fetus affected by intrauterine growth restriction.

During labor also FHR is monitored to detect fetal distress. Normal baseline fetal heart rate is 110–160 beats/minute. A fetus suffering from intrapartum hypoxia can display loss of FHR variability, FHR deceleration or fetal tachycardia. FHR deceleration can be of three types: early, late and variable. Early decelerations coincide with peak of the uterine contraction and are caused by fetal head compression. These are usually associated with a favorable fetal outcome. Variable decelerations as the name implies vary in shape, depth, and duration. They usually coincide with uterine contraction and usually have a favorable outcome. Late decelerations start and return to baseline more gradually (> 30 seconds). They start and reach their nadir after the onset and

peak of uterine contractions. Recurrent late decelerations are non-reassuring and indicate need of delivery of the fetus.

### IN A NUTSHELL

1. Fetal growth is influenced by genetic potential, intrauterine environment, transplacental supply of nutrients and maternal exposure to environmental agents.
2. Teratogenic influence of environmental, infectious and metabolic agents can cause various birth defects during first two months of pregnancy (embryonic phase).
3. Most of fetal micronutrient accretion also occurs in the third trimester. Premature birth or uteroplacental placental insufficiency leads to deficiency of micronutrients such as iron, calcium, phosphorous and magnesium in fetus.
4. Fetal well-being can be monitored by observing physiological changes in fetal heart rate and nervous system functions such as fetal tone and movements.
5. Fetuses with intrauterine growth restriction are at significant risk of perinatal morbidity, mortality and long-term growth and metabolic complications.

### MORE ON THIS TOPIC

- Kliegman RM. Intrauterine growth restriction. In: Martin RJ, Fanaroff AA, Walsh MC, editors. *Fanaroff and Martin's neonatal-perinatal medicine: diseases of the fetus and infant*. 9<sup>th</sup> ed. Philadelphia: Saunders/Elsevier; 2011. pp. 245–75.
- Macones GA, Hankins GD, Spong CY, et al. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines. *Obstet Gynecol*. 2008;112:661–6.
- Mayer C, Joseph KS. Fetal growth: a review of terms, concepts and issues relevant to obstetrics. *Ultrasound Obstet Gynecol*. 2013;41:136–45.
- Regnault TRH, Limesand SW, Hay WW Jr. Factors Influencing Fetal Growth. *Neoreviews*. 2001;2:e119.
- Sadler TW, Langman J. *Langman's Medical Embryology*. 12th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012.

## Chapter 11.2

# Maternal Influence on the Fetus

Jayashree Mondkar, Swati Manerkar

Fetal growth and development depends upon the maternal environment in utero, placental function and the inherent growth potential of the fetus. If all influences are conducive, fetal outcome is optimal. Adverse influences have far reaching consequences extending beyond fetal and neonatal period, right into adulthood.

## MATERNAL NUTRITION

The fetus gains 85% of its birth weight in the last half of pregnancy and depends upon maternal nutrient intake and on maternal endogenous substrate stores as precursors for fetal tissue synthesis. In utero growth of the fetus also requires an appropriate endocrine milieu. Insulin and insulin-like growth factors are the chief growth hormones in utero. Fetal insulin promotes the deposition of glycogen and adipose tissue. It also stimulates amino acid uptake and protein synthesis in muscle. Other fetal hormones, such as growth hormone, thyroid hormone and corticosteroids, have less well-defined effects on fetal growth.

Prepregnancy weight and pregnancy weight gain are two important independent variables that affect fetal growth. Mothers with low prepregnancy body mass index (BMI) less than 19.8, are more likely to deliver a baby with fetal growth restriction unless pregnancy weight gain is optimal.

The nutritional intake of the mother during pregnancy is also an important determinant of fetal weight gain. As fetal growth accelerates in the latter half of pregnancy, the requirement for nutrients increases. Substrate deficiency during this period has been shown to result in an overall reduction in birth weight. A reduction by 300–500 g in birth weight has been observed in acute famine states. Thus, maternal weight gain during pregnancy is a surrogate marker for fetal growth and weight gain. Poor weight gain by 16 weeks' gestation may predict low birth weight. Mothers with a normal BMI (19.8–26) may require a weight gain of 11.5–16 kg for optimal fetal outcomes. Underweight mothers may require a pregnancy weight gain of 12.5–18 kg to prevent fetal growth restriction. Nutritional supplementation during pregnancy has shown to improve fetal weight. Additional calories, rather than protein supplementation, have been shown to correlate best with enhanced fetal weight. An average intake of 1,500 kcal/day during pregnancy is recommended.

There is substantial evidence that micronutrient deficiency particularly maternal iron deficiency anemia increases the risk of preterm delivery and subsequent low birth weight. Multicomponent micronutrient supplementation has also been shown to enhance fetal growth in developing countries.

Other factors that influence maternal nutrition and thereby fetal growth include maternal age below 18 years, young unmarried mothers, short interpregnancy interval less than 2 years, chronic maternal illnesses, low socioeconomic status, heavy work during pregnancy.

## CHRONIC MATERNAL PROBLEMS

### Maternal Medical Problems

Maternal medical problems, like chronic hypertension, heart disease, pulmonary disorders, sickle cell anemia affects fetal and neonatal outcomes through uterine ischemia, hypoxemia or both resulting in intrauterine growth restriction (IUGR), perinatal asphyxia and their consequent morbidities.

### Hypertension

Hypertension is the most common medical problem in pregnancy, affecting 10–15% of all pregnant women. Uncontrolled hypertension whether chronic or gestational hypertension, has profound effects on the fetus and neonate and is a major cause of perinatal mortality and morbidity. Women with hypertensive disorders are at higher risk for preterm delivery and placental abruption, and their fetuses are at risk for IUGR due to the uteroplacental insufficiency, decidual ischemia and decidual thrombosis.

Mortality and morbidity in growth restricted, small for gestational age (SGA) infants are increased compared with those who are appropriate for gestational age. SGA infants at birth have many clinical problems that include perinatal asphyxia, meconium aspiration syndrome, pulmonary hypertension, impaired thermoregulation, hypoglycemia, polycythemia and hyperviscosity; SGA infants are at higher risk for impaired physical growth, neurodevelopment and difficulties with attention span. Cognitive performance is generally lower in SGA infants at the ages of 1–6 years compared with those who are appropriate for gestational age. Adults who were SGA infants could be at higher risk for ischemic heart diseases and essential hypertension.

### Diabetes

Uncontrolled maternal diabetes during pregnancy is associated with significant perinatal morbidity and mortality. Maternal hyperglycemia and the resultant fetal hyperinsulinemia are central to the pathophysiology of diabetic complications of pregnancy.

Uncontrolled periconceptional type I and type II diabetes are associated with a fourfold increase in the rate of congenital malformations compared to nondiabetic pregnancies. All organ systems including cardiac, central nervous system, genitourinary, musculoskeletal systems may be affected. Cardiac defects especially transposition of great vessels is the most common anomaly in infants of diabetic mothers. Sacral dysgenesis and caudal regression syndrome are also far commoner in babies of periconceptional diabetic mothers.

Glycemic control during embryogenesis is a critical factor in the genesis of diabetes-associated birth defects. Congenital malformation rate was noted to be nine-fold higher in the poorly controlled group ( $HbA_{1c} \geq 7.5$ ) than in the well-controlled group ( $HbA_{1c} < 7.5$ ). However, the risk of delivering a malformed infant in well-controlled periconceptional diabetics is equivalent to that in the general population.

Putative mechanisms causing malformations due to fetal hyperglycemia during embryogenesis include excessive formation of oxygen radicals in the mitochondria of susceptible tissues, leading to the formation of hydroperoxides, which inhibit prostacyclin. The resulting excessive production of thromboxanes and other prostaglandins may disrupt vascularization of developing tissues. Reduced levels of arachidonic acid and myoinositol and accumulation of sorbitol and trace metals in the embryo have also been implicated. Infants of gestational diabetic mothers are at the same risk for congenital anomalies as the nondiabetic population.

Fetuses of all types of uncontrolled diabetic mothers are at increased risk of the effects of fetal hyperglycemia and hyperinsulinism. Maternal hyperglycemia stimulates fetal hyperinsulinemia, which in turn accelerates fuel utilization and growth. The growth acceleration is more evident by 24 weeks. There is excessive adipose tissue deposition, visceral organ hypertrophy, and acceleration of body mass accretion causing macrosomia, often with birth weight greater than 4,000 g. Head growth remains normal despite marked degrees of hyperglycemia. The central deposition of fat is a key characteristic of diabetic macrosomia and causes problems associated with vaginal delivery in these pregnancies. Macrosomia is associated with the increased likelihood of operative delivery, shoulder dystocia, and brachial plexus injury.



The important neonatal morbidities include metabolic problems like hypoglycemia, hypocalcemia, respiratory distress, need for assisted ventilation, meconium aspiration, polycythemia, hyperbilirubinemia, etc. Some neonates of gestational diabetic mothers may present with hypertrophic cardiomyopathy with a thickened myocardium and significant septal hypertrophy.

### Thyroid Disturbances

For the first 10–12 weeks of pregnancy, the baby is completely dependent on the mother for the production of thyroid hormone. By the end of the first trimester, the baby's thyroid begins to produce thyroid hormone of its own. Transfer of thyroxine T4 during the first trimester from the mother to the fetus is of great importance because fetal brain development appears to depend on maternally derived T4. Maternal hypothyroidism during early gestation can lead to neurologic damage of the fetus even if the fetus is subsequently euthyroid. The baby, however also remains dependent on the mother for ingestion of adequate amounts of iodine, which is essential to make the thyroid hormones. Maternal hypothyroidism and hyperthyroidism can affect the baby.

### Hyperthyroidism

Eighty to eighty-five percent of maternal hyperthyroidism occurs due to Graves disease. Inadequately treated maternal hyperthyroidism can result in early labor and pre-eclampsia. Fetal effects include fetal tachycardia, fetal growth restriction, prematurity and stillbirths. Also the transplacental passage of thyrotropin (TSH) receptor stimulating antibodies can cause transient neonatal thyrotoxicosis. If the TSH receptor suppressing antibodies are excessive in a mother with earlier Graves disease, fetal hypothyroidism may occur. In the mother on antithyroid therapy, fetal hyperthyroidism is rare as antithyroid drugs also cross the placenta.

Antithyroid drug therapy with methimazole (MMI), propylthiouracil (PTU) is used for the treatment of hyperthyroidism. Both the drugs cross the placenta and can potentially affect the baby's thyroid function. MMI is best avoided in the first trimester due to possible association with aplasia cutis congenita, tracheoesophageal fistula and choanal atresia. Fetal hypothyroidism and goiter can occur even with doses in the therapeutic range for the mother. Beta-blockers can be used during pregnancy to help treat significant palpitations and tremor due to hyperthyroidism. Breastfeeding can continue as usual, and PTU is the drug of choice in lactating women as it is highly protein bound.

Thus, infants of mothers with Graves disease can present with hyper- or hypothyroidism. The baby will require periodic assessment of his/her thyroid function to ensure maintenance of normal thyroid status.

### Hypothyroidism

The common causes of maternal hypothyroidism are the autoimmune disorder, Hashimoto thyroiditis and iodine deficiency. Pregnant women who are under producing thyroxine are, therefore, at risk of having children with lower intelligence quotients and learning problems, such as attention-deficit hyperactivity disorder. The hypothyroid mother needs treatment with levothyroxine throughout pregnancy. Fetal effects include preterm birth, IUGR, congenital anomalies, goiter, fetal and perinatal death. Neurodevelopmental impairment may occur especially if both fetus and mother are hypothyroid. Women who are well-controlled during pregnancy have good pregnancy outcomes.

The newborn baby needs to be screened for hypothyroidism after birth and treatment with levothyroxine (10–15 µg/kg/day) needs to be started by 2 weeks of life if detected to be thyroid deficient so as to ensure normal brain development.

## Autoimmune Disorders

A number of maternal autoimmune and alloimmune disorders can cause fetal effects of varying severity due to transplacental transfer of antibodies.

### Maternal Idiopathic Thrombocytopenic Purpura

Thrombocytopenia of the fetus or newborn is caused by active transplacental transfer of the antiplatelet antibodies in about 10% of mothers with idiopathic thrombocytopenic purpura (ITP). A low platelet count increases the risk of hemorrhage; however intrauterine fetal hemorrhage is not common with ITP. Babies are at increased risk of cerebral hemorrhage due to birth trauma or bleeding subsequently in the neonatal period.

### Maternal Antinuclear Antibodies

Antinuclear antibodies are produced in various maternal immunological diseases. Antidouble-stranded DNA (anti-dsDNA) antibodies that are specific for systemic lupus erythematosus and anti-Ro and La antibodies can cross the placenta and cause neonatal lupus in 1% of infants. Infants present with cardiac, dermatologic, hepatic, and hematologic manifestations. The skin lesions on the face and scalp, often have a periorbital distribution and may be present at birth. Maternal anti-Ro and anti-La antibodies and complement components are deposited in fetal heart tissues, leading to inflammation, calcification, necrosis, and fibrosis of the conducting tissue leading to heart block that is often complete and irreversible and may be combined with cardiomyopathy. About 10% of fetuses with congenital heart block are born with hydrops fetalis and congestive heart failure.

### Maternal Antiphospholipid Antibodies

Maternal antiphospholipid antibodies promote clotting in arteries and veins (i.e., thrombophilia) by activation of endothelial cells, via oxidant-mediated injury to endothelium, and by modulating the regulatory function of coagulation proteins. Women with APLA have a high incidence of recurrent miscarriage (three or more consecutive losses of pregnancy). Other potential complications of pregnancy include preeclampsia, placental insufficiency, fetal growth impairment, preterm birth, maternal thrombosis (including stroke), and complications of treatment.

## Alloimmune Disorders

When small amounts of fetal blood enter the maternal circulation through breaks in the fetomaternal interface, these fetal blood cells are recognized as antigens by the maternal immunologic system and provoke an immune response. On a subsequent stimulus, the antibodies response being immunoglobulin G (IgG), cross into fetus causing cell destruction. The two important prototypes of alloimmune disorders are erythroblastosis fetalis and neonatal alloimmune thrombocytopenia.

Red cell alloimmunization occurs due to materno-fetal red cell antigen incompatibility, the commonest being RhD incompatibility. However, ABO, any of the minor group antigens, like C, E, Kell, etc., can also cause hemolytic disease in the newborn. Maternal antibodies caused by transplacental transfer of fetal cells and stimulation of the maternal immune system cross in to the fetal circulation and cause hemolysis of fetal red cells. The severity if the disease increases with subsequent sensitized pregnancies from mild to severe hyperbilirubinemia after birth to severe anemia and hydrops fetalis in utero.

The condition is preventable by administering to the mother anti-D immunoglobulins at 28 weeks and at term in the first and all subsequent conceptions when maternal antibody titers are negative. Monitoring maternal antibody titers during pregnancy is needed. Once titers are positive, close fetal surveillance by ultrasound and middle cerebral arterial Doppler is required.

Neonatal alloimmune (also known as isoimmune) thrombocytopenia (NAIT) has a pathogenesis similar to Rh disease. A mother with the human platelet antigen-1a (HPA-1a) negative platelets is sensitized by antigen-positive fetal platelets gaining access to the maternal circulation via breaches in the placental barrier. As a result, the mother produces antiplatelet antibodies that cross the placenta and destroy the fetal platelets. Fifty percent of NAIT cases manifest during the first pregnancy. This is believed to be due to higher immunogenicity of the platelet antigen and by the smaller size of the platelets, which facilitates their fetomaternal transfusion.

Most neonates are asymptomatic, and the thrombocytopenia is detected by a blood count performed for other perinatal causes. In some cases, neonates present with generalized petechiae, hemorrhage into abdominal viscera, excessive bleeding after venepuncture or circumcision, or, in extreme cases, abnormal neurologic manifestations secondary to intracranial hemorrhage. The platelet count commonly decreases further during the first week after birth. Antenatal intracranial bleeds in the fetus may occur.

## MATERNAL INFECTIONS

Pregnant women are exposed to infections in the community through all trimesters. Manifestations of infection in the mother may be most trivial hence remain unnoticed yet may have devastating effects on the fetus. Infection in the mother does not always mean the baby will be affected. For many infections, the risk to the baby varies when contracted at particular stage of pregnancy. When infection is transmitted vertically in utero the resulting fetal-neonatal infection is called a congenital infection. When infection is contracted during labor, it is described as a perinatally acquired infection.

The effects of congenitally acquired infection may be quite different from and more severe than the effects of the same infection acquired after birth especially when acquired in the period of organogenesis. The risk is highest when a primary infection occurs compared to a reinfection in the mother wherein protective antibodies are already present and protect the fetus to a large extent.

Infection of the embryo or fetus can result in death and resorption of the embryo, abortion, stillbirth or livebirth of a premature or term infant who may or may not be normal. The effects of in utero infection appear in the live-born infant as low birth weight, developmental anomalies, congenital disease or none of these. Infections acquired in utero may persist after birth and cause significant abnormalities soon after birth or may not be recognized for months or years.

The infant is protected from the microbial flora of the mother's genital tract by the maternal membranes. If delivery is delayed after membrane rupture, the vaginal microflora can ascend and in some cases produce inflammation of fetal membranes, umbilical cord, and placenta. Fetal infections can also occur from aspiration of infected amniotic fluid. Some viruses are present in the genital secretions [herpes simplex virus, cytomegalovirus, or human immunodeficiency virus (HIV)] or blood (hepatitis B virus or HIV). If delivery follows shortly after membrane rupture, the infant may be colonized during passage down the birth canal.

## MATERNAL DRUG EXPOSURE

In most situations, the risk of adverse fetal effects of medication taken by the mother is not known. Timing of exposure of the drugs is important. The most critical period for teratogenic effects of drugs is believed to be 15–60 days after conception. Drugs taken after organogenesis can affect growth and development of the fetus, in particular the developing brain. The FDA has categorized pregnancy risk of medications as A to D and category X. Category C and D medications put the fetus at increased risk of teratogenesis and category X drugs are contraindicated in pregnancy.

## LATE PREGNANCY AND LABOR

Though the antepartum period may pass off uneventfully problems in the late third trimester or labor may put the fetus at risk for perinatal asphyxia and adverse outcomes. Besides spectrum of pregnancy-associated hypertensive disorders, antepartum hemorrhage may cause prematurity, perinatal asphyxia or can also cause neonatal shock. Any problems that prolong the second stage of labor may also predispose the baby to perinatal asphyxia.

## Adverse Intrauterine Environment:

### Long-term Outcomes

There is sufficient evidence to demonstrate association between small size at birth and the risk of chronic adult diseases, such as coronary artery disease, hypertension, stroke, type 2 diabetes mellitus, and osteoporosis. This hypothesis was first put forth by David Barker and is called the *Barker hypothesis*. Malnutrition during gestation that includes macronutrients or micronutrients causes intrauterine adaptation of the fetus for survival despite adversity by conserving energy supply at the expense of growth, ensuring a reduced fetal demand, resulting in the birth of a small baby. These adaptations generate a *thrifty phenotype* which persists after birth. With the availability of nutrients after birth, catch-up growth occurs which tends to increase deposition of white adipose tissue resulting in adiposity, particularly visceral adiposity; a rearrangement of skeletal muscle mitochondria; and increased oxidative injury. These changes set the stage for metabolic syndrome, diabetes mellitus, and coronary artery disease in adulthood.

### IN A NUTSHELL

1. Prepregnancy weight and pregnancy weight gain are two important independent variables that affect fetal growth.
2. Micronutrient deficiency particularly maternal iron deficiency anemia increases the risk of preterm delivery and subsequent low birth weight.
3. Chronic hypertension, heart disease, pulmonary disorders, diabetes and anemia in the mother cause uterine ischemia or hypoxia; and may result in IUGR, perinatal asphyxia and their consequent morbidities.
4. Infection of the embryo or fetus acquired from mother can result in abortion, stillbirth, prematurity, IUGR, developmental anomalies, congenital disease. Infections acquired in utero may persist after birth and cause significant abnormalities soon after birth or may not be recognized for months or years.
5. The most critical period for teratogenic effects of drugs taken by the mother is believed to be 15–60 days after conception.

## MORE ON THIS TOPIC

- Barker DJ, Thornburg KL. Placental programming of chronic diseases, cancer and lifespan: a review. *Placenta*. 2013;34:841-5.
- Burchett SK. Viral Infections. In: Cloherty JP, Eichenwald EC, Hansen AR, Stark AR (Eds). *Manual of Neonatal Care*. 7<sup>th</sup> ed. USA: Lippincott Williams, Wolters Kluwer; 2011. pp. 588-623.
- Christian P, Stewart CP. Maternal micronutrient deficiency, fetal development, and the risk of chronic disease. *J Nutr*. 2010;140:437-45.
- Kawai K, Spiegelman D, Shankar AH, Fawzi WW. Maternal multiple micronutrient supplementation and pregnancy outcomes in developing countries: meta-analysis and meta-regression. *Bull WHO*. 2011;89:402-411B.
- Petroff MG. Review: Fetal antigens—identity, origins, and influences on the maternal immune system. *Placenta*. 2011;32:S176-81.
- Ramos GA, Moore TR. Endocrine disorders in pregnancy. In: Gleason CA, Devaskar Su (Eds). *Avery's Diseases of the Newborn*. Philadelphia: Elsevier Saunders; 2012. pp. 75-91.

## Chapter 11.3

# Transition of the Fetus to Newborn

Siddarth Ramji

Fetal life and physiology are very different from what is expected of it once it delivers as a neonate and has to exist in the extrauterine environment. The fetus for its existence derives its nutrition, and oxygenation, via the placenta, which also serves as an organ of excretion for the fetus. The fetus is thermally insulated and immunologically protected. However, the process of birth requires the fetus to navigate the transition to its neonatal life by making adaptations in its respiratory, cardiovascular, gastrointestinal and renal systems, and has also to make major metabolic adjustments. Understanding these physiological changes is key to the management of disorders in the newborn resulting from the transitional maladaptation. This chapter will focus the physiologic adaptations that take place in the newborn during this transition from intrauterine to extrauterine life.

## PULMONARY AND RESPIRATORY CHANGES

The first prerequisite is that the lungs must begin to function as an organ of gas exchange. This requires the establishment of pulmonary ventilation through expansion of lungs after birth and establishment of pulmonary circulation. For pulmonary ventilation to be established, it is important that the fetal lung be cleared of its fluid to receive air with onset of breathing after birth, and establishment of adequate respiratory efforts after birth.

### Clearance of Lung Fluid

Fetal lung is essentially secretory, and presence of fluid in fetal lungs is critical to its development. At birth since the neonate needs to start breathing, this fluid has to be cleared rapidly. The switch from secretion to absorption in the distal epithelium of the lung at birth is facilitated by the interaction of epinephrine, glucocorticoids, thyroid hormones and oxygen. The clearance of lung fluid at birth is triggered by the onset of labor, which results in a sudden increase in fetal catecholamines. They in turn, acting via the  $\beta$ -adrenoceptors on the type II alveolar cells, promote active sodium absorption due to increased  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase activity. The  $\beta$ -adrenoceptor mediated sodium reabsorption is primed by T3 and glucocorticoids, which in turn operate by upregulating the maturation of this absorptive process by the expression of amiloride-sensitive sodium channel [epithelial sodium channel (ENaC)]. The rise in alveolar partial pressure of oxygen ( $\text{PaO}_2$ ) with the first breath is in part responsible for the activation of the  $\text{Na}^+$  pump, which is activated by the binding of the oxygen responsive nuclear factor kappa-light-chain-enhancer of activated B-cells (NF- $\kappa\text{B}$ ) to  $\alpha$ -ENaC promoter. The expression of ENaC appears to be delayed in infants born by cesarean section which partly explains the delayed clearance of lung fluid in such infants and increased risk of transient tachypnea in these newborns. Since ENaC expression is increased in late gestation, it also explains the higher risk of delayed fluid clearance in very preterm neonates.

### Initiation of Breathing

Cessation of placental gas exchange results in transient hypoxia which triggers the medullary respiratory center. It is also believed that the decrease in environmental temperature, and tactile, visual and auditory stimuli have a role in initiating breathing efforts after birth.

The first few breaths, especially crying against a closed glottis, increase end expiratory pressure allowing air to remain at the end of expiration in the alveoli, resulting in the establishment of a functional residual volume (FRC). The adequacy of surfactant in the alveoli facilitates the persistent of FRC by lowering surface tension. The net result is an increase in the alveolar  $\text{PaO}_2$  which facilitates reabsorption of lung fluid, as described above, into the pulmonary circulation. Increased alveolar oxygen also results in decreased pulmonary resistance and enhanced pulmonary and lymphatic flow.

## FETAL TO NEONATAL CIRCULATION

### Fetal Circulation

The fetal circulation is a *parallel circuit* characterized by low systemic resistance and high pulmonary resistance, with shunts at the level of ductus venosus, ductus arteriosus (DA) and foramen ovale (FO). The gas exchange takes place in the intervillous spaces of the placenta with  $\text{PO}_2$  in the umbilical artery being 15–25 mm Hg, and in the umbilical vein, it being 30–35 mm Hg. Almost two-third of the blood from the umbilical vein (receiving blood from the placenta) bypasses the liver via the ductus venosus to enter the inferior vena cava (IVC) and then the right atrium. Almost 50% of this oxygenated blood from the umbilical vein is preferentially shunted across the FO into the left atrium and ventricle and perfuses the head, neck and upper trunk. The remainder of the blood from the IVC mixes with the blood from the superior vena cava ( $\text{PO}_2$  12–14 mm Hg) and enters the right ventricle and the pulmonary artery. Since the pulmonary vascular resistance is high and systemic resistance is low (placental circulation being a low-pressure circuit) most of this blood (with lower oxygenation) is shunted into the descending aorta via the DA to perfuse the lower part of the body (Fig. 1).

### Neonatal Circulation

In contrast, the extrauterine circulation is one in *series* with no shunts (Fig. 2). The pulmonary vascular resistance is lower than the systemic resistance. The gas exchange occurs in the lungs at the alveolar-capillary interface with an arterial  $\text{PO}_2$  of more than 60 mm Hg.

### Cardiovascular Adaptation at Birth

Two significant events enable this adaptation to take place: (1) decrease in pulmonary vascular tone, and (2) increase in systemic vascular resistance due to loss of placental circulation.

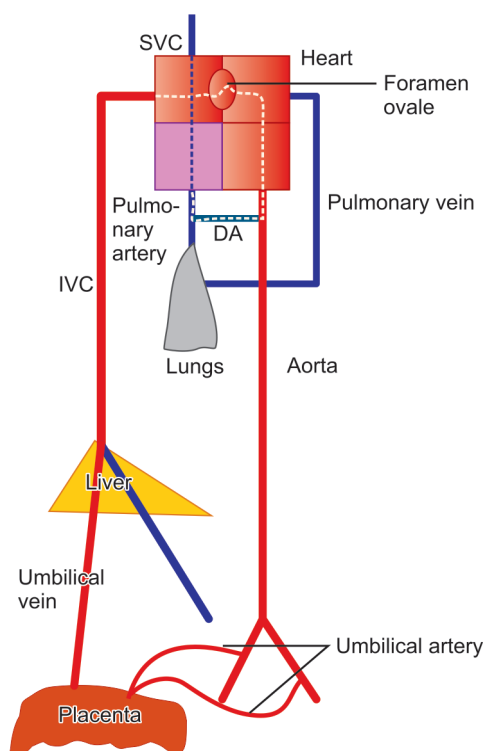
#### Decrease in Vascular Resistance

The initiation of respiration and the consequent expansion of alveoli decrease the alveolar hydrostatic pressure on the pulmonary capillaries contributing to decrease in the pulmonary vascular resistance. The increase in venous oxygen pressure consequent to onset of breathing appears to influence the decrease in pulmonary vascular tone. This is probably mediated by arachidonic acid metabolites such as prostaglandins, thromboxane and leukotrienes. Evidence suggests that these agents probably trigger another substance endothelial derived relaxing factor which is identical to nitric oxide, which may be the final common pathway through which vasodilatation is achieved.

#### Loss of Placental Circulation

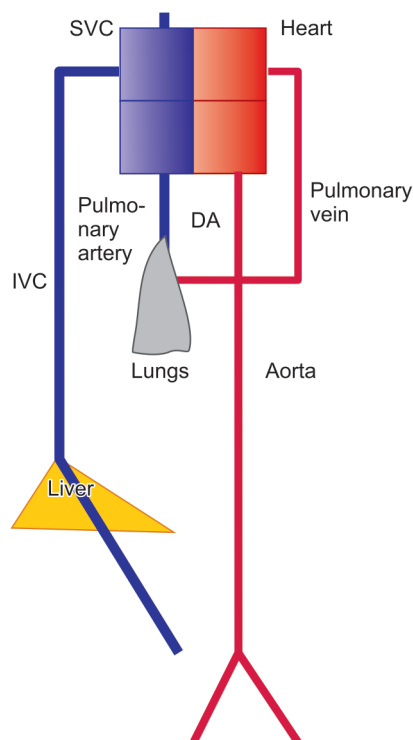
The loss of placental circulation at birth by cutting of the cord, results in increase in systemic pressure. The consequent increase in descending aortic pressure decreases the right to left shunting at the level of DA. Simultaneously, the increase in pulmonary flow decreases the pressure in the right atrium and increases the pressure in the left atrium resulting in closure of the FO, and decrease in the right to left shunting at the atrial level.





**Figure 1** Fetal circulation

Abbreviations: DA, ductus arteriosus; IVC, inferior vena cava; SVC, superior vena cava.



**Figure 2** Neonatal circulation

Abbreviations: DA, ductus arteriosus; IVC, inferior vena cava; SVC, superior vena cava.

### Ductal Closure

Ductal closure occurs in two stages. In healthy term neonates, functional closure begins at birth and is complete by 96 hours. The functional closure of the DA is probably mediated by the increase in muscle tone due to increased oxygen levels in blood and decrease in levels of prostaglandins that dilate the vessels. This functional closure is followed by anatomic closure due to endothelial proliferation and fibrosis.

However, this phase of transition is vulnerable to reversal to the fetal circulatory stage with reversal of shunts due to hypoxia, acidosis and infection resulting in the state of *persistent pulmonary hypertension of the newborn*.

### THERMAL REGULATION AND METABOLIC ADAPTATION

The fetus in utero was largely protected from the factors influencing thermal losses such as evaporation, radiation, convection and conduction. Even though the newborn can generate heat by nonthermal thermogenesis, in a sick and tiny neonate this mechanism may become ineffective especially in the presence of hypoxia and nutritional deprivation.

The fetus receives a steady supply of glucose from the placenta at a rate of 4–6 mg/kg/min. In the latter half of gestation, almost half of the glucose supplied to the fetus is stored in the fetus as glycogen. However, when the cord is cut, it results in a fall in blood glucose levels during the first 2 hours after birth. This fall in glucose together with the increase in catecholamines due to the stress of birthing process stimulates enzymes such as hepatic phosphorylase which induces glycogenolysis to facilitate supply of glucose to the newborn infant. Hepatic glycogenolysis and gluconeogenesis is the only source of fuel for the newborn after birth till feeding is established. Glucose oxidation contributes to about 70% of the energy needs of the brain. The neonatal brain is able to use alternate fuel sources for bridging this gap by utilizing mainly ketones and to a far lesser extent lactate. The key adaptation at birth is the glucagon surge with its low insulin/glucagon ratio that results in glucagon mobilization. Similarly, changes also take place in amino acid and lipid metabolism.

### Adaptation in Preterm

In contrast to the commonly held belief, preterm neonates do not have lower levels of plasma glucose than term infants. This is probably due to the more aggressive feeding policies practiced in neonatal units at present. However, they are unable to mount an appropriate ketogenic response to decreasing blood glucose levels. The low ketone levels are probably due to a combination of impaired lipolysis and ketogenesis. Unlike term neonates, no change is noted in the gut hormones after the first enteral feed, but after repeated bolus feeding surges in gut hormones are seen by the end of the first week.

### Adaptation in Growth-retarded Neonates

Failure of metabolic adaptation is more frequently seen in growth-retarded neonates than those who have grown appropriately. The possible reasons for this include depletion of glycogen reserves, decreased phosphoenolpyruvate carboxylase activity, limited mobilization and subsequent oxidation of fatty acids and relative functional hyperinsulinism. Their gluconeogenic capacities are also lower as evidenced by increased levels of gluconeogenic precursors such as lactate and alanine. Feeding of human milk appears to promote normal adaptation in this group of infants.



## FEEDING ADAPTATION

There is very little demand on the fetal digestive tract. However, after birth, the baby has to feed using its digestive tract and therefore compelled to make rapid adaptive changes. The gastrointestinal tract has to undergo rapid maturation. The infant has to be able to suck and also coordinate its sucking, and swallowing with its breathing. The maturation of this coordinated process is complex and matures slowly in preterm. This often is the reason why even late preterm infants also stay a longer time in hospital. The intestinal peristalsis has to mature rapidly to eliminate the meconium (composition: water about 80%, intestinal secretions, dead mucosal cells, bile and pancreatic juices, mucus, lanugo and vernix) and be able to accommodate the milk fed to the newborn.

## RENAL ADAPTATION AND FLUID BALANCE

Placenta is the primary organ for excretion, fluid and electrolyte balance in the fetus. But after birth, the kidney has to adapt to take over these functions. To be able to maintain fluid and electrolyte homeostasis, there is a rapid increase in renal blood flow after birth and over the first 2 weeks glomerular filtration also increases by two-fold. Most aspects of renal function are immature at birth and these are more obvious in the preterm neonate. The maximum concentrating ability of the neonatal kidney is less than that of the adult and are also less capable of handling water load. Immature tubular functions often result in increased water and electrolyte losses which have to be compensated especially in the preterm infant. Extrauterine life also imposes increased risk of insensible water losses (particularly at birth) which predispose especially the preterm neonates, to hypothermia, dehydration and risks of hyponatremia. The immature glomerular functions also predispose neonates to bicarbonate loss and acidosis.

## HEMATOLOGIC CHANGES

The predominant hemoglobin in the fetus is fetal hemoglobin which is characterized by its high affinity for oxygen. This is due to its decreased binding to 2,3-glycerophosphate compared to adult

hemoglobin. Production of adult hemoglobin in fetal life starts in late gestation while the production of fetal hemoglobin is switched off at birth. The newborn has a high hemoglobin at birth (average of 17 g/dL), which falls by 8–12 weeks to its nadir of about 10 g/dL.

## CIRCADIAN RHYTHM

The fetal circadian rhythms are established as early as 20 weeks of gestation. The regulatory mechanism for the fetal diurnal rhythm is unclear. After birth it takes about 3 months for the sleep and wakefulness circadian rhythm to be established.

### IN A NUTSHELL

1. The most significant transition at birth is from placental dependent gas exchange to lung dependent gas exchange. This is facilitated by fetal lung fluid clearing in late gestation and with onset of labor.
2. Circulatory adaptation results in a shift from a *parallel* fetal circulation to a circulation in *series* with closure of shunts at the levels of ductus arteriosus and foramen ovale and increased pulmonary flow facilitated by decrease in pulmonary vasculature resistance.
3. Metabolic adaptation involves gluconeogenic and glycogenolytic mechanism to maintain euglycemia soon after birth till adequate feeding is established. These are impaired in preterm and growth retarded infants which predispose them to increased risk of hypoglycemia.
4. Feeding of breastmilk facilitates postnatal gut adaptation.

### MORE ON THIS TOPIC

- Barker PM, Oliver RE. Clearance of lung fluid during the perinatal period. *J Appl Physiol.* 2002;93:1542-48.
- Polin RA, Fox WW, Abman SH. *Fetal and Neonatal Physiology.* 4<sup>th</sup> ed. Philadelphia: Elsevier Saunders; 2011.
- Platt MW, Deshpande S. Metabolic adaptation at birth. *Semin Fetal Neonatal Med.* 2005;10:341-50.
- Sansoucie DA, Cavaliere TA. Transition from fetal to neonatal circulation. *Neonatal network.* 1997;16:1-12.

## Chapter 11.4

# Neonatal Mortality and Morbidities: An Overview

Aparna Chandrasekaran, M Jeeva Sankar

The neonatal period, the first 28 days of life, carries the highest risk of mortality per day than any other period during the entire childhood. The daily risk of mortality in the first 4 weeks of life is about 30-fold higher than the period from 1 month to 59 months of age. Indeed, of every two children who die before reaching 5 years of age, one dies in the first 28 days of life. Still, newborn health did not receive the attention it deserves until a few years ago. This resulted in a slow decline in neonatal mortality rate (NMR) in most countries which hampered their chances of achieving the Millennium Development Goal-4 (MDG 4) by year 2015. The fact that neonatal deaths are largely unaffected by *traditional* child health interventions like immunization, oral rehydration therapy, oral antibiotics for pneumonia, etc., has rightly turned the spotlight on those interventions that are known to reduce the neonatal mortality. This has led to significant gains in the last 4–5 years but a lot needs to be done to compensate for the early years of inertia.

This chapter provides an overview of the burden, trends, and causes of neonatal mortality, and the burden of common morbidities at both global and country level. **Box 1** enlists the common terminologies related to perinatal and neonatal mortality along with their definitions.

## NEONATAL MORTALITY: BURDEN, TRENDS, AND GOALS

### Global

Around 2.9 million newborns die every year across the globe (2012 estimates). The number has declined from 4.4 million in 1990 to 2.9 million in 2012, a reduction by nearly 35% which is lower than the decline of about 50% in postneonatal child mortality during the same period. The current global NMR is 21 per 1000 livebirths, the rate varying from 1 per 1000 livebirths (Japan) to 49.5 per 1000 livebirths (Sierra Leone). The MDG 4 targeted a reduction in under-5 deaths by two-thirds by year 2015 from the baseline of 1990. While some countries are on track to achieve this goal, many countries are not. Looking beyond 2015, the countries have now committed themselves to *Every Newborn* target of fewer than 12 per 1000 livebirths and 10 per 1000 livebirths by 2030 and 2035, respectively.

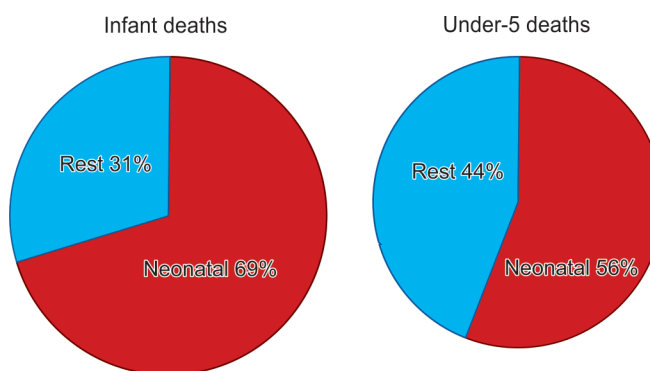
### India

About 0.78 million neonates die every year in India, the highest for any country in the world. Indeed, India alone contributes to more than a quarter of global neonatal deaths. The total number of deaths has declined from 1.32 million in 1990 which translates into a reduction of about 42%. In contrast, the postneonatal child deaths declined by more than 50% during the same period. The disproportionately slow decline in neonatal mortality has led to an increasing proportion of child deaths occurring in the neonatal period—from 46% in 1990 to 57% in 2012.

The current (2014) NMR of India is 28 per 1000 livebirths, much higher than the global average. Given the current infant mortality and under-five mortality rates of 40 and 49 per 1000 livebirths respectively, about 70% of infant deaths and more than half of under-five child deaths in the country occur during the neonatal period (**Fig. 1**). The NMR in 2012 varied from 7 per 1000 livebirths in Kerala to 39 per 1000 livebirths in Madhya Pradesh and Odisha

### BOX 1 Common terminologies and their definitions

- **Neonatal death:** The death of a live born infant during the period that commences at birth and ends 28 completed days after birth
- **Neonatal mortality rate (NMR):** Number of deaths among all livebirths during the first 28 days of life expressed per 1000 livebirths
- **Early neonatal mortality rate (ENMR):** Number of neonatal deaths less than 7 days of life expressed per 1000 livebirths
- **Late neonatal mortality rate (LNMR):** Number of neonatal deaths between 7 days and 28 days of life expressed per 1000 livebirths
- **Infant mortality rate:** Probability of dying between birth and one year of age expressed per 1000 livebirths
- **Under-5 child mortality rate:** Probability of dying between birth and five years of age expressed per 1000 livebirths
- **Stillbirth:** The death of a fetus weighing at least 500 g (or if birth weight unavailable, after 22 completed weeks of gestation or crown heel length of 25 cm or more) before the complete expulsion from its mother
- **Perinatal mortality rate:** Number of deaths of fetuses weighing at least 500 g (or if birth weight unavailable, after 22 completed weeks of gestation or crown heel length of 25 cm or more) plus the number of early neonatal deaths per 1000 total births.



**Figure 1** Neonatal deaths as a percentage of infant and under-5 deaths in India

Source: SRS Statistical Report, 2012.

(**Fig. 2**). The early neonatal mortality rate (ENMR), deaths in the first week of life, is 22 per 1000 livebirths, while late NMR is 6 per 1000 livebirths. The first week of life alone accounts for 45% of total under-5 child deaths. Unfortunately, the rate of decline in early NMR is much lower than that of late NMR (**Fig. 3**).

The projected NMR of India for year 2035, assuming the same rate of reduction in NMR from 1990 to 2012, is 16 per 1000 livebirths, much higher than the *Every Newborn* target of fewer than 10 per 1000 livebirths. This underlines the need to implement and scale-up simple and effective interventions on an urgent basis across different settings.

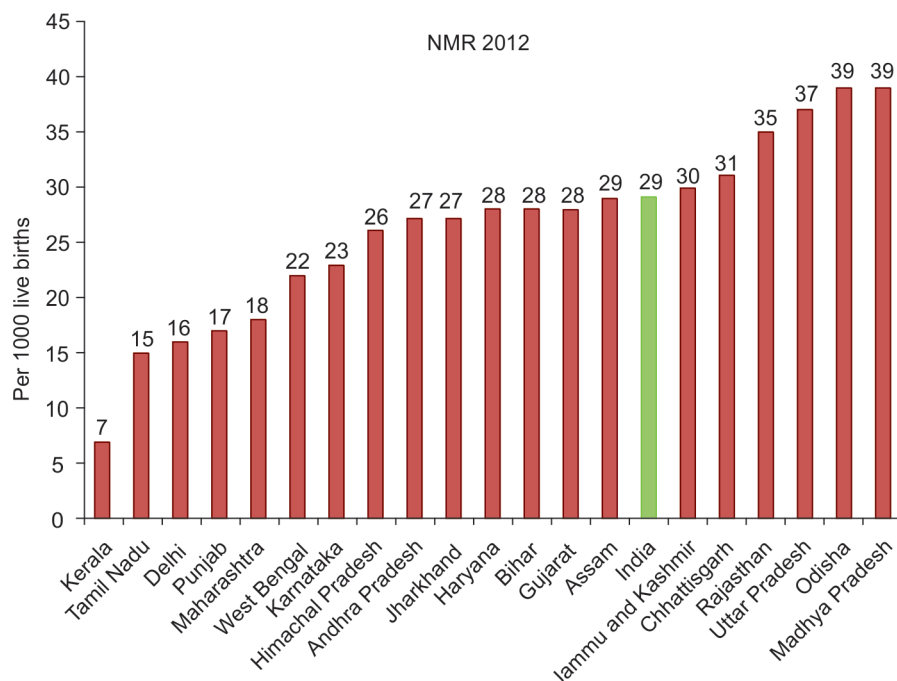
## WHERE DO NEWBORNS DIE?

### Global

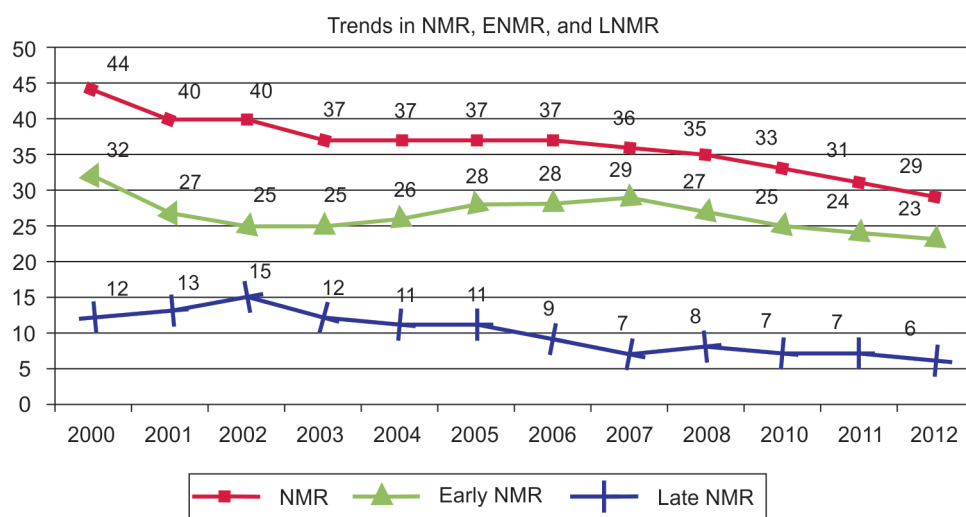
Most of the neonatal deaths (about 99%) occur in low- and middle-income countries. Only five countries, India, Nigeria, Pakistan, China, and Democratic Republic of Congo, account for more than half of these deaths.

### India

Four states, Uttar Pradesh, Madhya Pradesh, Bihar, and Rajasthan, alone contribute to about 55% of total neonatal deaths in India (**Fig. 4**). Together, these four states account for about 15% of *global* neonatal deaths. The proportion of neonatal deaths occurring in the health facility ranges from 5% in Jharkhand to more than 80%



**Figure 2** Neonatal mortality rate (NMR) of India and larger Indian states  
Source: SRS Statistical Report, 2012.



**Figure 3** Trends of neonatal mortality rate (NMR), early neonatal mortality rate (ENMR) and late neonatal mortality rate (LNMR) in India  
Source: SRS Statistical Reports (2000-2012).

in Kerala. More than half of neonatal deaths occur at home in all states except those with least NMR and high rates of institutional births namely, Kerala, Tamil Nadu, and Delhi. The NMR in rural areas is twice that of urban areas—33 versus 16 per 1000 livebirths. The discrepancy is more marked (i.e., a difference of 60% or more) in Andhra Pradesh, Assam, Jharkhand, and Kerala.

## WHY DO NEWBORNS DIE?

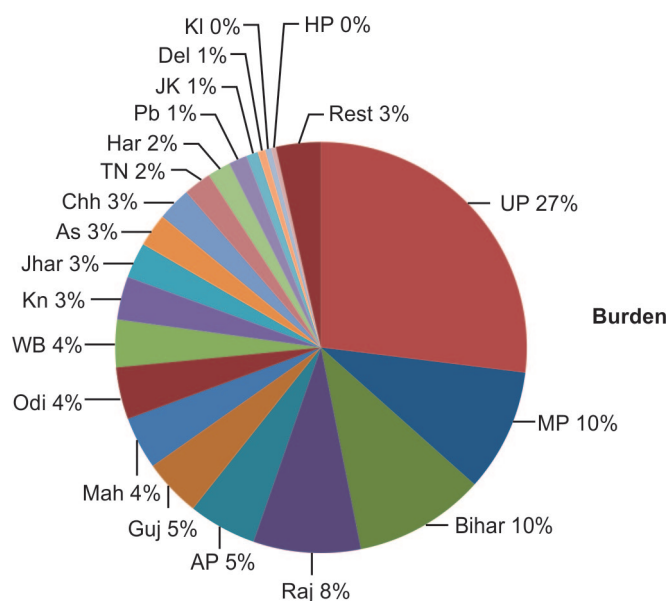
### Global

A systematic analysis of causes of neonatal and childhood deaths identified complications from preterm birth (35%), infections

(sepsis/meningitis/pneumonia/tetanus/diarrhea; 27%), and intrapartum-related conditions (birth asphyxia; 23%) to be the three major causes of neonatal deaths across the globe.

### India

The same three conditions, preterm birth complications, infections, and intrapartum-related conditions/birth asphyxia, cause majority of deaths in India as well. But as compared to global figures, a higher proportion of infection-related deaths occur in India (**Fig. 5**). In addition to the direct causes, a host of other socioeconomic, demographic, and other factors play an indirect role in causing neonatal deaths. The NMR among the poorest 20%



**Figure 4** Burden of neonatal deaths in Indian states

Note: 'Rest' includes smaller states like Uttarakhand, Goa, and all union territories

(AP–Andhra Pradesh; As–Assam; Chh–Chhattisgarh; Del–Delhi; Guj–Gujarat; Har–Haryana; HP–Himachal Pradesh; Jh–Jharkhand; JK–Jammu and Kashmir; KI–Kerala; Kn–Karnataka; Mah–Maharashtra; MP–Madhya Pradesh; Odi–Odisha; Pb–Punjab; Raj–Rajasthan; TN–Tamil Nadu; UP–Uttar Pradesh; WB–West Bengal)

of the population is more than double the NMR of the richest 20%. Girls do have a lower *biological* risk of mortality during infancy but a higher *social* risk of neonatal and infant mortality due to sub-optimal nutrition and reluctance of parents to seek early and optimal healthcare. Other social factors like early maternal age at childbirth and less than optimal birth spacing also contribute to the high mortality and morbidities.

## WHEN DO NEWBORNS DIE?

### Global

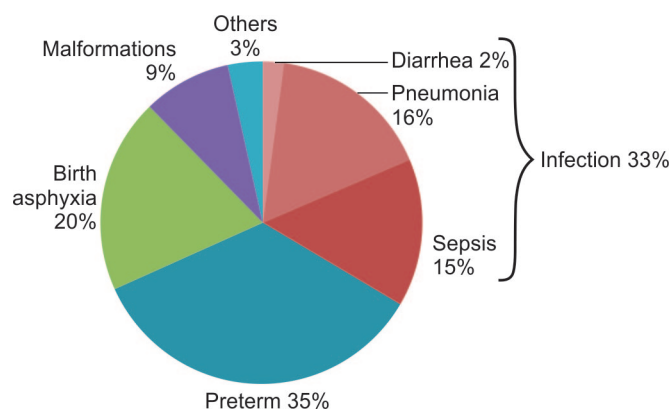
Of the total deaths that occur during the neonatal period, about 75% occur in the first week of life. The first three days of life alone account for more than half of the total neonatal deaths.

### India

The timing of overall and cause-specific neonatal deaths in India is not different from the global figures. About three-fourths of the total neonatal deaths occur in the first week of life, the first day alone accounting for more than one-third of the deaths (**Figs 6A and B**). Almost all asphyxia related deaths and majority of prematurity related deaths (83%) happen within the first week of life but more than half of infection related deaths occur after the first week.

## PERINATAL MORTALITY AND STILLBIRTH RATE

The perinatal mortality rate (PMR) is defined as the number of stillbirths and infant deaths of less than 7 days per 1000 total births (livebirths and stillbirths) during the year while stillbirth rate (SBR) is defined as the number of stillbirths per 1000 total births during the year.



**Figure 5** Causes of neonatal deaths in India

The current perinatal mortality rate of India (2013) has been estimated to be 28 per 1000 births. It ranges from 17 per 1000 births in urban areas to 31 per 1000 births in rural areas. As with NMR, the perinatal mortality rate is not uniform across the country; the PMR of Kerala is only 9 per 1000 births whereas that of Odisha is 35 per 1000 births.

The SBR of India for the year 2013 is estimated at 4 per 1000 births. The figures of both SBR and PMR are likely to be underestimates, as stillbirths are extremely difficult to capture. Also, there is a great room for misclassification of these deaths. Interestingly, the SBR for year 2009, as estimated by the international agencies, was 22.1 per 1000 births while the SRS estimate for year 2010 was only 7 per 1000 births.

## NEONATAL MORBIDITIES

While mortality is just the proverbial tip of iceberg, the morbidities constitute the huge base that remains hidden and often does not receive the due attention it deserves. **Box 2** provides definitions for the common neonatal morbidities.

### Global

The profile of neonatal morbidities is likely to be different across the globe because of the differences in demographic and social characteristics, ethnicity, economic status, and more importantly, the availability and quality of intrapartum and postnatal care. A large network study involving one hospital each in six countries of South East Asia Region (SEAR) identified low birth weight (LBW) (< 2500 g; 19.0%), prematurity (13.1%), birth asphyxia (8.7%), neonatal jaundice (6.4%), and sepsis (5.7%) to be the most common morbidities among livebirths at these tertiary care hospitals.

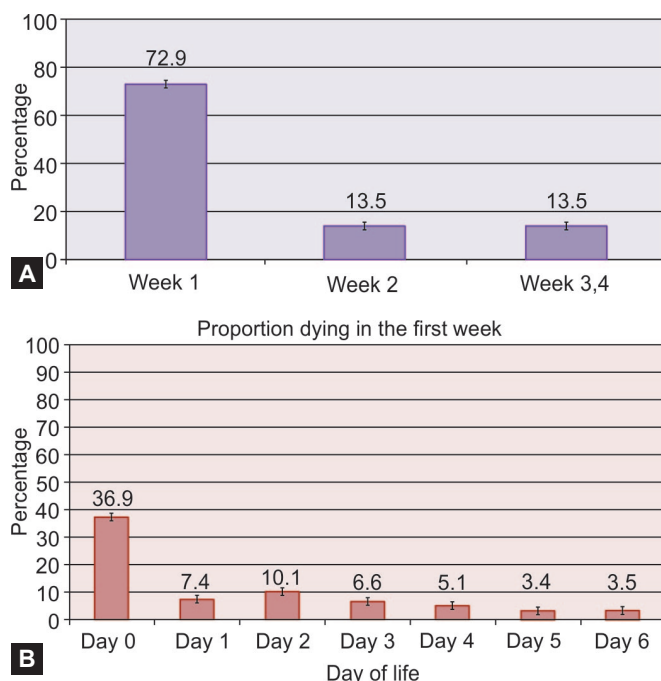
### India

The common morbidities reported in a large multicenter study involving 18 major hospitals across India include LBW, preterm births, birth asphyxia, neonatal jaundice, and sepsis among others (**Table 1**). The figures might be an overestimate of the true incidence in the population, as many of the study hospitals cater to high-risk pregnancies. A community-based study from Gadchiroli, Maharashtra involving 763 neonates found LBW, breastfeeding problems, neonatal infections, umbilical sepsis, and hypothermia to be the common morbidities (**Table 2**). Only 12.8% neonates did not suffer from any of the morbidities. The major neonatal morbidities are described in detail in the subsequent sections. A brief summary of the burden of the most common and severe morbidities is provided here.



### Low Birth Weight/Preterm Birth

Globally, a total of 18 million babies are born every year with a LBW, i.e., less than 2500 g. About 60% of them are born at term after fetal growth restriction while the rest are due to prematurity. Around 14 million neonates were born preterm, i.e., before 37 weeks of gestation, every year in the world.



**Figures 6A and B** Timing of neonatal deaths in India. (A) Distribution of neonatal deaths (week-wise); (B) Proportion of neonates dying in the first week of life

Source: Sankar MJ 2015 (Systematic review-under publication).

#### BOX 2 Definition of common neonatal morbidities

**Low birth weight (LBW):** Birth weight less than 2500 g

**Preterm:** Gestational age of less than 37 completed weeks (i.e. less than 259 days)

**Respiratory distress:** Presence of at least 2 of the following criteria: respiratory rate > 60/min, Subcostal/intercostal recessions and expiratory grunt/groaning

**Neonatal sepsis (Culture positive):** Presence of clinical picture suggestive of septicemia, pneumonia or meningitis along with the isolation of pathogens from blood or CSF or urine or pathological evidence of sepsis on autopsy

**Neonatal sepsis (Culture negative):** In a neonate having clinical picture suggestive of septicemia, the presence of any one of the following criteria is sufficient for assigning probable diagnosis of sepsis:

- Maternal risk factors: maternal fever or foul smelling liquor or prolonged rupture of membranes (> 24 hours)
- Positive septic screen (two of the five parameters namely, TLC (< 5000/cmm, band to total polymorph ratio of > 0.2, absolute neutrophil count less than 1800/cmm, C-reactive protein > 1 mg/dL and micro ESR > 15 mm in 1st hour)
- Radiological evidences of pneumonia

**Birth asphyxia:** Apgar score of less than 7 at 1 min of age

**Hypothermia:** Skin temperature below 36.5°C

**Hypoglycemia:** Whole blood glucose of less than 40 mg/dL

**Umbilical sepsis:** Presence of redness or swelling, with or without pus, in the skin surrounding the umbilical cord stump

**Hyperbilirubinemia:** Serum bilirubin greater than 15 mg/dL in a term neonate or < 15 mg/dL in a preterm neonate, and requiring treatment in the form of phototherapy or exchange transfusion

**Major congenital malformation:** A malformation that is life threatening or requires surgical correction.

In India, about 30% of all livebirths, 7.5 million, are born with a LBW. This accounts for 42% of the global burden, the largest for any country. The relative proportion of term growth restricted infants and preterm infants are almost the same as the global figure. Around 3.5 million neonates are born preterm every year in the country. This constitutes a quarter of the total preterm births.

Low birth weight/preterm infants are at higher risk of dying in the neonatal period and beyond, when compared to term normal birth weight (NBW) babies. Community-based studies indicate that the LBW infants are at 11–13 times increased risk of dying than NBW infants. Indeed, more than 80% of total neonatal deaths occur among LBW/preterm neonates. These infants are also at a higher risk of asphyxia, sepsis, hypothermia, and feeding problems. LBW increases the odds of underweight, stunting, and wasting in the first 5 years of life; about 28% of underweight and stunting, and 22% of wasting at 6 months of age can be attributed to LBW. Preterm/LBW infants are also at high risk of major neurodevelopmental disabilities. Around 10% of LBW infants have major disabilities at 3 years of corrected age. The mean IQ of LBW infants at six years, though within normal limits, are significantly lower than that of NBW infants. LBW infants are also predisposed to a variety of adult onset diseases in later life because of the anomalous programming of affected fetuses.

**Table 1** Incidence of selected morbidities in babies born in health facilities of India

Morbidity	Incidence (%) (N = 145,623)
Low birth weight (LBW)	31.3
Preterm	14.5
Birth asphyxia	8.4
Neonatal jaundice	3.3
Sepsis	3.0
Hypoxic ischemic encephalopathy (HIE)	1.4
Respiratory distress syndrome (RDS)	1.2
Seizures	1.0
Hypoglycemia	0.9
Cardiac malformations	0.5

**Table 2** Incidence of selected morbidities in community settings in India

Morbidity	Incidence (%) (N = 763)
Low birth weight	41.9
Breastfeeding problems	25.6
Umbilical sepsis	19.8
Neonatal sepsis/pneumonia	18.0
Hypothermia	17.0
Skin infections	12.4
Conjunctivitis	12.3
Prematurity	9.8
Birth asphyxia	6.2
Diarrhea	5.5
Abnormal jaundice	1.7
Hemorrhage	1.4
Congenital malformations	1.3

## Neonatal Sepsis

Neonatal sepsis encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections. Studies from developing countries report an incidence ranging from 30 to 170 per 1000 livebirths, whereas those from the developed countries report rates of only 1 to 3 per 1000 livebirths. The burden of neonatal sepsis is huge in India. Hospital based studies suggest an incidence of 30 per 1000 livebirths, while community-based studies indicate an incidence of 2.7–17%. Sepsis is the most common morbidity in neonates referred to a hospital from home/another health facility; up to 60% of these neonates are labeled as having neonatal sepsis during their hospital stay. Nearly one-fifth of neonates with sepsis die in the hospital; the figure rises to up to 50% for those with culture proven sepsis. They stay longer in the hospital, consume more resources, and are also at a high-risk of major neurodevelopmental disabilities at a later age.

## Birth Asphyxia

Intrapartum related conditions or birth asphyxia not only results in neonatal deaths but also accounts for a significant proportion of stillbirths. It is difficult to estimate the true burden of asphyxia because of the different definitions used in studies from different countries. Community-based studies from India report an incidence of 2–16.2%, with the reported case fatality rates ranging from 38.5% to 74%. The incidence of moderate and severe asphyxia was 2.8% and 5.6%, respectively in a large multicenter study involving 18 major hospitals across India; the case fatality rate was relatively low at about 8.7%.

## REDUCING THE BURDEN OF NEONATAL MORTALITY AND MORBIDITY

### Global

Newborn health has received an unprecedented attention by researchers, policymakers, and governments and global funding agencies in the last few years. This has helped in identifying the effective interventions that are likely to reduce the neonatal mortality, preparing roadmaps for their implementation/scale-up in low-and middle-income country settings, and mobilizing finances and other support to facilitate the entire process. The most critical interventions thus identified are enlisted in **Figure 7**. These interventions span across the antenatal, labor and delivery, and postnatal periods, which underscores the importance of *continuum of care* from the adolescent period of the prospective mother to the childhood period of her progeny.

It has been estimated that increased coverage and quality of the listed interventions can avert 71% of the neonatal deaths and 33% of stillbirths by year 2025. Most of this effect is attributable to those interventions that are delivered at health facilities. Among these interventions, the ones with the maximum benefit are those that are delivered during labor and childbirth, followed by those related to care of small and sick newborns. Institutional births and facility-based care of sick neonates therefore assume a critical role in reducing the burden of neonatal mortality and morbidities.

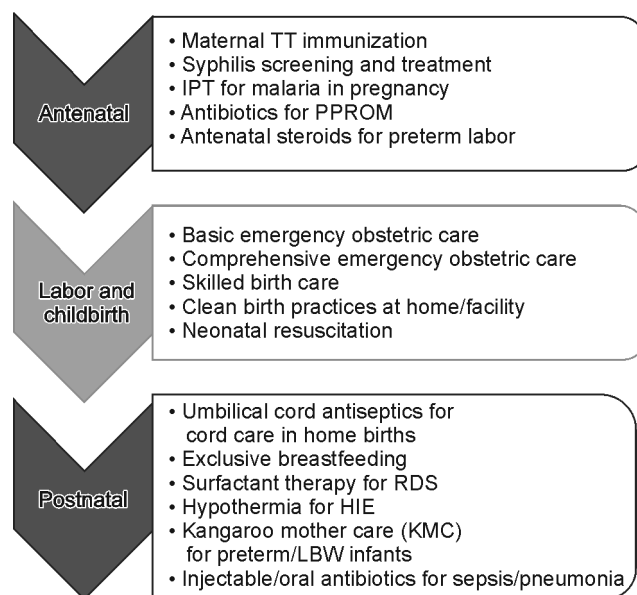
Many developing countries have taken sincere efforts to improve the rates of institutional births in the last decade. For example, India introduced a conditional cash transfer scheme, *Janani Suraksha Yojana (JSY)*, in mid-2005 to promote births in the health facilities, following which there has been a huge surge in the rates of institutional births. But this quantum increase has not readily translated into a major reduction in the neonatal or perinatal

mortality rates. The primary reason for this discrepancy is the sub-optimal quality of care at birth and during the postnatal period in the health facilities. The situation is almost similar in most developing countries. The key is therefore to improve the quality of care in the health facilities. Recent estimates indicate that addressing the quality gap for institutional births alone would prevent 1.3 million neonatal deaths and 0.5 million stillbirths globally every year.

## India

India has witnessed a significant improvement in neonatal health after the introduction of National Rural Health Mission (NRHM) in mid-2005. Apart from the JSY, the country has launched several new initiatives under NRHM to improve the neonatal care. The Facility-based Newborn Care aims to build a three-tier system of neonatal care encompassing the Primary Health Centers, the Community Health Centers, and the District Hospitals. The Home-based Newborn Care program allows home visiting by the Accredited Social Health Activists (ASHAs) for neonatal examination, sickness detection, and family counseling. The *Janani Shishu Suraksha Karyakram (JSSK)* entitles mothers and infants to free transportation, care, medicines, diagnostics, and blood products in all public facilities. The recently launched *Rashtriya Bal Suraksha Karyakram (RBSK)* focuses on screening infants for selected birth defects and developmental delays. The newly created Special Newborn Care Units (SNCUs) in the district hospitals across the nation cater to more than 0.6 million newborn babies each year.

Notwithstanding this newfound focus on neonatal health, the annual rate of reduction in NMR and ENMR still lags behind IMR and U5MR. India is likely to miss the MDG-4, if effective interventions known to reduce NMR and in particular, ENMR, are not implemented and/or scaled up in the next 2–3 years. The country has to increase the coverage of key interventions and also improve the quality of care in health facilities on an urgent basis.



**Figure 7** Interventions to reduce neonatal mortality  
 Abbreviations: TT, tetanus toxoid; IPT, Intermittent preventive treatment; PPRM, preterm prelabor rupture of membranes; RDS, respiratory distress syndrome; HIE, hypoxic ischemic encephalopathy; KMC, Kangaroo mother care.

## IN A NUTSHELL

1. Around 2.9 million newborns die every year across the globe; India contributes to one-fourth of the global burden of newborn deaths.
2. In India, about 0.78 million neonates die every year—the highest for any country in the world.
3. About 70% of infant deaths and more than half of under-five child deaths in India occur during the neonatal period.
4. Globally, 99% of newborn deaths occur in developing nations. In India, four states—Uttar Pradesh, Madhya Pradesh, Bihar, and Rajasthan—alone contribute to about 55% of total neonatal deaths.
5. The major causes of neonatal deaths are prematurity (35%), infections (27%) and intrapartum-related conditions (birth asphyxia; 23%); the profile is not different in India, except for the fact that the proportion of deaths due to infections is higher than the global average.
6. Of the total deaths that happen during the neonatal period, three-fourths occur in the first week of life, and one half within the first 3 days.
7. Almost all asphyxia-related deaths and majority of prematurity related deaths (83%) happen within the first week of life but more than half of infection related deaths occur after the first week.
8. The perinatal mortality and stillbirth rates of India are 28 per 1000 births and 7 per 1000 births, respectively; these are, however, likely to be underestimates of the true burden of perinatal deaths and stillbirths.
9. The most common neonatal morbidities include low birth weight (LBW), preterm births, birth asphyxia, sepsis, and neonatal jaundice.
10. Implementation of select evidence-based interventions during antenatal, labor and child birth, and postnatal periods can avert 71% of neonatal deaths and one-third of the still births across the globe by 2025.

## MORE ON THIS TOPIC

- Bang AT, Reddy HM, Baitule SB, et al. The incidence of morbidities in a cohort of neonates in rural Gadchiroli, India: seasonal and temporal variation and a hypothesis about prevention. *J Perinatol*. 2005;25(Suppl 1):S18-28.
- Baqui AH, Darmstadt GL, Williams EK, et al. Rates, timing and causes of neonatal deaths in rural India: implications for neonatal health programmes. *Bull World Health Organ*. 2006;84:706-13.
- Bhutta ZA, Das JK, Bahl R, et al. The Lancet Newborn Interventions Review Group; The Lancet Every Newborn Study Group. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *Lancet*. 2014 May 19.
- Chaudhari S, Bhalerao MR, Chitale A, Pandit AN, Nene U. Pune low birth weight study—a six year follow up. *Indian Pediatr*. 1999;36:669-76.
- Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: when? Where? Why? *Lancet*. 2005;365:891-900.
- Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet*. 2012;379:2151-61.
- National Neonatal Perinatal Database. Report for the year 2002–03. From: [http://www.newbornwhocc.org/pdf/nnpd\\_report\\_2002-03.PDF](http://www.newbornwhocc.org/pdf/nnpd_report_2002-03.PDF). Accessed Sep 27, 2014.
- Paul VK, Sachdev HS, Mavalankar D, et al. Reproductive health, and child health and nutrition in India: meeting the challenge. *Lancet*. 2011;377:332-49.
- Registrar General of India. Sample Registration System (SRS) Statistical Report 2012. New Delhi: 2013.
- Save the Children. State of India's Newborns 2014. New Delhi: 2014
- UNICEF, WHO, The World Bank, and United Nations. Levels & Trends in Child Mortality. Report 2013 - Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation. New York: 2013.

## Chapter 11.5

# Organization of Neonatal Care

Subhash Chandra Shaw, Vinod K Paul

Neonatal health is the key to child survival. Organized newborn care that started in India in the early sixties at a few teaching hospitals has taken a center stage in the country's national child health programs ever since the Child Survival and Safe Motherhood program was launched in 1992 when essential newborn care was introduced. Neonatal health strategies are linked closely to maternal care including antenatal care, institutional deliveries, emergency obstetric care (EmOC) and postnatal care.

There are two broad domains of neonatal care in the public health system in India: the home-based newborn care (HBNC) and the facility-based newborn care (FBNC). In addition, neonatal care is provided in large government hospitals (in medical colleges, maternity hospitals) and the private sector hospitals. HBNC is provided by Accredited Social Health Activists, who are the frontline community health workers. They pay seven visits to mothers and newborns (on days 1, 3, 7, 14, 21, 28 and 42 of birth) for home births, and six visits to the facility-born babies (no visit on day 1). The babies are weighed and examined for sickness. Mothers are counseled on newborn care and postpartum care. Sick neonates are referred. FBNC is extremely important in reducing neonatal mortality. The next sections will dwell in detail on care of neonates in facilities, mainly in public health sector.

## LEVELS OF CARE

It is a system of tiered perinatal and neonatal care, based on the capacity and capability of their hospitals and physicians to handle the degree of complexity of the patients referred to them. The broad objectives of this categorization are to achieve quality of care to all newborns, maximum utilization of resources, and reasonable cost-effectiveness.

## American Academy of Pediatrics Classification

The updated classification of American Academy of Pediatrics consists of basic care (level I), specialty care (level II) and subspecialty care (level III, level IV; **Table 1**). The neonatal unit should be located near maternity areas, in particular, the delivery rooms. For practical purposes, for 2,000 deliveries, an 8–10 bedded nursery is required. The general physical norms of level II onwards units include: space of 10 m<sup>2</sup> for each baby, 24 × 7 water supply with enough wash basins, electricity backup, thermal-controlled environment that maintains temperature at 26–28°C and 12 air changes per hour, 8–12 electrical outlets per baby bassinet/incubator, at least 100 foot candle light intensity, and sound level not exceeding 75 decibels. The main newborn care area should be complemented by mothers' room, waiting area, nurse and doctor duty rooms, utilities room, pharmacy, area for total parenteral nutrition, stores, etc. For level III/IV nursery, the ratio of nurse to bed will be 1:1 or higher. For level II unit, it may be 1:2. In recent time, a developmentally conducive environment in the nurseries is promoted. This has comfortable day-night pattern, toys for individual babies and gentle music.

The neonatal units are technology intense. Incubators, radiant warmers, weighing scales, phototherapy units, infusion pumps, monitoring devices, continuous positive airway pressure machines, ventilators, etc., are integral part of neonatal units. The norms for these are provided in various accreditation systems including those of the National Neonatology Forum. In addition, neonatal units must have impeccable infection control norms and systems.

## Facility-based Newborn Care

As per Indian public health standards, newborn care facilities are provided at three levels, i.e., maternal and child health (MCH) level I, MCH level II and MCH level III (**Table 2**).

*Newborn care corner* is a space within any delivery room (labor room or operation theatre) in any health facility where immediate care is provided to all newborns at birth. This area is mandatory for any health-care facility conducting deliveries.

**Table 1** Levels of neonatal care (American Academy of Pediatrics)

Level of care	Capabilities	Provider types
Level I Well newborn nursery	Neonatal resuscitation at every delivery, postnatal care to stable term newborn infants, stabilize and care for infants born between 35 weeks and 37 weeks gestation who remain physiologically stable, stabilize ill and those born at < 35 weeks gestation until transfer to a higher level of care	Pediatricians, family physicians, nurse practitioners
Level II Special care nursery	<i>Level I capabilities plus:</i> Care for infants born ≥ 32 weeks of gestation and weighing ≥ 1,500 g, provide care for infants convalescing after intensive care, provide mechanical ventilation for brief duration (< 24 hours) or continuous positive airway pressure or both, stabilize infants born before 32 weeks of gestation and weighing < 1,500 g until transfer to a neonatal intensive care facility	<i>Level I health providers plus:</i> Pediatric hospitals, neonatologists and neonatal nurse practitioners
Level III Neonatal intensive care unit	<i>Level II capabilities plus:</i> Provide sustained life support, provide comprehensive care for infants born < 32 weeks gestation and weighing < 1,500 g and infants born at all gestational ages and birth weight with critical illness, ready availability to full range of pediatric medical subspecialists, pediatric surgical specialists, pediatric anesthesiologists and pediatric ophthalmologists, full range of respiratory support including conventional and/or high-frequency ventilation and inhaled nitric oxide, perform advanced imaging with interpretation on an urgent basis, including CT, MRI and echocardiography	<i>Level II health providers plus:</i> Pediatric hospitals, neonatologists and neonatal nurse practitioners
Level IV Regional neonatal intensive care unit	<i>Level III capabilities plus:</i> Capability to provide surgical repair of complex congenital or acquired conditions, facilitate transport and provide outreach education, full range of medical and surgical subspecialists at the site	<i>Level III healthcare providers plus:</i> Pediatric surgical subspecialists



**Table 2** Levels of care of neonatal care facilities under the National Rural Health Mission, India

Health facility	All newborns at birth	Sick newborns
MCH Level I Primary health center (PHC)/subcenter (SC)	Newborn care corner in labor room	Prompt referral
MCH Level II Community health center (CHC)/first referral unit (FRU)	Newborn care corner in labor room and in operation theater	Newborn stabilization unit
MCH Level III District hospital	Newborn care corner in labor room and in operation theater	Special care newborn unit (SCNU)

Abbreviation: MCH, maternal and child health.

*Newborn stabilization unit* is situated within or in close proximity of a maternity ward where sick babies and low birth weight (LBW) infants greater than and equal to 1,800 g can be cared for during short periods. All community health centers/first referral units (CHCs/FRUs) need to have a neonatal stabilization unit, in addition to the newborn care corner.

*Special Care Newborn Unit (SCNU)* on the other hand is a neonatal unit which can provide special care (all care except assisted ventilation and major surgery) for sick newborns and LBW infants less than 1,800 g. All facilities with more than 3,000 deliveries (most district hospital and some subdistrict hospitals) per year should have SCNU.

Expected services to be provided at all newborn care facilities, as planned by Ministry of Health and Family Welfare, Government of India, are care at birth of all newborns (prevention of infection, provision of warmth, resuscitation, early initiation of breastfeeding and weighing of newborn), care of normal newborn (breastfeeding/feeding support) and immunization services. However, the level of care of sick newborn differs as mentioned in **Table 3**.

## SETTING UP OF NEWBORN CARE FACILITIES

- *Newborn care corner* An area about 20–30 square feet in size within labor rooms or operation theatre is required for setting up a newborn care corner and should be equipped with a radiant warmer, weighing scale, foot operated pump suction, syringe hub cutter and resuscitation kit.
- *Newborn stabilization unit* Comprises of at least four beds with a total of at least 200 square feet (50 square feet/bed) area with two beds in postnatal ward dedicated for rooming in. There should be 24 hours uninterrupted power and water supply. It should have high-intensity phototherapy units, laryngoscope set and electronic baby weighing scale.
- *Special care newborn unit* Recommended number of beds is 12 for 3,000 deliveries per year. Four beds are to be added for each 1,000 additional deliveries. On an average, a total area of 100 square feet per patient (50 square feet for patient care area and 50 square feet for ancillary area) is required. The ancillary area includes separate areas for hand washing and gowning area, nurses work station, clean area for mixing fluids and medications, doctors duty room, mother's area for breastmilk expression, unit store and a side lab. The number of rooming in beds required is 30% of SCNU beds. Each SCNU should have oxygen supply system with oxygen concentrators, pulse oximeters, electronic sphygmomanometer, multichannel monitor, electrocardiogram unit, mobile X-ray machine, transport incubator and electrical autoclave machine. The

needs of human resources as followed by Ministry of Health and Family Welfare, Government of India, are shown in **Table 4**.

More than 70% of newborns are normal and need minimal care and another 10% need supervised care at home. Supervised care at CHC and level II hospitals comprise about 16–18% of all newborns and level III is needed by 2–3% of all newborns. In a population of 1000,000, there will be 20,000–25,000 child births per year. There will be 1,800 neonates (8%) requiring hospital care, i.e., 60 beds for sick, premature and LBW neonates. There will be a need of five SCNU of 12 beds each per district. At least 60% of these beds should ideally be in government hospitals and rest in private setup.

Neonatal care must be linked to EmOC. EmOC includes services aimed at improving the availability, accessibility, quality and use of services for the treatment of complications that arise during pregnancy. Good quality EmOC should be universally available and accessible and all women should deliver their infants in the presence of a skilled birth attendant and these should be integrated into the health system.

At MCH level I, there should be a facility for basic EmOC. Basic EmOC includes administering antenatal steroids, administering parenteral antibiotics, administering uterotonic drugs (i.e., parenteral oxytocin), administering parenteral anticonvulsants for

**Table 3** Services at different levels of neonatal care under National Rural Health Mission, India

Newborn care corner	Newborn stabilization unit	Special care newborn unit
Identification and prompt referral of <i>at risk</i> and <i>sick</i> newborn	<ul style="list-style-type: none"> <li>• Management of low birth weight infants <math>\geq 1,800</math> g with no other complication</li> <li>• Phototherapy for newborns with hyperbilirubinemia</li> <li>• Management of newborn sepsis</li> <li>• Stabilization and referral of sick newborns and those with very low birth weight</li> <li>• Referral services</li> </ul>	<ul style="list-style-type: none"> <li>• Management of low birth weight infants <math>&lt; 1,800</math> g</li> <li>• Managing all sick newborns (except those requiring mechanical ventilation and major surgical interventions)</li> <li>• Follow-up of all babies discharged from the unit and high-risk newborns</li> <li>• Referral services</li> </ul>

**Table 4** Human resource recommendations for newborn care in India

Personnel	Newborn care corner	Newborn stabilization unit	Special care newborn unit
Doctor	1	1	3–4
Nurse	1	4	10
Auxiliary Nurse Midwife	1	-	-
Training in	Navjat Shishu Suraksha Karyakram (NSSK)	Facility-based IMNCI (F-IMNCI)	Facility-based newborn care (FBNC)
Duration of training	2 days	11 days for those who have not been trained in IMNCI and 5 days for those who are already trained in IMNCI	4 days training followed by 2 weeks of observership

Abbreviation: IMNCI, integrated management of neonatal and childhood illness.

pre-eclampsia and eclampsia (i.e., magnesium sulfate), manual removal of the placenta, removing retained products of conception (e.g., manual vacuum extraction, dilation and curettage), performing assisted vaginal delivery (e.g., vacuum extraction, forceps delivery), performing basic neonatal resuscitation. At MCH level II, there should be provision of cesarean section and blood transfusion in addition.

### Accreditation Guidelines for Levels of Care in India

National Neonatology Forum of India has published recently, the accreditation guidelines for neonatal units in the country. The classification of newborn units as level IA, level IB, level IH (subcenter or equivalent), level IIA, level IIB, level IIIA and level IIIB are based on criteria that include patient-care load, number of deliveries or capability of caring for neonates of a certain gestational age or birth weight, etc. (Table 5).

### ORGANIZING KANGAROO MOTHER CARE

Kangaroo Mother Care (KMC) is an evidence-based intervention for stable preterm/LBW infants. KMC is initiated in stable preterm/LBW neonates in the facilities and continued at home after discharge. Unstable or sick preterm/LBW neonates are cared for in the SCNUs. For such babies, their mothers provide breastmilk/feeding and other care. In addition, KMC is initiated under supervision of the nurses/doctors in the SCNUs by their mothers when babies become stable. With further improvement, babies are transferred out from the SCNU to the mother in the postnatal care where KMC is continued till discharge.

It is evident that mothers have an overwhelming role in the care of preterm/LBW neonates, in particular, for optimum KMC. It is therefore essential that each hospital that has an SCNU ensures that there is a provision of beds for the mother-baby dyads to facilitate KMC and other care. Accordingly, it is recommended that each hospital with a NICU or a nursery or an SCNU should have a KMC unit.

A KMC unit of eight beds would be required for a typical 20 bedded neonatal unit or SCNU and should be built as an extended part of the new/upcoming SCNUs. For the existing SCNUs, it should be located as close to the SCNU as possible in the existing/new premises. Air temperature should be maintained at 24–26°C with relative humidity of 50–60%. It should be well-lighted and well-ventilated and for each eight-bedded room a total of 1,500 square feet space is needed.

There should be adult hospital beds with railings (eight in number) with comfortable semireclining chairs next to each infant bed for mothers to impart KMC (eight in number). There should be provision of a resuscitation kit, oxygen cylinder and hood, clinical thermometers, a weighing machine, a refrigerator to keep breastmilk and drugs and a room thermometer.

### TRANSPORT SYSTEM

As a consequence of development of different levels of neonatal care, there has been an increased emphasis on in utero transfer of at risk mothers to the next higher center as shown in studies from Canada and New Zealand where the outcome of very LBW babies was found to be better in inborn rather than outborn babies. Many a time when the transfer of mother is not feasible, there should be a system in place to transport after birth from lower to higher level unit. Neonatal transport brings the intensive care environment to critically ill infants before and during inter and intrahospital transports. In India, neonatal transport is mostly self-transport by parents or done by the source hospital by utilizing private ambulances and semi-trained or ill-trained personnel. When the staff is less experienced, the risk of adverse events on such transports can be greater than with well-equipped and trained staff. Whereas organized transport services provide almost the same level of monitoring and the quality of care during the transport that is available in the advanced care facility. Ideally, it should have the ability to provide mechanical ventilation, multiple fluid infusion therapy and cardiorespiratory monitoring along with provision

**Table 5** National Neonatal Forum (NNF) levels of neonatal care for India

Levels of care	Gestational age and birth weight	Patient load (No. of admission in a year)	Comments
IA			NCC at PHC
IB	≥ 1,500 g, ≥ 32 weeks	≥ 100	NSU at CHC, FRU
IH			Government subcenter or equivalent
IIA	≥ 1,000 g, ≥ 30 weeks	≥ 200	Availability of CPAP Services of trained pediatrician in neonatology
IIB	≥ 1,000 g, ≥ 30 weeks	≥ 300	In addition, short-term basic ventilation
IIIA	Includes below 1,200 g		<i>Desirable elements in addition:</i> Prolonged conventional ventilation ROP screening High-risk follow-up services Metabolic screening Broad specialty course in pediatrics or short fellowship in neonatology
IIIB	Includes below 1,200 g		<i>In addition:</i> Advanced ventilation therapy including surfactant High-frequency ventilation In-house CT/MRI Neonatal surgical interventions DM/DNB program in neonatology

**Abbreviations:** NCC, newborn care corner; NSU, newborn stabilization unit; SCNU, special care newborn unit; PHC, primary health center; CHC, community health centers; FRU, first referral units; CPAP, continuous positive airway pressure; ROP, retinopathy of prematurity.

**Table 6** Description of neonatal transport system

Components	Comprised of	Comments
Human resources	Physician trained in neonatology Physician/nurse managing equipment, ambulance, personnel, communication and documentation Other skilled transport team members	All team members should be able to provide basic care to sick neonates: Keeping them warm during transport Asepsis Monitoring vitals Skilled in essential procedures like establishing venous access Providing positive pressure ventilation
Vehicle and equipment	Vehicle	Source of oxygen Power supply Sufficient light Secure fixation of incubator, monitors, infusion pumps Minimization of shaking, draught of air
	Equipment	Thermal support equipment ideally a transport incubator, if not then thermocol box, plastic wrap, insulating blankets or while doing Kangaroo mother care with mother Respiratory support equipment Suction and monitoring equipment Parenteral infusion equipment, medications
Communication and family support		Information about the newborn's clinical condition and prognosis Opportunity to ask and have questions answered by the team Information about the anticipated time frame of the transport and about the receiving hospital If the mother is accompanying the baby, then addressing her medical needs during transfer and after reaching referral hospital
Documentation and consent form		Patient demographic details (name, age, sex, gestational age and weight, place and name of referring hospital) Reason for transfer Detailed perinatal history, labor and delivery, neonatal resuscitation Current patient status, therapy and laboratory data Potential for deterioration and need for advance therapy like mechanical ventilation and exchange transfusion or diagnostic evaluation Referral note with provisional diagnosis and treatment given so far Consent form from parents
Feedback to referring unit	Verbal or written communication to the members of referring team	Details of medical illness, likely diagnosis, prognosis and likely duration of stay Reverse transport once stable

of maintenance of temperature. Till recently no functional model of either emergency response systems or assured transport for pregnant women or their babies existed in India. The components of an organized neonatal transport system are shown in **Table 6**.

### IN A NUTSHELL

1. Newborn care is classified into different levels of care to optimize neonatal outcome, for using the available resources effectively.
2. India has developed country-specific norms for neonatal care.
3. Neonatal care is closely linked to the levels of EmOC available in the health system.
4. An important component of organized neonatal care is a good medical transportation system.

### MORE ON THIS TOPIC

- American Academy of Pediatrics. Levels of neonatal care. *Pediatrics*. 2012;130:587-97.
- Bhakoo ON, Kumar P. Current challenges and future prospects of neonatal care in India. *Indian J Pediatr*. 2013;80:39-49.
- Chien LY, Whyte R, Aziz K, et al. Improved outcome of preterm infants when delivered in tertiary care centers. *Obstet Gynecol*. 2001;98:247-52.
- Facility-Based Newborn Care Operational guide. New Delhi: Ministry of Health and Family Welfare, Government of India; 2011.
- National Neonatology Forum Accreditation Guidelines. New Delhi; 2013.
- Neogi SB, Malhotra S, Zodepy S, Mohan P. Does facility based newborn care improve neonatal outcomes? A review of evidence. *Indian Pediatr*. 2012;49:651-8.
- Sen A, Mahalanabis D, Singh AK, et al. Impact of a district level sick newborn care unit on neonatal mortality rate: 2-year follow-up. *J Perinatol*. 2008;29:150-5.

# Section 12 NORMAL NEWBORN

**Section Editor** Siddarth Ramji

## Chapter 12.1

### Delivery Room Care of the Newborn

Siddarth Ramji

There are about 26 million births each year in India (which is almost one-fifth of the global burden) and of these, almost 0.8 million infants die before the age of 1 month (2012 data). India's share of neonatal deaths is almost one-third of the global neonatal deaths. Most common reasons for these deaths include causes related to asphyxia, infection and prematurity/low birthweight. Most of these neonatal deaths are preventable.

#### Why Care at Birth is Important?

Almost a third of all neonatal deaths in India occur within the first day of life. A baby's survival soon after delivery and thereafter is totally dependent on the caregivers and the mother. It is, therefore, important to provide the right care at birth to reduce the risk of mortality in the newborn infant.

#### IMMEDIATE NEWBORN CARE AT BIRTH

Every newborn infant, irrespective of his or her place of birth, gestation and birthweight, requires care that is essential for their survival. The components of *Essential Newborn Care* are summarized in **Box 1**. Over 90% of newborns would require all the steps of essential newborn care except resuscitation.

1. Deliver baby onto mother's abdomen/a dry warm surface next to mother
2. Dry the baby and wrap in warm dry towel
3. Assess breathing; if not breathing/gasping, initiate resuscitative steps
4. Cut the cord after 1–2 min of birth
5. Place baby on skin-to-skin contact with mother and initiate breastfeeding
6. Give vitamin K to all newborns
7. Weigh all newborns at birth.

#### BOX 1 Components of essential newborn care

- Delivering baby onto mother's abdomen
- Drying the baby and wrapping in warm dry towel
- Assessing newborn breathing; to initiate resuscitation if not breathing or is gasping
- Delay cord clamping to about 1–2 min after birth (except in babies needing resuscitation)
- Placing the baby on skin-to-skin contact with mother and initiating breastfeeding
- Giving vitamin K to all newborns
- Weighing all newborns at birth.

*Provision of warmth* The newborn infant at birth should be received in dry, warm and clean linen/towels and placed on the mother's abdomen without cutting the cord (**Fig. 1**). If it is not possible, the infant may be placed next to the mother on a warm surface. The baby should be immediately dried, including the scalp, and the wet linen discarded (**Fig. 2**). The infant should be rewrapped in fresh, dry and warm clean linen/towel.

The room where the baby delivers should be maintained at around 28°C. During delivery and soon after the baby's birth, it must be ensured that there are no fans running or windows open, which can result in heat loss through convective currents.

*Checking for breathing* If the baby is crying vigorously, the baby needs no other resuscitative care. *Routine suction of oral cavity must*



**Figure 1** Placing baby on mother's abdomen immediately after birth



**Figure 2** Drying the baby at birth





**Figure 3** Baby in skin-to-skin contact with mother in delivery room

be avoided in vigorous babies as it may result in vagal stimulation and apnea and/or bradycardia.

If the baby is not breathing or has gasping breathing efforts, it must be immediately separated from the mother by cutting the cord, placed under a radiant warmer and appropriate resuscitation steps initiated to establish adequate breathing in the newborn.

**Initiating skin-to-skin care and breastfeeding** After the cord is cut (about 1–3 min of birth), the baby should be placed prone between the mother's breast in skin-to-skin contact position (**Fig. 3**) and delivery room staff must assist mother to secure the baby. Wrap baby and mother with another prewarmed dry sheet.

It is vitally important for the mother and her infant that breastfeeding should be initiated within an hour after birth. The delivery room staff should ensure that breastfeeding is initiated as soon after delivery as possible. The advantages to the mother are that it aids in uterine involution (induced by release of oxytocin secondary to the suckling reflex), thus decreasing the risk of postpartum hemorrhage. The benefit to the baby is increased maternal-infant bonding, provision of nutrition and immunity (from colostrum). The baby can be supported by the delivery room staff so that it can suck on the mother's breast while in skin-to-skin contact in the prone position. Even mothers who deliver by cesarean section or assisted delivery should be supported for early breastfeeding and should not be separated from their newborns.

**Cord, skin and eye care** The umbilical cord should be cut with sterile scissors/blade about 2.5 cm from the abdominal skin surface. There is no evidence that use of local antiseptics prevent subsequent umbilical infection. The cord is best left dry without any application.

The infant should be cleaned to remove blood, mucus or meconium from its surface. Take care *not to remove* the vernix as it protects the newborn's skin from injury. Bathing the baby soon after birth is not recommended. Bathing should be postponed to a later date till the baby's temperature remains warm and stable.

The baby's eyes can be cleaned at birth with sterile cotton soaked in sterile water or normal saline. Each eye should be cleaned using a separate swab. Routine use of local antiseptic drops for prophylaxis is not recommended.

**Prevention of infection** To prevent infection at the time of birth, the principles of the 5 Cleans are universally adopted. It includes:

- Clean surface for delivery of mother and baby
- Clean hands (wash hands well with soap and water and preferably use gloves while conducting a delivery)
- Clean and sterile blade for cutting the cord

- Use a clean cord tie
- Umbilical cord to be kept clean and dry

**Vitamin K and immunizations** All newborn infants should be given 1 mg of intramuscular vitamin K soon after birth. This helps to prevent hemorrhagic disease of the newborn.

Depending on the local immunization policy, newborns should be administered the appropriate immunization in the delivery room such as the hepatitis vaccine or the oral polio vaccine.

**Risk identification** An important task of the attending physician in the delivery room is identifying newborn infants at high risk of morbidity or mortality. Such newborns need to be provided special care.

- **Birth asphyxia** Infants who do not establish spontaneous breathing by 5 min after birth would all need referral to a special care unit to manage postasphyxial problems such as convulsions, hypoglycemia, shock, renal failure, respiratory problems, etc. Even some neonates in need of assisted ventilation for more than 2 min may need observation in neonatal special care units for the first 24 hours.
- **Congenital malformations** Infants may have minor or major malformations. Those malformations which increase the risk of morbidity or mortality would need transfer to neonatal intensive care unit (NICU) or referral. Some of these that can be detected in the delivery room include meningomyelocele, hydrocephalus, large omphalocele, esophageal atresia, anal atresia and diaphragmatic hernia.
- **Low birthweight** Every baby must be weighed at birth. Newborns with birthweight less than 2,500 g (low birthweight) are at increased risk of illness. However, it is newborn infants who are less than 2,000 g who generally need to be assessed more carefully and most of infants less than 1,800 g may need care in special care neonatal units.
- **Preterm newborns** Preterm newborns (< 37 weeks gestation) need special care because many of them are at risk of feeding problems, hypothermia and infection.
- **Respiratory distress** Newborns with respiratory rates greater than 60 breaths/min, those with chest retractions or grunting would all need referral to a special care neonatal unit so that they can get appropriate respiratory support.

**Assessment before transfer out of delivery room** All babies should be assessed for stability before they are transferred out of the delivery room. A newborn should be shifted out with the mother if stable as per the following criteria:

- Normal temperature (36.5–37.4°C)
- No oozing from cord
- No respiratory distress
- Pink color
- Vigorous

**Flow chart 1** provides an algorithm for care of baby in the delivery room.

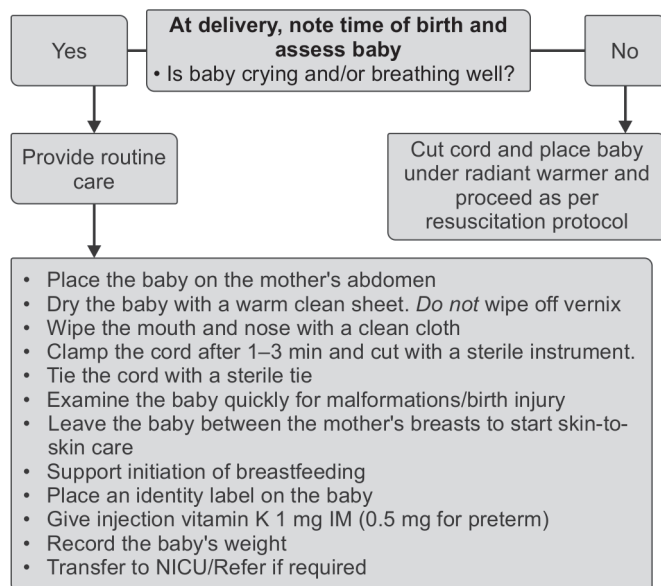
## NEWBORN CARE CORNER

It is essential that every delivery room has a newborn care corner. This is a space within the delivery room for facilitating immediate care of the newborn, especially for those who need resuscitation or those at-risk babies who are awaiting referral or transfer to a special care newborn unit. **Box 2** provides a list of equipment and supplies that should be available in the corner.

## NEONATAL RESUSCITATION

Approximately 10% of newborns require some assistance to begin breathing at birth; about 1% needs extensive resuscitative measures to survive. The ABCs of resuscitation are the same for babies as for

**Flow chart 1** An algorithm for providing care at birth to a newborn infant



Abbreviations: IM, intramuscular; NICU, neonatal intensive care unit.

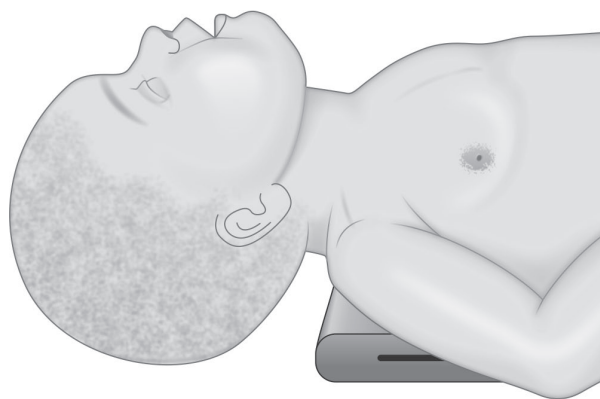
#### BOX 2 Essential equipment and supplies for a newborn care corner

- **Equipment:**
  - Radiant warmer with bassinet
  - Suction equipment
  - Weighing machine
  - Self-inflating resuscitation bag (500 mL) with masks (size 0, 1)
  - Oxygen source
  - Laryngoscope (straight blade, size 0, 1)
  - Wall clock
  - Room thermometer
- **Supplies:**
  - Clean baby sheets
  - Sterile cord ties
  - Sterile gloves
  - Sterile blade/scissors
  - Mucus extractors
  - Suction catheters (10F, 12F)
  - Feeding tube (6F, 8F)
  - Endotracheal tubes (3 mm, 3.5 mm)
  - IV cannula (24G)
  - Drugs (Injection epinephrine, normal saline, injection vitamin K).

adults. Ensure that the *Airway* is open and clear. Be sure that there is *breathing*, whether spontaneous or assisted. Make certain that there is adequate *circulation* of oxygenated blood. Newly born babies are wet following birth and heat loss is great. Therefore, it is also important to maintain body temperature during resuscitation.

#### Determining if a Baby Needs Resuscitation

The need for resuscitation in a baby is determined by looking at the breathing of the baby. Babies who are vigorously crying or have good visible regular chest movements do not need any resuscitation. Babies who are apneic or gasping (deep, single irregular inspiratory efforts) need resuscitative assistance. **Flow chart 2** provides the neonatal resuscitation guidelines adapted for India from the International Liaison Committee on Resuscitation (ILCOR) 2010 guidelines.



**Figure 4** Positioning of the baby with shoulder roll in place

#### Initial Steps of Resuscitation

Once the decision for resuscitation has been taken, the initial steps should be initiated immediately. The components of initial steps include the following:

- Drying
- Positioning
- Clearing airway
- Provision of tactile stimulus

The baby should be placed under a radiant warmer, dried if already not done earlier. The baby must be positioned with neck slightly extended by placing a shoulder roll (**Fig. 4**). The airway would need to be cleared with a mucus extractor and if the infant is still not breathing, then tactile stimulus by flicking the soles or rubbing the back may be carried out to initiate breathing.

**Meconium-stained amniotic fluid** Suction should not be done routinely in vigorous babies even if there is meconium-stained amniotic fluid. In nonvigorous babies who are born through meconium-stained amniotic fluid, oral suction should be followed by tracheal suction (to clear the upper airway of meconium) before provision of tactile stimulus.

#### Assessment of Baby

The baby's breathing and heart rate should be assessed after provision of initial steps. If the baby has good breathing efforts and the heart rate is more than 100 beats/min (assessed by auscultation of heart beats and counting for 6 sec and multiplying by 10 to get beats per minute), continue providing routine essential care as described in **Flow chart 1**.

- **Baby has poor breathing efforts/is apneic or has a heart rate less than 100 beats/min** One must initiate positive pressure ventilation (PPV) with bag and mask. One must also consider connecting a pulse oximeter to the right wrist of the baby to assess oxygenation as cyanosis in the baby at birth is a poor indicator of the adequacy of oxygenation.
- **Adequate breathing efforts, heart rate greater than 100 beats/min and has respiratory distress** Connect a pulse oximeter to the right wrist of the baby to assess oxygenation and provide supplementary oxygen titrated to the target oxygen saturations for the age of the baby as shown in **Box 3**, by using an oxygen blender and adjusting the inspired oxygen concentration ( $\text{FiO}_2$ ). If the newborn is a preterm infant, and facilities are available, then CPAP may be initiated in the delivery room before transfer to NICU.

#### Positive Pressure Ventilation

Positive pressure ventilation is initiated if one of the following indications exists:

```
graph TD
    Start([Note the time  
Receive baby in dry, warm linen]) --> Q1{Is baby breathing/crying?}
    Q1 -- No --> Box1[• Cut cord immediately and place under radiant warmer  
• Provide initial steps (dry, position, clear airway, tactile stimulus)]
    Q1 -- Yes --> Q2{Gasping, apnea or HR < 100 bpm?}
    Box1 --> Q2
    Q2 -- No --> Q3{Labored breathing or persistent cyanosis?}
    Q2 -- Yes --> Box2[Initiate PPV using room air]
    Box2 --> Q4{Heart rate after 5 inflations: < 100 bpm?}
    Q4 -- No --> Box3[Baby breathing well and heart rate > 100 bpm]
    Q4 -- Yes --> Box5[Look for Chest Rise; if not  
• Ensure open airway  
• Reduce leaks  
• Consider increasing pressure]
    Box3 --> Q5{PPV < 1 min}
    Box5 --> Q5
    Q5 -- Yes --> Box6[Observational care with mother]
    Q5 -- No --> Box7[Postresuscitation care in NICU]
    Box7 --> Box8[If heart rate < 60 bpm and chest rising  
• Continue PPV, add 100% oxygen, consider intubation  
• Start chest compressions 3 compression to 1 breath]
    Box8 --> Box9[Consider:  
• Hypovolemia  
• Pneumothorax]
    Box9 --> Box8
    Box8 --> Box10[Baby breathing well and heart rate > 100 bpm]
    Box10 --> Box7
    Box11[If heart rate not detectable or < 60 bpm  
Administer epinephrine (1:10000), 0.1–0.3 mL/kg IV; If endotracheal route give 0.5–1.0 mL/kg] --> Box8
```

### BOX 3 Target oxygen saturations in the first 10 min after birth

*Acceptable productual SpO<sub>2</sub>*

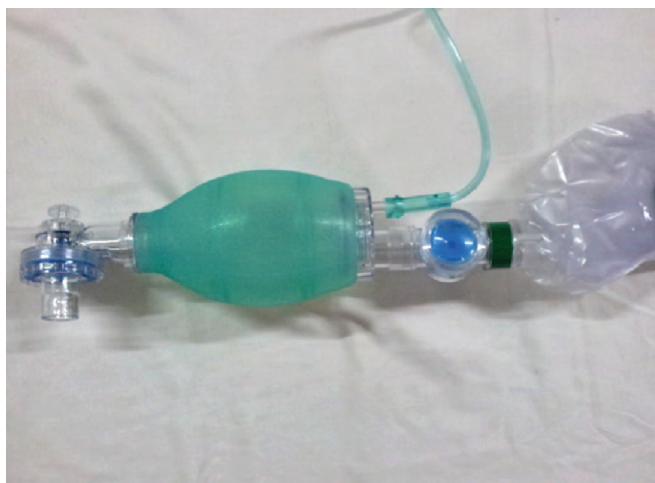
1 min:	60–65%
2 min:	65–70%
3 min:	70–75%
4 min:	75–80%
5 min:	80–85%
10 min:	85–90%.

- Has persistent central cyanosis or low oxygen saturation, despite free-flow oxygen increased to 100%.

Positive pressure ventilation can be provided with either a self-inflating bag (**Fig. 5**) or a T-piece resuscitator (**Fig. 6**). PPV is provided at a rate of about 40 breaths/min. In term babies, PPV should be initiated with room air and then titrated based on oximetry readings. In preterm babies too it is advisable to initiate PPV with room air and then subsequently titrate with pulse oximetry readings. The baby should be assessed for effectiveness of PPV after 30 s of the procedure.

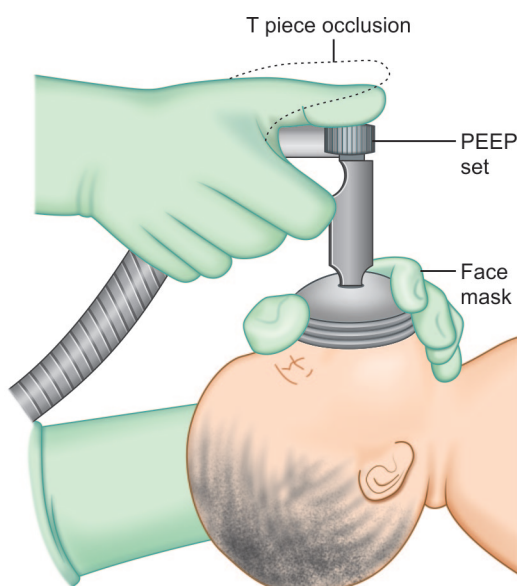
**Effective ventilation** Prompt increase in heart rate, appearance of spontaneous breathing efforts, improvement in color and muscle tone are good indicators of effectiveness of PPV. If the baby





**Figure 5** Self-inflating bag with oxygen tubing and reservoir

Source: Reprinted with permission from National Neonatology Forum (NNF), India.



**Figure 6** T-piece resuscitator

Abbreviation: PEEP, positive end-expiratory pressure.

Source: Reprinted with permission from National Neonatology Forum (NNF), India.

requires less than 1 min of PPV, then further care can be provided by observing with the mother. *PPV can be stopped when baby has good spontaneous breathing efforts and has a heart rate greater than 100 beats/min.*

**Not improving** If the baby is not improving, i.e., no spontaneous breathing or no rise in heart rate, the following actions should be considered based on the assessment of the baby.

- *If the heart rate is more than 60 beats/min but less than 100 beats/min* Continue PPV as long as the baby is improving and reassess every 30–40 sec.
- *If the baby's heart rate is below 60 beats/min despite 30 sec of effective PPV* Continue PPV, increase oxygen supplementation to 100% and consider initiating chest compressions.

## Chest Compressions

Chest compressions would need two health-care personnel. Chest compression should be coordinated with ventilation. If the baby has not been intubated, one should consider endotracheal intubation before initiating chest compressions. Chest compressions and ventilation should be provided in a ratio of 1:3 for at least 1 min before the baby is reassessed. Chest compressions are discontinued when heart rate goes above 60 beats/min. However, if the heart rate remains less than 60 beats/min, one must consider use of medications.

## Medications

**Epinephrine** Epinephrine is indicated when the heart rate does not go above 60 beats/min after PPV and chest compressions. It is administered intravenously in a dose of 0.1–0.3 mL/kg of a 1:10,000 solution.

**Volume expansion** Volume expansion should be considered in a baby in shock with evidence of blood loss (as in antepartum hemorrhage). Ringer's lactate or 0.9% saline can be used in dose of 10 mL/kg.

## Discontinuation of Resuscitation

If there is no heart rate despite of all the resuscitative steps outlined above or no progress is made in some situations as in the case of an extreme preterm, resuscitation efforts may be discontinued.

### IN A NUTSHELL

1. All neonates at birth must be provided essential newborn care.
2. Essential newborn care includes drying of baby, delayed cord clamping, skin-to-skin care, early initiation of breastfeeding, cord and eye care, vitamin K and weighing all newborns.
3. Neonatal resuscitation in the delivery room is indicated in babies who do breathe adequately at birth.
4. The steps of resuscitation include initial steps, PPV, chest compressions and medications.

## MORE ON THIS TOPIC

Beck D, Ganges F, Goldman S, et al. Care of the Newborn—Saving Newborn Lives. Reference Manual. Washington DC, USA: Save the Children; 2004.

Perlman JM, Wylie J, Kattwinkle J, et al. Part II. Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Circulation. 2010;122:S516–S538.



## Chapter 12.2

# Assessment of the Newborn

Harish Chellani, Sugandha Arya

Assessment of a newborn, like any other age group involves detailed history and physical examination. In this chapter, we shall discuss assessment of an apparently well newborn in the first few days of life. The purpose of this assessment is to identify high-risk neonates for further management. Another important purpose is to identify common early neonatal problems which predominantly need only parental reassurance.

## HISTORY

History taking for assessment of a newborn not only involves postnatal history but also antenatal and intranatal history in detail as these factors have a significant impact on newborn's health. Most of the components of history can be obtained from mother and relatives but some of the components may need enquiring the obstetrician especially the details of labor and delivery. History taking for newborn assessment should include sociodemographic data, maternal medical history, family history (particularly for congenital malformations, metabolic disorders, hearing impairment and mental retardation), maternal obstetric history (including details of the present pregnancy particularly antepartum and intrapartum details) and details of the baby at and after birth (need for resuscitation, feeding and any neonatal morbidity and immunization).

## NEWBORN EXAMINATION

Newborn examination requires patience, gentleness and flexibility of routine. Overall visual and auditory appraisal of the naked newborn offers more information than careful organ examination. Baby should be naked particularly during initial examination but should not be kept uncovered for more than a minute or two as neonates may easily become hypothermic particularly in colder months. The baby should preferably be under a radiant warmer during examination. The examination of the newborn should preferably be carried out in the mother's presence as it helps in allaying her doubts and anxiety about the infant.

Adequate information during systemic examination is best obtained when the infant is asleep or in a state of quiet wakefulness; the crying infant can often be quietened by placing on the mother's lap and conducting a further examination in that position. To ensure continued cooperation of the baby during the examination, the examiner's hands must be warm and dry. The physical examination of the baby should be conducted soon after birth. This first examination is done to determine:

- Whether the baby has any congenital abnormalities (**Fig. 1**).
- To categorize the baby in the birthweight and gestational age groups to determine the level of care needed.
- To detect any other disorder which may affect the neonatal course and which may require urgent attention.

Following the initial examination, a detailed physical examination of the newborn should be conducted at 24 hours of age, as by this time, most infants have recovered from the physical stress of labor and can withstand greater handling. A further detailed physical examination is desirable before the baby is discharged from the hospital.



**Figure 1** Microcephaly (head circumference 29 cm) with congenital talipes equinovarus deformity in a term baby

## General Examination

### Initial Observation

The initial observations on the neonate should include:

- **Posture of the baby**—The full-term infant lies in an attitude of flexion similar to the position assumed in utero. The preterm infant usually lies in extended position.
- **Color**—Pallor may represent anemia, shock or hypoxia. Peripheral cyanosis may be present for a short while after birth even in normal neonates which disappear once the child's temperature is stabilized. The presence of jaundice should also be noted.
- **Cry**—Cry of a term neonate is vigorous. Feeble, soft or high-pitched cry is abnormal.

### Physiologic Parameters

**Temperature**—Routine temperature recording should be done by the axillary method. Axillary temperature recording is as good as rectal and safer than rectal with less risk of injury or infection. A digital thermometer needs to be switched on for recording the temperature. It is recorded by placing the bulb of thermometer against the roof of the dry axilla, free from moisture. The baby's arm is held close to the baby to keep the thermometer in place (**Fig. 2**). The temperature is read when the thermometer beeps. If mercury thermometer is used, then the temperature is read after 5 min. Normal axillary temperature is 36.5–37.5°C. Rectal temperature recording is not done routinely. However, it is the best guide for



**Figure 2** Recording the temperature in newborn

core temperature in cold sick neonates. The baby's temperature can be reliably assessed by human touch. The warm and pink feet of the baby indicate that the baby is in thermal comfort.

**Respiratory rate, heart rate and capillary refill time**—These are discussed later along with the examination of cardiorespiratory system.

### Anthropometry

All neonates should have the following anthropometric measurements recorded:

- **Weight** Weight should be recorded accurately using an electronic weighing machine. If electronic weighing machine is not available, then use beam balance or spring balance. Babies weighing less than 2,500 g are called low birthweight babies.
- **Length** Length should be measured on an infantometer taking care that knees are fully extended and the feet are perpendicular to the horizontal (**Fig. 3**). Length of a term neonate at birth is about 45–50 cm.
- **Head circumference** This is measured at the level of the supraorbital ridges and maximal parietal prominences (**Fig. 4**). The head circumference of term newborn is about 33–35 cm and should be recorded 24–48 hours after birth to obviate the effects of birthing process on the skull.

### Gestational Assessment

Gestational assessment by physical and neurologic criteria needs to be carried out in all babies where the date of the last menstrual period of the mother is not known or unreliable. Soon after birth, assessment of gestation is to be made by using physical criteria as the newborn may not be in an optimal state for neurologic examination. Physical features in a newborn which suggest prematurity (i.e., gestation period of less than 37 weeks) are detailed in the **Box 1**. After 24 hours of age, as baby stabilizes, detailed gestational assessment using both physical and neuromuscular criteria can be done by various scoring methods, e.g., *expanded new Ballard's scoring* or *Dubowitz*



**Figure 3** Measuring the length of the newborn using an infantometer



**Figure 4** Measuring the head circumference of the newborn

### BOX 1 Physical criteria for assessing gestation

- **Deep sole creases** are absent or are limited to anterior one-third of the sole
- **Genitalia** Testes are at the external ring. Scrotum is small with few rugosities. Labia in female infants are widely separated with prominent clitoris
- **Breast nodule** is less than 5 mm in diameter or not perceptible. It may also be small in term growth retarded babies
- **Ear cartilage** is deficient and has poor elastic recoil
- **Skin** is smooth, pink with visible veins. Fuzzy or wooly hair called lanugo may be present.

*scoring*. Expanded *New Ballard's scoring* (**Box 2**) is widely used in practice and its video demonstration is available at [www.ballardscore.com](http://www.ballardscore.com).

**Neuromuscular maturity** Details of maneuvers for assessing gestation using neuromuscular criteria are summarized below.

- **Posture** Observe the infant in supine position. Observe the degree of flexion of upper limbs and lower limbs and score according to the criteria one is using.
- **Square window** Flex the hand of the baby on his forearm between your thumb and index finger (**Fig. 5**). Apply enough pressure to get as full flexion as possible and measure the angle between the hypothenar eminence and the ventral aspect of the forearm and score accordingly.
- **Arm recoil** With the infant in supine position, flex the forearms for 5 sec, and then fully extend at the side of the trunk by pulling on the hands, and then release. Observe the degree of flexion at elbows after the release.
- **Popliteal angle** With the infant in supine position and his pelvis flat on the table, hold the thigh in knee-chest position by your left index finger and thumb supporting the knee. Then extend the leg by gentle pressure from your right index finger behind the ankle (**Fig. 6**) and measure the popliteal angle in this position.
- **Scarf sign** With the baby supine, take the baby's hand and try to put it around the neck and as far as possible around the opposite shoulder (**Fig. 7**). Observe how far the elbow is going across the midline.
- **Heel to ear** With the baby supine, draw the baby's foot as near to the head as it will go without forcing it (**Fig. 8**). Observe the distance between the foot and the head and the degree of flexion at the knee joint.

### Skull



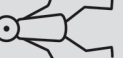


























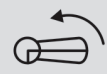

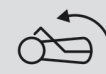

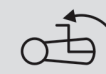
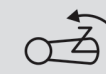
The skull should be examined for abnormal shape (as in craniosynostosis), sutural separation (for hydrocephalus) and abnormal swelling (e.g., cephalohematoma, encephalocele). One must assess the size of the anterior fontanel (normal size is  $20 \pm 10$  mm); very small anterior fontanel may indicate craniosynostosis or be seen in microcephalic heads, while large fontanelle may indicate hydrocephalus (if associated with sutural separation) or insufficient membranous ossification as seen in growth-retarded neonates or congenital vitamin D deficiency. Hydranencephaly if suspected can be detected by transillumination of the skull. Any significant and persistent abnormality in shape or size of the skull should be evaluated by cranial tomography.

### Eyes

Attempts to force open the eyelids of a newborn are likely to result in failure. Gentle tilting of the head back and forth (doll's eye maneuver) will succeed in opening the newborn's eyes. The



**BOX 2** Expanded new Ballard's score for gestation assessment*Neuromuscular maturity*

Score	-1	0	1	2	3	4	5
Posture							
Square window (wrist)	 >90°	 90°	 60°	 45°	 30°	 0°	
Arm recoil		 180°	 140–180°	 110–140°	 90–110°	 <90°	
Popliteal angle	 180°	 160°	 140°	 120°	 100°	 90°	 <90°
Scarf sign							
Heel to ear							

*Physical maturity*

<i>Skin</i>	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled		
<i>Lanugo</i>	None	Sparse	Abundant	Thinning	Bald area	Mostly bald			
<i>Plantar surface</i>	Heel-toe 40–50 mm: –1 < 40 mm: –2	> 50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior 2/3 of sole	Creases over entire sole		<b>Score</b>	<b>Weeks</b>
<i>Breast</i>	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola 3–4 mm bud	Full areola, 5–10 mm bud		–10	20
<i>Eye/ear</i>	Lids fused loosely: –1 Tightly: –2	Lids open, pinna flat, stays folded	Slightly curved pinna, soft, slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm instant recoil	Thick cartilage, ear stiff		–5	22
<i>Genitals (male)</i>	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending few rugae	Testes down, good rugae	Testes pendulous, deep rugae		0	24
<i>Genitals (female)</i>	Clitoris prominent, labia flat	Clitoris prominent, small labia minora	Majora and minora equally prominent	Majora large, minora small	Majora large, minora small	Majora cover clitoris and minora		5	26
								10	28
								15	30
								20	32
								25	34
								30	36
								35	38
								40	40
								45	42
								50	44

**Figure 5** Square window sign**Figure 6** Popliteal angle



**Figure 7** Scarf sign



**Figure 8** Heel to ear. Note that the pelvis is fixed and the thigh is flexed parallel to the trunk. The foot is held by the examiner and the leg extended as far as possible to measure the distance from the ear

eyes should be carefully examined for jaundice, subconjunctival hemorrhage, iris abnormalities, or any other corneal abnormality. Examine for opacity which may be due to cataract, or corneal injury or dystrophy. If the cataract is posterior, it is detected by absence of red reflex on ophthalmoscopy.

### Mouth

The mouth should be examined for cleft palate, deciduous teeth and retention cysts. Extraction of deciduous teeth is usually not indicated. On the hard palate on either side of raphe, there may be accumulation of epithelial cells known as *Epstein pearls*. Both retention cysts and *Epstein pearls* disappear spontaneously within few weeks of birth.

### Ears

Evidence of external ear malformation may be a marker of associated renal anomalies. Hearing impairment is a serious disorder which affects speech and development. Universal screening of all newborns is recommended to ensure early detection of hearing impairment for timely intervention. The infants who are at high risk of hearing loss include those with ear malformations, family history of deafness, birthweight less than 1,500 g, had evidence of bilirubin encephalopathy, infants who required exchange transfusion for hyperbilirubinemia or who had meningitis or birth asphyxia.

### Skin

The skin of a preterm neonate is thin and pink unlike that of a term neonate in whom it is paler. Loose wrinkled skin with peeling suggests intrauterine malnutrition or postmaturity. Parchment like skin with peeling may be seen in congenital ichthyosis. An extraordinary division of the body from forehead to pubis into red and pale halves is harlequin color change, a transient and harmless condition.

### Developmental Dysplasia of Hip

It should be ruled out in all newborns. Each hip should be examined separately. There are two ways of doing it:

1. **Ortolani test** With newborn supine on the examining table, place the index and middle fingers along the greater trochanter and place the thumb on the medial aspect of the thigh. Stabilize the pelvis by placing the thumb and ring finger of the opposite hand on top of both anterior iliac crests simultaneously (**Fig. 9**). Flex the hip to 90° and abduct while lifting the leg with hip in neutral external or internal rotation. If a palpable clunk is felt as the dislocated femoral head reduces into the acetabulum, it indicates developmental dysplasia of hip.
2. **Barlow test** In this test, we try to dislocate or subluxate a located but unstable hip. Hold the thigh and stabilize the pelvis in the same way as in Ortolani's test. With hip in neutral external or internal rotation and at 90° of flexion, adduct the leg with mild posteriorly directed pressure applied to the knee. If a palpable clunk is felt, it indicates developmental dysplasia of hip.

Abnormal intrauterine posture can result in what appears to be a *talipes deformity*. If feet can be dorsiflexed to the extent that dorsum of foot touches the tibial skin, this excludes a pathological talipes equinovarus deformity. If developmental dysplasia of hip or pathological talipes deformity is suspected, the newborn infant should be referred to an orthopedic surgeon for further evaluation and management.

### Spine

The spine must be examined for presence of tuft of hair, pigmentation, lipoma or hemangioma (as these may indicate an occult spina bifida), meningocele—or meningomyelocele (**Fig. 10**) or a pilonidal sinus.



**Figure 9** Ortolani's maneuver: The limb is in adducted position with the examiner's thumb on the lesser trochanter and the fingers supporting the greater trochanter. The pelvis is supported on the opposite side by the other hand





**Figure 10** A neonate with *meningocele* in the lumbar region with a tuft of hair

## Systemic Examination

### Cardiorespiratory System

**Respiratory rate** The respiratory rate of a newborn is normally between 40 breaths/min and 60 breaths/min. Auscultation and percussion of chest are of limited diagnostic value in a newborn. As a general rule, if the infant has good color and no respiratory distress, there is unlikely to be a major cardiorespiratory problem. The severity of respiratory distress may be assessed by the presence or absence of tachypnea (RR > 60 breaths/min) or by the presence or absence of use of accessory muscles and nasal flaring. There are different scoring systems to assess the respiratory distress in a newborn—*Silverman score*, *Downe's score*, *ACoRN score* (**Table 1**).

Note for any abnormal bulge in either hemithorax or in the supraclavicular region. If heart sounds are better heard on right side, this may be due to dextrocardia or shift of heart to right side. Shift of heart may be due to pneumothorax or diaphragmatic hernia. Transillumination of the chest may suggest the presence of pneumothorax. In case of a diaphragmatic hernia, the abdomen is usually scaphoid and bowel sounds may be auscultated in the chest.

Normally the breath sounds are bronchovesicular. If there is suspicion of pulmonary pathology because of respiratory distress or diminished breath sounds, obtain a chest radiograph.

**Heart rate** The heart rate in a newborn may vary normally from 120 beats/min in relaxed sleep to 160 beats/min during activity. The femoral pulses should always be palpated to exclude coarctation of aorta. Murmurs heard in the newborn period may be transient while significant heart disease may exist in the absence of murmur.

**Blood pressure** needs to be recorded only in sick neonates. It may be recorded by auscultatory method if stethoscope head is small enough. The Doppler method, using a transducer in the cuff can

accurately measure systolic and diastolic pressure. Noninvasive blood pressure monitors based on oscillometry also give accurate results. Palpatory and flush methods only give systolic pressure. The normal blood pressure in a neonate has wide range, systolic 50–80 mm Hg and diastolic 25–50 mm Hg.

**Capillary refill time** Good perfusion signifies adequacy of circulation. Poor perfusion indicates hypotension. A simple and reliable clinical indicator of perfusion is capillary refill time (CRT). To measure CRT, the skin over the mid-sternum or forehead is pressed with a finger for 5 sec so that it blanches. The finger is then lifted and time taken for refilling of the capillaries and return to original skin color is noted. Normal CRT is 3 sec or less. CRT may also be prolonged due to hypothermia because of peripheral vasoconstriction.

### Abdomen

The abdominal shape may offer important clues to underlying problems. A scaphoid abdomen suggests the presence of diaphragmatic hernia, a fullness in the flank may indicate a renal mass and a tense distended abdomen at birth may indicate intrauterine intestinal perforation, commonly due to meconium ileus.

The umbilicus should be examined soon after birth for the presence of two umbilical arteries and one umbilical vein. A single umbilical artery is usually associated with presence of other congenital malformations. In subsequent examinations of the umbilicus, one should look for umbilical hernia, granuloma or evidence of infection (erythema, induration or seropurulent discharge).

The liver in the newborn is normally about 2–2.5 cm below the right costal margin. The tip of the spleen may be normally palpable. Remember that there may be situs inversus. Both kidneys are usually palpable during the first 2 days of life. Large palpable kidneys may be due to cystic or hydronephrotic changes or a tumor (e.g., nephroblastoma).

**Genitalia** Phimosis in the newborn is invariably physiologic and needs no intervention. Hypospadias is a condition in which urethral opening is on the ventral surface of the penile shaft (**Fig. 11**). The ideal age for repair of hypospadias in a healthy infant is 6–12 months. A hydrocele in the newborn mostly disappears spontaneously during the first 1 or 2 years of life. The testes should be palpated for their presence in the scrotal sac. In females the labia must be parted and examined for imperforate hymen or vaginal cysts. Disorder of sex development should be suspected in the following situations: Bilateral cryptorchidism, unilateral cryptorchidism with hypospadias, penoscrotal or perineoscrotal hypospadias even if both testes are descended, apparently female genitalia with enlarged clitoris or inguinal hernia or asymmetry of labioscrotal folds, or cloacal exstrophy.

**Esophagus and anus** The esophagus and anus should be checked for patency in all neonates at birth in the labor room. The infant should be examined for esophageal patency by passing an orogastric tube. If mother has history of polyhydramnios or there

**Table 1** ACoRN scoring system for respiratory distress in newborn

Score	Respiratory rate	Cyanosis	Air entry	Grunt	Retraction	Prematurity
0	< 60 breaths/min	Nil	Normal	None	Nil	≥ 34 weeks
1	60–80 breaths/min	In room air	Mild decrease	Audible with stethoscope	Mild	30–34 weeks
2	> 80 breaths/min	In > 40% FiO <sub>2</sub>	Marked decrease	Audible with unaided ear	Moderate	< 30 weeks

Note: A score of more than 8 indicates need for ventilatory assistance.



**Figure 11** Penile hypospadias



**Figure 12** Rooting reflex in a newborn

is frothing or excessive salivation, one should suspect esophageal atresia. Rule out anal atresia by inspecting the anal opening at the normal site.

### Neurologic Examination

Probably the most reliable information that can be obtained regarding neurological status is while handling the baby during the preceding physical examination. Symmetry of movements, body tone, posture and response to handling can be evaluated while examining other organs. To reliably interpret the results of the newborn neurologic examination, the baby should be more than 24 hours of age and should be examined about 1 hour after a feed when baby is likely to be in an appropriate state of quite wakefulness.

**Alertness and spontaneous movements** The neonate's state of alertness—sleeping, quite wakefulness or crying should be noted. Absence of spontaneous movements in one or more limbs should prompt further examination, e.g., Erb's palsy usually revealed by lack of motion of the shoulder and arm; the arm will lie beside the body in response rather than being normally flexed with fist near mouth.

**Cry** Newborn's cry is probably one of the most sensitive indicators of neurologic well-being. The intensity and pitch should be noted. A high-pitched cry may suggest raised intracranial pressure seen in babies with severe birth asphyxia or meningitis. Seventh nerve palsy can also be detected (mouth drawn to one side) while the baby is crying.

**Neonatal reflexes** A number of primitive neonatal reflexes can be elicited in a healthy term neonate. Absence of reflex responses indicates general depression, central or peripheral motor dysfunction.

- **Sucking and rooting reflexes** When the nipple of breast or finger is brought into contact with infant's cheek, he seeks the nipple or finger (rooting reflex) (**Fig. 12**). Stimulation of the upper and lower lips produces movement of the lip and tongue in the direction of the stimulus (sucking reflex). Sucking reflex is feeble in the sick and preterm infants.
- **Moro's reflex** To elicit the Moro's reflex, hold the baby at an angle of about 45° from the table and then suddenly let the head fall back a short way. Alternatively, baby is placed supine and the back of the head is supported on the palm of the hand an inch or so above the table. Rapid release of the hand causes sudden movement of the cervical region which initiates the reflex as it is a vestibular reflex. The response consists of abduction and extension of the arms. The hands open but the fingers remain curved (**Fig. 13**). This phase



**Figure 13** Eliciting Moro's reflex

is followed by adduction of the arms. The response is also accompanied by crying, extension of the trunk and head with movement of legs. Infants with cerebral damage have exaggerated or absent response. An asymmetric response is seen in Erb's palsy, spastic hemiplegia and fracture of the humerus or clavicle.

If the above neurological screening is normal, there is rarely a need for detailed neurologic examination of the newborn.

## COMMON PHYSIOLOGICAL NEONATAL PROBLEMS

Most mothers do observe their babies carefully and are often worried about minor physical peculiarities or problems, which are of no serious consequence. She must be adequately informed and appropriately advised regarding minor problems to prevent undue anxiety of the mother.

**Regurgitation of milk** Most of the neonates take out small amount of curdled milk soon after feed. Child is usually active and vomitus is never yellow or green colored and baby looks healthy. To decrease the problem, mother should be advised regarding burping after feed and reassured regarding benign nature of the problem.

**Transitional stools** It is the transition from meconium (sticky thick green or black stools passed during first 2-3 days of life) to the yellow homogenous stool of a breastfed infant and is physiological. It starts on the 3rd or 4th day of life, is yellowish green and may be watery and contains some mucus.

The frequency of stools is increased (up to 10–15/day) and usually decreases by 10 days of life. It must be differentiated from diarrhea as it causes neither pathological weight loss nor dehydration. Transitional stool requires no treatment except parental reassurance.

**Erythema toxicum** The rash usually appears on the 2nd or 3rd day of life. It is scattering of erythematous macules, papules and even vesicles. It occurs commonly over the trunk, face and extremities while palms and soles are spared. It is to be differentiated from pyoderma in the vesicular state. Microscopy reveals eosinophils in erythema toxicum and cultures of vesicular fluid are sterile. The rash disappears spontaneously in 1–3 days. Reassurance of parents is all the treatment that is required.

**Mongolian spots** They are pigmented lesions found at birth in more than 50% of black *Native American or Asian* infants and occasionally in white ones. The area most commonly involved is the lumbosacral region but occasionally in the upper back, shoulders, arms, buttock and legs may be involved. The lesions may be small or large, grayish-blue or bluish-black in color, irregularly shaped and always macular. The lesions need no treatment except reassurance to parents as they tend to disappear within 1st year of life.

**Neonatal jaundice** Jaundice is a common physical finding (manifesting as yellowness of the skin of the face) when the serum bilirubin level exceeds 5 mg/dL during 1st week of life. As the degree of jaundice increases, there is cephalopedal progression of jaundice. Jaundice should be considered nonphysiological if it has appeared within 24 hours of age, stains the palms and soles or persists beyond 10–14 days of life.

### IN A NUTSHELL

1. Assessment of a newborn requires detailed antenatal, natal and postnatal history.
2. Obtain details of labor and delivery from obstetrician or obstetric records.
3. Examination of a newborn should be done in a warm room with warm hands.
4. There should be flexibility of routine and examination may not be done in a particular sequence.
5. Visual and auditory appraisal gives more information than detailed systemic examination.
6. Percussion and auscultation are of limited diagnostic value in newborns.
7. High-risk newborns should be identified for further examination and management.
8. Thorough search for minor and major malformations should be done.
9. Reassure parents regarding common minor or transient neonatal problems.
10. Plan any appropriate investigations required depending on history and examination findings for further assessment.

### MORE ON THIS TOPIC

- Carlo WA. Physical Examination of the Newborn Infant. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, Behrman RE (Eds). *Nelson Textbook of Pediatrics*, 19th Edition. Philadelphia: Elsevier Saunders; 2011. pp.532–6.
- Smith JB. Initial Evaluation: History and Physical Examination of the Newborn. In: Gleason CA, Devaskar SU (Eds). *Avery's Diseases of the Newborn*, 9th Edition. Philadelphia: Elsevier Saunders; 2012. pp.277–99.



## Chapter 12.3

# Care of the Normal Newborn

Somashekhar Nimbalkar

Neonatal mortality accounts for more than 50% of the under-5 mortality in the South-East Asian region and India contributes to the maximum number of deaths. Most of these deaths occur in neonates who are high-risk, but faulty caregiving practices can result in morbidity and resultant death in some cases even amongst normal newborn infants [those who are term gestation with birthweights more than 2,500 g and who did not need care in a neonatal intensive care unit (NICU) for normal transition after birth]. This chapter would attempt to address the routine care of the newborn infant beyond the delivery room and during the first few days of life.

### WHERE SHOULD THE NORMAL INFANT BE CARED?

Normal newborn infants should always be roomed-in with their mothers (*Rooming-in* refers to care of newborn with its mother and not in a separate nursery). The normal newborn infants are to be placed in skin-to-skin contact with the mother (*Kangaroo position*). Some facilities place the infant in separate cot/bassinet adjacent to the mother's bed. The advantages of rooming-in are depicted in **Box 1**.

#### BOX 1 Advantages of rooming-in

- Leads to improved bonding, as mother is always available to care for her infant
- Encourages and improves exclusive breastfeeding
- Reduces the chances of infection
- Reduces the chances of hypothermia and promotes *Kangaroo* mother care
- Improves the mother's confidence in caring for her baby
- It reduces the need for nursing personnel to care for the infant.

It is safe for a newborn infant to sleep with its mother. Some mothers may want rest and sleep after delivery and may express a desire to have the baby separated for some time. This should be discouraged; mothers and their families should be counseled on the advantages of rooming-in.

### CLOTHING THE BABY

A great deal of thermal control can be achieved by bedding in and *Kangaroo* mother care. In many regions of India, there are cultural practices related to clothing. As a result of these cultural taboos, newborn infants are often left unclothed for several hours or days, except may be for a thin piece of cloth, which places the infant at increased risk of hypothermia. It then becomes the responsibility of the healthcare provider to ensure adequate provision of *Kangaroo* mother care in the interim and counsel the family about the need of adequate clothing. In tropical conditions, a newborn infant would need a cotton vest and a loosely fitting gown that ties at the back with a disposable or washable diaper. If the temperatures are cold, they would need additional layers of woolen caps, socks and blankets to keep them warm when not in skin-to-skin contact. Newborn clothing should not be tight; they should be loose and comfortable to wear and warm.

### BABY IDENTIFICATION

Quality guidelines require patient identification to be a cornerstone of patient safety in hospitals. Neonates and mothers should have separate registered hospital numbers but their identification tags should be similar. The baby identification tag should have its hospital number, gender, date of birth, its mother's name and mother's hospital identification number. Additional details may be required as per individual hospital policy or existent state regulations. Tags should be placed in the infant's wrist or ankle and preferably made of soft plastic material which will not tear and are amenable to cleaning. Bar coding of tags may be considered if resources are available.

### FEEDING THE BABY

The newborn infant should be breastfed soon after birth in the delivery room. Thereafter it is important that mothers exclusively breastfeed their newborn infants on a demand schedule and offer no prelacteal or other feeds. As families get nuclear, most mothers are not in the know of the required skills of breastfeeding. Most mothers would want to breastfeed their babies and healthcare providers should help them successfully establish breastfeeding and not assume that they have the required skills. Early initiation of breastfeeding has great benefits and this should be ensured by healthcare providers. Imparting skills to mothers and family is important. Rooming-in mother and baby would ensure successful breastfeeding. It is equally important to counsel mothers to take of her own health as it would impact lactation.

### BATHING THE BABY

Neonates should not be given a bath soon after birth especially to remove the vernix. Vernix should not be removed as it protects the newborn skin and would get removed on its own over the first few days. Apart from chances of cross-infection, the preparation for a bath often makes the infant susceptible for hypothermia. The only exception for this may be when the infant is covered with blood. If the bath water is maintained at 36°C, then infant comfort is maximum and heat loss is avoided. A bathing routine initiated after 7th day of life does not impact the skin barrier or its environmental adaptation. A daily bath is not required especially if thermal environment cannot be managed. Washing and drying the groins, genital and buttocks every time the diaper is changed is sufficient. Soap is not required and should never be used on newborn's face. Alkaline soaps do increase the pH of the skin and do interfere with the function and development of the acid mantle. Mild synthetic detergents do not cause any adverse events and are akin to plain water. Bathing does not influence healing of the umbilical cord or skin microflora colonization which occurs in the first 2–3 days of life. However, it is important that where possible mothers may be taught how to bathe their infants before discharge from the hospital. It is important to emphasize that the room must be warm and the infant dried immediately after the bath.

In the Indian subcontinent often massage with oil is given before bath in most homes. The oil utilized varies by region and its health effects are not studied. However often during this process oil may be blown into the infant's nose/ear, which is not safe and should be avoided.

### CORD CARE

The current evidence recommends dry cord care with no application of medication on the cord. Napkins when used



should be folded well below the umbilical stump. The length of the stump should be such that it is not easily soiled by urine or stool. The cord falls off by the end of the 1st week and this separation is mediated by inflammatory processes at the junction with abdominal skin. At the time of separation the cord can be seen as moist, sticky and smelly and may show cloudy mucoid material which may be misinterpreted as pus. Alcohol (70% isopropyl alcohol) should not be used for application to the cord in the hope that it will keep the cord dry as this causes a delay of separation by 1–2 days than dry cord care. The same results occur with application of antiseptics.

## EYE CARE

There is no role of routine antimicrobial prophylaxis. In case there is discharge due to conjunctivitis antibiotic drops are to be instilled. Sometimes unilateral eye discharge can occur due to obstruction of the nasolacrimal duct. Caregivers should be taught massage of the middle canthus to resolve this issue over the course of the month.

## STOOLING PATTERN

Parents are often concerned by the stools that the neonate passes. A delay in passage of stools beyond 24 hours should initiate measures for evaluation as almost all neonates pass stools by 24 hours of life. Most neonates pass stools after each feed. The gastrocolic reflex is well preserved and every time the stomach becomes full, the ileocecal valve relaxes initiating a bowel movement. This is often interpreted as indigestion and this concern needs to be addressed as the mother may doubt her suitability of her breastmilk for the infant. Parents should be counseled regarding the transitional stooling pattern, its frequency (which may be up to 10–12 times/day) and consistency that may be loose and persist up to even 3 weeks.

## URINATION

The term neonate should pass urine by 48 hours of life with 95% neonates passing urine within 24 hours of life. A delay in voiding beyond 24 hours should alert the physician to renal and postrenal causes of delayed voiding. Almost 15% neonates void at the time of delivery and care should be taken to ensure that this is recorded. A normal renal ultrasound (prenatal) in association with a normal physical examination and passage of urine by 72 hours should preclude further testing. The neonate is expected to pass urine at least 6 times/day after the 3rd day of life. Frequency less than that may be reason to evaluate if the infant is receiving adequate breastmilk. The nappies are sometimes stained pink due to urate crystals and this does not require any intervention.

## PHYSICAL EXAMINATION

This is described in detail in the previous chapter. Assessments are done immediately after birth to rule out detectable malformations which can be life-threatening. Anthropometry, particularly weight and head circumference, is of special importance and needs to be recorded and also conveyed to parents. Detailed daily physical examination is not necessary unless the baby is unwell or parents have specific complaints. However it is advisable, if at discharge a detailed examination is done and recorded for future reference.

*Weight pattern* Newborns should not be weighed everyday. They should be weighed at birth and if still in hospital then between the 3rd and 5th day of life and at discharge. Normal newborns

lose about 7–10% of their birthweight in the first few days and regain their weight by 7–10 days of life. When infants do not regain birthweight, one must evaluate adequacy of milk intake by the infant. After the initial weight loss, they gain weight at the rate of about 25 g each day.

## PREVENTION OF INFECTION

The caregivers should wash their hands before touching or caring for the baby. They should also wash their hands after changing diaper or napkin. After removal of the diaper, it should be disposed of in a bucket or plastic bag which can be closed. Sick children and adults should be kept away from the newborn.

## IMMUNIZATION

Hepatitis B should be administered as early as possible after birth while Bacillus Calmette Guerin (BCG) and oral poliovirus vaccine (OPV) before hospital discharge. A dose of hepatitis B vaccine given within 12 hours of birth can prevent vertical transmission by 75–90%. Before discharge there should be brief discussion of various vaccines that will be administered over the following years. This should include a reference to the immunization card and the cost of vaccines if any. A detailed discussion of vaccines can be deferred to the first or second postnatal visit in the first fortnight after delivery.

## COMMON NEONATAL PROBLEMS

*Vaginal discharge* Many female infants have a mucoid/bloodstained vaginal discharge in the first few days after delivery due to withdrawal of maternal hormones. If noticed during examination, it is prudent to draw the attention of the relatives to this and explain how to clean the area and keep it dry and reassure them about the temporary nature of the discharge.

*Breast enlargement* Neonates of either gender can have enlargement of breasts due to influence of maternal hormones. There might be milk secretion too. They can remain enlarged for even a month. Parents should be counseled against squeezing/massaging them.

*Nasal block and sneezing* The newly born neonate can sneeze due to external fluid blocking the nose. Also the small size of the nose makes it susceptible for blockage due to collection of mucoid secretions. The neonate usually clears this by sneezing and multiple sneezes should not cause concern. Often this is interpreted as cold and one must avoid using medications for the same. Prescribing normal saline to clear the nose works well if it affects baby's feeding/sleep.

*Behaviors that are normal* Yawning, hiccups, passing wind, straining with bowel movements, crying before urination, trembling of chin, quivering of lips, burping, startle reflex, clearing of throat, gurgling sounds, trembling and jitteriness of arms and legs while crying are all normal. Often the breathing patterns can induce anxiety. Newborns can take rapid, progressively deeper breaths, or have long pauses (< 6 sec) without turning blue. Noises can be caused by movements or breathing during sleep.

*Fever* If the newborn develops fever in the 1st week of life, it is usually attributable to infection or overheating due to environmental temperature. However, if these are ruled out, then dehydration fever should be considered in the setting of loss of more than 10% of birthweight and a well-appearing baby. Plasma osmolality will be more than 310 mOsmol/L. Ensuring increased fluid intake in the form of frequent breastfeeding will result in normalization of the temperature.

## NEWBORN SCREENING

**Hearing assessment** Congenital hearing loss affects about 3–4 infants per 1,000 livebirths. Detection of hearing loss in neonatal period and early infancy allows targeted management which can improve hearing outcomes. Strategies for newborn hearing screening vary but a two-step process with a specificity of 0.99 is commonly used. Automated otoacoustic emission (OAE) screening initially followed by auditory brainstem response in those who fail is often the preferred approach. Parents need to be counseled about the importance of not missing these screens, as early intervention including cochlear implants has improved outcomes.

**Newborn metabolic screening (NBS)** Screening newborns for inborn errors of metabolism is mandatory in most developed countries. In many states of India, NBS has been introduced in large public hospitals and many private hospitals also offer NBS. The tests offered in NBS vary with laboratories and the technologies used for NBS also vary. Tandem mass spectroscopy is most commonly used for NBS. Few drops of blood are collected from the heel of the newborn on a special filter paper after day 1 and usually on day 3, these dried blood spots are transported via regular mail to the laboratories. Reports are usually dispatched by a week. NBS is usually done for common disorders such as hypothyroidism, phenylketonuria, galactosemia, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and congenital adrenal hyperplasia. Positive screening tests need to be confirmed by using confirmatory tests to eliminate false positive results. Infants with confirmed tests would need to be put on appropriate treatment at the earliest. For details, see Chapter 3.19.

## DISCHARGING A NORMAL NEWBORN

A normal newborn should ideally be discharged after 72–96 hours after delivery if it is free from any illness including significant jaundice, immunized, has a mother who is breastfeeding confidently and the mother is healthy. At times parents insist on discharge within 24 hours. In such cases the infant should be followed up between 3 days and 5 days of life to check for breastfeeding establishment and development of any jaundice. At discharge all mothers should be given a road to health card which has the details of the baby's birthweight and immunization details.

**Sleeping position** It is recommended that neonate be placed on the back, on a firm mattress, without any compressible material in the sleeping area to prevent accidental suffocation.

**Car seats** In urban areas, parents should be informed about the use of car seats for neonates and infants. These seats must always be rear facing and strapped onto the back-seat of the car.

**Washing clothes** Laundry detergents containing fragrances and dyes should be avoided while washing clothes of newborn infants. Additional rinsing should be advised to remove all detergents.

**Communication with family** Communication with family should begin before the delivery and continue during the delivery process and in the postnatal period too. Most parents are very receptive to messages during the postpartum period. However, mothers may be in pain, and exhausted and sometimes not in a position to receive advice. Hence, instead of standardizing time of communication it should be adjusted to when the parents are likely to receive it well. Since parents with healthy newborns will receive advice which is

generic, it may be better to deliver it to the extended family as well. This allows grandparents to interact and resolve queries.

In the Indian milieu, decision-making is often done not by parents but by grandparents and extended family and hence getting them involved is in the best interest of the newborn. Using multimedia and videos has shown to improve receptiveness of advice and it also allows parents to receive it at a time that suits them. Daily communication should also emphasize on breastfeeding, infection control, thermal management and the health of the mother. She should be told that if the baby cries she should respond by picking up the baby, talking to it, establishing eye-to-eye contact and addressing the cause of crying (messy diaper, hunger, etc). This should usually stop crying and the newborn will gaze at the mother. These repeated interactions promote infant and maternal bonding and hence mother should be encouraged to carry out most of the care of their babies. It is to be emphasized that most mothers are anxious and may not have understood all messages that were given in the first few meetings. Hence, emphasizing the elements of baby care on an everyday basis will improve the understanding of the mother. It will also empower her to ask questions which she may have hesitated to ask on the first few days. Communication at discharge should be detailed with advice on immunization, baby care and danger signs (**Table 1**).

## POSTPARTUM DEPRESSION

Postpartum depression is quite common and occurs in about 10% of mothers. It is different from postpartum blues that may occur in the first week of life and it has serious consequences for the care of the newborn and infant through the 1st year of life. Postpartum depression can interfere with maternal-infant bonding, adversely affect cognitive and language development in the infant and, hence, needs to be detected by the pediatrician during the postpartum visits by the mother. Simple screening tools such as *Edinburgh Postpartum Depression Scale* are available to detect it and have been validated in many Indian languages. Postpartum depression can be well managed by various available therapies, such as pharmacotherapy, psychotherapy or their combinations.

Care of the normal newborn involves less of diagnosis and more of anticipation and counseling. Combining art and science skillfully to advise new parents to ensure adequate care of the

**Table 1** Danger signs in a neonate

- Breathing less than or equal to 30 or more than or equal to 60 breaths/min, grunting, severe chest indrawing, blue tongue and lips, or gasping.
- Refusal to feed or suck at breast
- Feels cold to touch or axillary temperature less than 35°C
- Feels hot to touch or axillary temperature equal to or greater than 37.5°C
- Red swollen eyelids and pus discharge from the eyes
- Convulsion/fits/seizures
- Jaundice/yellow skin (at age less than 24 hours or more than two weeks) involving soles of the feet and palms of the hands.
- Pallor
- Bleeding
- Repeated vomiting, swollen abdomen, no stool after 24 hours

newborn is the endpoint that needs to be achieved. The timing of this care allows physicians the window of opportunity to bring about adoption of appropriate healthcare practices by parents which has a far-reaching impact on the life of the newborn.

### IN A NUTSHELL

1. Mother and newborn infant should always be roomed-in after birth.
2. Bathing the newborn should be deferred to end of 1st week.
3. Umbilical cord should be left dry; no applications should be made in a healthy cord.
4. *Kangaroo mother care* should be encouraged in the 1st week.
5. Newborn babies should be discharged only if they are breastfeeding well, have no major illness and have been immunized.
6. During hospital stay and at discharge communicate with parents and extended family regards care of the infant at home.

### MORE ON THIS TOPIC

- Agarwal R, Jain A, Mehta S, et al. Care of the Normal Newborn. In: Agarwal R, Jain A, Mehta S, Sankar JM, Paul JS, Gurur G (Eds). NNF Evidence Based Clinical Practice Guidelines 2010. New Delhi: NNF Publication; 2010.
- Buescher JJ, Bland H. Care of the Newborn. In: Rakel RE, Rakel DP. Textbook of Family Medicine, Eighth Edition. USA: Elsevier/Saunders; 2011.
- Cartlidge PH, Shah DK, Rennie JM. Care of the normal term newborn baby. In: Rennie JM (Ed). Rennie and Robertson's Textbook of Neonatology, Fifth Edition. USA: Churchill Livingstone; 2012.
- Dyer JA. Newborn skin care. *Semin Perinatol*. 2013;37:3-7.
- Greenfield D, Theron G, de Groot H, et al. Primary Newborn Care: A learning programme for professionals. In: Woods DL (Ed). Perinatal Education Programme. Cape Town: Electric Book Works; 2008.
- Kinzie B, Gomez P. Basic maternal and newborn care: A guide for skilled providers. Baltimore: MNH program/JHPIEGO; 2004.
- Singh M. The art, science and philosophy of newborn care. *Indian J Pediatr*. 2014;81:552-9.
- Taylor JA, Wright JA, Woodrum D. Routine Newborn Care. In: Gleason CA, Devaskar SU (Eds). *Avery's Diseases of the Newborn*, Ninth Edition. Expert Consult-Online. Elsevier Health Sciences; 2011.

## Chapter 12.4

# Maintenance of Temperature

Suksham Jain, Ravish Singhal

The human newborn is a homeothermic mammal but has a limited capacity to maintain its core temperature against adverse environmental conditions because they are not able to generate adequate shivering response. During pregnancy, maternal mechanisms transfer heat from placenta to the fetus and maintain intrauterine temperature, keeping it 0.3–0.5°C higher than that of the mother.

Incidence of hypothermia in neonatal period in various studies in India (temperature < 35–35.6°C) has been reported up to 17% and it increases to 48% when a temperature less than 36°C was used to define hypothermia. Hypothermia in neonates is more due to lack of awareness of keeping the infant warm than due to lack of technology. Even during resuscitation more emphasis is given to achieving adequate oxygenation and cardiac output, and temperature is often overlooked. Hypothermia can result in poor somatic growth, and severe hypothermia can even lead to death.

### PHYSIOLOGY OF THERMAL CONTROL

After birth, the neonate is exposed to a hostile extrauterine environmental temperature. The newborn moves from an ambient intrauterine temperature of 37–25°C as air replaces the intrauterine amniotic fluid in which the baby was surrounded. As the amniotic fluid on the skin surface begins to evaporative soon after birth, there is a tremendous heat loss at the rate of 0.58 kcal/mL of water lost. This brings into play mechanisms that attempt to maintain the body temperature in the euthermic range. It is important to understand that temperature is a balance between mechanism of heat production and heat loss which can be summarized in the following equation:

$$\text{Temperature} = [\text{Heat production}] - [\text{Heat loss due to (evaporation + convection + radiation + conduction)}]$$

### Heat Production

When an infant is exposed to cold or heat, the temperature is sensed through peripheral thermal receptors which are found

over the entire surface of the skin, and as a first response leads to dermal vasoconstriction. At the same time central thermoreceptors are also stimulated and these send signals to the hypothalamic regulatory center. Efferent signals from the hypothalamic nuclei result in an increase in sympathetic activity and this action results in the release of norepinephrine from the diffuse innervation at the surface of brown adipose tissue and the stimulation of thyroid-stimulating hormone release, which in turn stimulates a rise in thyroxine levels from the thyroid gland. The released norepinephrine activates monodeiodinase, which converts thyroxine to triiodothyronine, which upregulates the production of an uncoupling protein (thermogenin) in the brown adipose tissue. Brown tissue is present in axilla, perinephric, interscapular, medistinal and paraspinal areas. It acts as a source of nonshivering thermogenesis (**Flow chart 1**) and second sympathetic effector organ. The uncoupling of mitochondrial oxidation from phosphorylation results in heat production from oxidation of free fatty acids, and the uncoupling of adenosine triphosphate synthetase. At the same time signals are also sent via the thalamus to the cerebral cortex, resulting in conscious perception of the change in environment, leading to changes in behavior and increased movement.

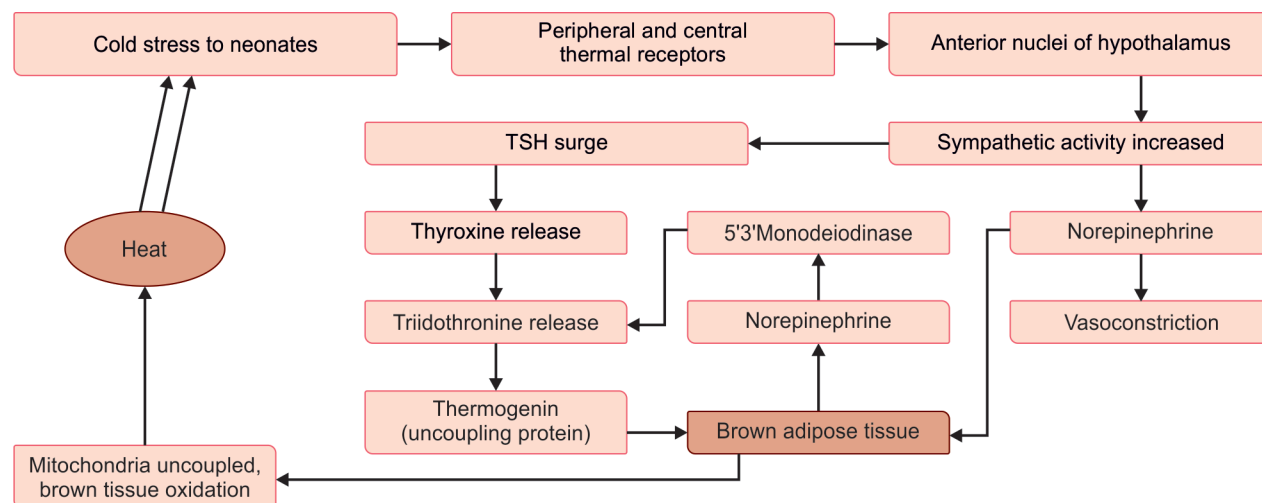
Preterm neonates are functionally poikilothermic due to some handicaps (**Box 1**). In the absence of external heat source due to ineffective heat production, they start losing temperature at a rate of 0.3–1°C/min and in the immediate postnatal period a wet preterm neonate may lose heat at a rate of 200 kcal/kg/min or greater.

### Heat Loss (Fig. 1)

#### Evaporation

This mechanism is most common source of heat loss at birth. Preterm transcutaneous evaporation of water in preterm babies is higher as compared to term babies and this results in higher evaporative heat loss. This is because preterm babies have poorer keratinization of stratum corneum that offers less resistance to diffusion of water. Heat loss in these babies is nearly 15 times more than a term neonate. Even a dry infant has evaporative losses in an environment with low humidity. Postnatally the skin matures rapidly so that by 2–3 weeks even the most immature babies have evaporative losses comparable to term babies.

Flow chart 1 Nonshivering thermogenesis

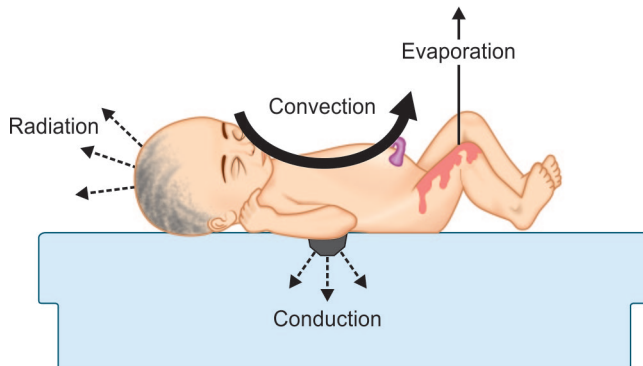


Abbreviation: TSH, thyroid stimulating hormone.



**BOX 1 Handicaps of preterm newborn in temperature regulation**

- Skin surface area to weight ratio is higher, in extremely preterm neonates heat dissipating area is five to sixfold greater than adults
- Less subcutaneous fat, hence, decreased thermal insulation
- Decreased heat production due to less brown fat, less uncoupling protein, thermogenin, less monodeiodinase in less than 32 weeks gestation babies
- Babies do not shiver like adults to generate heat, because muscle constriction-relaxation fibers are not yet myelinated
- Increased transepidermal water loss due to highly permeable skin, especially in extreme premature neonates
- Less glycogen stores in premature neonates and intrauterine growth retarded babies
- Caloric intake for thermogenesis and growth is limited in neonates and it is gestational age-dependent
- Oxygen consumption is limited in presence of pulmonary problems.

**Figure 1** Mechanism of heat loss in neonates**Convection**

Heat loss by this mechanism depends on the air speed and temperature difference between baby and its surroundings. It is a major source of heat loss in newborns exposed to cold, draughty environment.

**Radiation**

Heat is lost by radiation from the exposed surface of the baby to the surroundings depending upon the temperature difference, via infrared electromagnetic waves. Infant's posture affects radiant

heat loss, with more flexed posture reducing the exposed area and decreasing heat loss.

**Conduction**

Heat is lost to the cooler surface in contact with infant's skin. Heat loss is proportionate to difference in temperature of the baby and the cold object. However, due to use of insulating mattresses and blankets, this mechanism plays minimal role in neonatal heat loss.

**Definitions**

**Euthermia** Axillary temperature of 36.5–37.5°C or skin temperature of 36–36.5°C.

**Hypothermia** Temperature below 36.5°C. **Table 1** provides the grading for severity of hypothermia. Hypothermia frequently occurs in the following settings:

- Cold environment and low humidity
- Naked baby, cold linen and bathing in cold room
- Blood sampling, surgery and infusions
- Neonatal transportation.

**THERMAL NEUTRAL ENVIRONMENT**

Critical importance of environmental temperature on outcome and survival of newborn infants can be better understood by examining the effects on its metabolism. Hill defined a set of thermal conditions under which oxygen consumption is minimal even as body temperature is maintained in the normal range. *Thermoneutral environment* is an age and gestation-based band of environmental temperature wherein the infant's body temperature is maintained at minimal basal metabolic rate (measured by oxygen consumption). It allows calories to be used for growth and development rather than using them for thermoregulation. **Table 2** provides details of the thermoneutral temperature zones.

**TEMPERATURE ASSESSMENT**

- **Touch** Warm hands and feet indicate normal temperature, warm abdomen and cold extremities suggest cold stress; cold abdomen and extremities suggest moderate to severe hypothermia.
- **Thermometer** World Health Organization recommends use of low reading thermometer up to 30°C. Rectal temperature is measured by inserting the bulb up to a depth of 3 cm in term and 2 cm in preterm babies. It gives best idea of the core temperature. Axillary temperature is measured by placing the bulb high up in axilla and holding the thermometer perpendicular to the adducted arm.

**Table 1** Severity of hypothermia (WHO 1997)

Grade of hypothermia	Axillary temperature	Skin temperature
Mild hypothermia or cold stress	36–36.4°C (96.8–97.5°F)	35.5–35.9°C
Moderate hypothermia	32–35.9°C (89.6–96.6°F)	31.5–35.4°C
Severe hypothermia	<32°C (89.6°F)	<31.5°C

**Table 2** Thermoneutral zone for neonates

Birthweight	Environment temperature			
	35°C	34°C	33°C	32°C
<1,500 g	1–10 days	11 days to 3 weeks	3–5 weeks	After 5 weeks
1,500–1,999 g		1–10 days	11 days to 4 weeks	After 4 weeks
2,000–2,499 g		1–2 days	3 days to 3 weeks	After 3 weeks
≥2,500 g			1–2 days	After 2 days

Source: Hey et al., 1969.

- **Thermistor** Skin temperature is measured by a thermistor probe placed over abdomen in supine and flanks in prone position. False high readings are possible due to applying probe over interscapular region (area of brown fat), sandwiched between skin and mattress or due to tight fitting cloths. False low reading is possible in cases of loose probe attachment or probe placed over bony prominences.
- **Liquid crystal thermometry—thermospot** It has a 12 mm liquid crystal temperature dot which is placed on the newborn's skin, medial to and just above axilla. It turns black if baby is hypothermic and green if baby is eutermic. This simple method is most appropriate for use in community settings.

## CLINICAL SIGNS OF HYPOTHERMIA

- **Initial signs** Due to peripheral vasoconstriction in response to hypothermia, the skin may become pale, extremities feel cold, there may be acral cyanosis, and poor peripheral perfusion. Infants may appear irritable at this stage.
- **Later signs** If hypothermia persists, the infant may manifest with apnea, bradycardia, hypotonia, lethargy, weak cry and suck, abdominal distension, emesis and central cyanosis.
- **Prolonged hypothermia** If hypothermia is prolonged, the clinical manifestations could include hypoglycemia (due to increased metabolism and glucose consumption), hypoxemia and metabolic acidosis due to secondary anaerobic metabolism, which can result and be compounded decreased pulmonary blood flow due to increased pulmonary vascular resistance causing persistent pulmonary hypertension. Other features that could be seen include peripheral and facial edema, sclerema, subcutaneous necrosis, acute renal failure, necrotizing enterocolitis, coagulation defects, all of which could result in death. If the infant is jaundiced, there is increased risk of bilirubin encephalopathy due to acidemia and elevation of nonesterified fatty acids which compete with bilirubin for albumin-binding sites.
- **Chronic cold stress** The features are less dramatic and may manifest only as poor weight gain and/or progressive weight loss.

## PREVENTION OF HYPOTHERMIA

Pierre Budin, a French obstetrician, focused on temperature and thermal regulation. Silverman in the late 1950s and early 1960s reported the impact of temperature and humidity on neonatal outcome. It was noted that higher humidity also caused higher infant temperature, and improved survival.

### Warm Chain

The warm chain is a set of ten interlinked steps carried out at birth and later which will reduce the chances of hypothermia in all newborns:

1. **Warm delivery room (25–28°C)** After birth, newborn's temperature can drop at a rate of 0.1–0.3°C/min for core and skin temperature respectively. Delivery room needs to be prepared much in advance. The delivery room should be warm (at least 25–28°C) using heat convectors or heater (objective recording of room temperature may be done by using room thermometer), free from draughts from open windows and doors or from fans. One should avoid using air conditioners in summers/high-speed ceiling fans.
2. **Warm resuscitation corner (28°C)** The radiant warmer in the resuscitation corner should be switched on at least 20–30 minutes in advance and put into manual mode with 100% heater output.
3. **Immediate drying** After birth, the baby should be immediately dried with a dry towel, starting with the head. After drying thoroughly, the baby should then be covered with a second, dry towel and a cap put on its head. All linen should be pre-warmed.
4. **Skin-to-skin contact** Baby can be placed prone on mother's chest in skin contact after delivery even during delivery of placenta, and episiotomy suturing. Later on also skin-to-skin contact should be promoted in wards, during transportation and at home in all preterm babies for a minimum period of 4–6 hours per day.
5. **Breastfeeding** Breastfeeding should begin as soon as possible after birth, preferably within an hour.
6. **Bathing/weighing postponement** Bathing should be postponed in a term baby at least till next day. It is better to avoid bathing in hospital. Weighing should be done only after covering the baby adequately and making zero correction for clothing.
7. **Clothing and bedding** Newborns should be covered with one or two layers of clothes and in colder climate there should also be a cap, socks and hand gloves.
8. **Rooming in** In postnatal wards, babies and mother should be allowed to be together in the same bed and breastfed on demand.
9. **Warm transportation** In case of transport, whether to home, to another hospital/another section, thermal protection should be ensured.
  - All peripheral hospitals caring for high-risk mothers should go for in utero transfer as early as possible.
  - Stable babies including preterm and low birthweight babies should be transported well-wrapped and in skin-to-skin contact with mother.
  - Very low birthweight, unstable, admitted babies should be transported using an incubator. Temperature should be checked before and after transport.
10. **Training and awareness** All the health-care personnel involved in the newborn care should be adequately trained in maintenance of body temperature of baby as per steps of warm chain.

## Thermal Management in Preterm Neonates

### Polythene Occlusive Wraps

Recent resuscitation guidelines recommend use of polythene wraps for all babies less than 28 weeks. Baby after birth should be immediately brought under radiant warmer and wrapped in polythene bag below the neck without drying. Wrapping delivers radiant heat to baby while decreasing evaporative losses.

### Incubators (Fig. 2)

These are preferred over radiant warmers because insensible water loss is decreased and infant's temperature is regulated by controlling the air circulation. Evaporation losses are limited by using maximum relative humidity and radiation losses are minimized by double walls in the incubators. It has two modes of temperature control—air and skin servo mode. In air mode, desired environment temperature is set from the charts and heater output adjusts itself to reach that air temperature. This mode is preferred during procedures or when baby is stable and can be transferred to cot. In skin servo mode a skin sensor is attached to baby and temperature is set to 36.5°C. Heater output adjusts to keep baby constantly at this temperature. It is preferred in sick babies. Humidity is usually adjusted to provide 80–85% humidity. Humidifier chambers should be filled with sterile water only and should be changed daily, otherwise chances of infection can increase.

### Radiant Warmers (Fig. 3)

This system is good for babies more than 1,800 g as it allows easy access for procedures, but at the cost of increased insensible water loss. Heat is uniformly reflected onto the surface. They reduce conductive heat loss by warming the microenvironment. It has two modes, skin servo and manual mode. Baby is preferably kept on skin servo mode, where temperature is set at 36.5°C. Heater output adjusts to maintain this set temperature. Baby may get over-or underheated, so only one baby should be nursed in a warmer bassinet, and always check temperature every 15–30 minutes.

In case of preterm neonates, a cling wrap can be used across the walls of radiant warmer to decrease insensible water losses. When baby is nursed under a radiant warmer/incubator, head and legs should be covered, and clothed when stable.

### Kangaroo Mother Care (Fig. 4)

It has been the most effective, low cost method of temperature maintenance for a hemodynamically stable preterm neonate. It not only helps in thermal regulation but also facilitates breastfeeding, helps

in better cardiorespiratory stability, less infection rate, increased mother-baby bonding, better weight gain and early neonatal intensive care unit (NICU) discharge, and improved survival.

## MANAGEMENT OF HYPOTHERMIA

In all babies who are detected to have hypothermia, blood sugar must be estimated to check for hypoglycemia. It is also important to note that neonates with sepsis may also manifest with hypothermia, therefore in all babies with moderate to severe hypothermia, a sepsis screen must be done and if baby is unwell, antibiotics may be initiated after taking a blood culture. **Box 2** summarizes the management principles for a hypothermic newborn.

## HYPERTEHRMIA

It is defined as a temperature of more than 37.5°C. The causes of hyperthermia in the newborn are listed below:

- Environmental
- Over clothing, wrapping baby in too many layers especially in hot, humid climate
- Dehydration fever usually results from excess weight loss, presenting on day 3–4 of postnatal life; fever generally subsides with correction of breastfeeding problems or when extra feeds given properly
- Sepsis.

### Clinical Features

Baby is usually irritable and later becomes lethargic, has tachycardia, tachypnea, and a hot flushed face. Severe forms of hyperthermia can lead to shock, convulsions, even death in neglected cases.

### Management

Place the baby in a normal environment (25–28°C) away from heat source. Undress the baby partial/fully. Monitor hydration, weight, urine output and renal function. Give frequent breastfeeds. Give breastmilk or by *katori* and spoon if needed. Correct dehydration, if any. If temperature is more than 39°C, sponge can be done with tap water. While doing so do not use cold/ice water. Monitor temperature hourly till it becomes normal.



**Figure 2** Incubator for thermal maintenance



**Figure 3** Radiant warmer for thermal protection



**Figure 4** Kangaroo mother care for thermal protection

**BOX 2 Management principles for hypothermia****Mild hypothermia**

- Skin-to-skin contact
- Cover adequately
- Warm room
- Prevent heat loss by using radiant warmers, incubators, oil application, warm mattress
- Identify and treat the cause
- Monitor axillary temperature every 30 minutes

**Moderate to severe hypothermia/failure of re-warming in mild hypothermia/progressively falling temperature**

- Ensure no further heat loss, remove cold, wet clothes and cover baby adequately with prewarmed clothes
- Rapid re-warming till baby is 34°C (set radiant warmer manual mode—heater output 100%; skin mode, 36.5°C; incubator air mode, 38–39°C)
- Monitor vitals, skin temperature continuously and axillary every 30 minutes
- Oxygen and ventilation to maintain SpO<sub>2</sub>
- Inject vitamin K
- Intravenous fluid, maintain hydration and blood sugar
- Monitor blood pressure, urine output, renal function and serum electrolytes
- Monitor bilirubin.

**IN A NUTSHELL**

1. Neonates are prone to hypothermia due to limited capacity of thermal regulation, large body surface area and less subcutaneous fat.
2. Heat production is mainly restricted to nonshivering thermogenesis, which is poorly regulated in preterm neonates due to less brown fat.
3. Heat loss in neonates occurs by four main mechanisms: conduction, convection, evaporation and radiation.
4. In normothermic baby, both abdomen and feet are warm to touch.
5. Prevent hypothermia at all the levels: in delivery room, in postnatal wards, at home and during transportation, by training health personnel.
6. Special measures to be taken in preterm neonates in form of polythene occlusive wraps before drying in labor room, use of double-walled incubators, radiant warmers, skin-to-skin contact (kangaroo mother care).
7. Moderate to severe hypothermia is to be managed in NICU.
8. Hyperthermia in neonates may occur more commonly due to overclothing, raised environmental temperature and dehydration.

**MORE ON THIS TOPIC**

- Cramer K, Wiebe N, Hartling L, et al. Heat loss prevention: a systematic review of occlusive skin wrap for premature neonates. *J Perinatol*. 2005;25:763-9.
- Flenady V, Woodgate PG. Radiant warmers versus incubators for regulating body temperature in newborn infants. *Cochrane Database System Rev*. 2003;4:CD000435
- Gray PH, Flenady V. Cot-nursing versus incubator care for preterm infants. *Cochrane Database System Rev*. 2001;2:CD003062
- Laroia N, Phelps D, Roy J. Double wall versus single wall incubator for reducing heat loss in very low birthweight infants in incubators. *Cochrane Database System Rev*. 2007;2:CD004215
- McCall EM, Alderdice F, Halliday HL, et al. Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants. *Cochrane Database System Rev*. 2010;3:CD004210
- Perlman JM, Wyllie J, Kattwinkel J. Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Circulation*. 2010;122:S516-38.
- Scopes JW. Thermoregulation in the newborn. In: Avery CB. *Neonatology, Pathophysiology and Management of the Newborn*. 2<sup>nd</sup> ed. Philadelphia: JB Lippincott; 1981.pp.171-81.



## Chapter 12.5

# Breastfeeding and Lactation Management

NB Mathur

Exclusive breastfeeding is the most effective intervention to reduce infant mortality and is estimated to prevent 13% of under-5 child mortality in low-income countries. Supporting a breastfeeding mother can be time-consuming initially but pays off in a healthier population. Breastfeeding rates are influenced by socioeconomic factors, education and support services. Health professionals have a responsibility to prepare mothers for breastfeeding and promote and protect breastfeeding practices in the society. Recommended infant feeding practices include (i) timely initiation of breastfeeding within half an hour of normal delivery and within 4 hours of cesarean section; (ii) exclusive breastfeeding up to 6 months; (iii) timely initiation of complementary feeds at 6 months; and (iv) continuing breastfeeding well into the second year of life.

### TERMINOLOGY

**Exclusive breastfeeding** If an infant is fed no other food or drink except breastmilk, it is exclusive breastfeeding. The baby should not have been given even water or a pacifier.

**Predominant breastfeeding** If a breastfed infant is fed small amounts of another food or drink, such as water, or tea but is predominantly breastfed, it is almost exclusively breastfeeding or predominantly breastfeeding.

**Partial breastfeeding** If a baby has some breastfeeds and some artificial milk feeds, or other drinks; or has started supplementary feeds but continues to be breastfed, it is called partial breastfeeding.

**Token breastfeeding** If an infant mostly has other food, but still breastfeeds occasionally, it is called token breastfeeding.

**Bottle-feeding** This means feeding a baby from a bottle even if the feed is expressed breastmilk.

### TYPES OF BREASTMILK

#### Colostrum

Colostrum is secreted as early as second trimester and during the first week after delivery. It is thick, sticky and yellowish or clear in color. Colostrum contains large quantities of protective, anti-infective and growth factors and has more protein and vitamins A and K than mature milk. It should never be discarded. It enhances the development and maturation of the baby's gastro-intestinal tract. The anti-infective proteins and white cells provide the first immunization against the diseases that a baby encounters after delivery. Although colostrum is secreted in small quantities, it is sufficient to meet the caloric needs of a normal newborn in the first few days of life. Colostrum also has a mild purgative effect, which helps to clear baby's gut of meconium and helps to prevent jaundice by clearing the bilirubin from the gut. Being rich in growth factors, it stimulates the baby's immature intestine to develop in order to digest and absorb milk and to prevent the absorption of undigested protein. If a baby is given any other milk or food before colostrum, it can damage the intestinal mucosa and cause allergies.

#### Transition Milk

During the first 2 weeks, the breast secretions increase in quantity, change in appearance and composition and are called transition

milk. The immunoglobulins and protein contents decrease while fat and sugar contents increase.

#### Mature Milk

Mature milk increases in quantity and contains all the nutrients needed for healthy physical and mental development of the baby. The composition of mature milk changes even during a single feed to exactly suit the needs of a baby. The milk that comes at the start of a feed is called foremilk. *Foremilk*, which is watery, has a low level of fat and is high in lactose, sugar, protein, vitamins, minerals and water. It satisfies the baby's thirst and is produced in larger amounts than hindmilk. Mothers sometimes worry that their milk is too thin and need reassurance. It is important for a baby to have foremilk and hindmilk to get a complete meal and all the water and calories that the baby needs. Pooled breastmilk is predominantly foremilk and has poor caloric value. It is also heat treated which affects its anti-infective value adversely, *hindmilk* is richer in fat and whiter than foremilk. It satisfies the baby's hunger and supplies energy. There is, however, no sudden change from foremilk to hindmilk. The fat content increases gradually from the beginning to the end of a feed.

#### Preterm Milk

Milk produced by a woman who has delivered prematurely is called *preterm milk*. This milk has more protein, minerals, immunoglobulins, lactoferrin, lysozyme, and cells than term milk. Preterm milk is suited for the survival and growth of a preterm baby.

### BENEFITS OF BREASTFEEDING

Breastfeeding is economical, convenient and physiological. Breastmilk is rich in essential fatty acids, lactose, long chain polyunsaturated fats and phospholipids. It also supplies enzymes including amylase, lipoprotein lipase and lacto-peroxidases. These enzymes increase digestibility and also act as defense against microbes. Long-chain polyunsaturated fats promote brain growth and reduce the risk of dyslexia and hyperactivity. Biochemically breastmilk is superior to artificial milk. The protein in breastmilk is predominantly whey protein (80%) and is rich in  $\alpha$ -lactoglobulin and lactoferrin. Lactalbumin is rich in tryptophan, a precursor of serotonin which plays an important role as a neurotransmitter. Lactoferrin ensures absorption of iron and zinc is bacteriostatic. Breastfeeding ensures transfer of maternal antibodies and T-lymphocytes and provides protection against some infectious diseases. Exclusively breastfed babies have been shown to have higher intelligence quotient and may have higher mathematical abilities than artificially fed babies. They are also less prone to asthma and other allergic disorders later in life. Breastfeeding not only benefits the baby but is advantageous to the mother as well. Breastfeeding reduces postpartum bleeding, promotes early uterine involution and helps in spacing of children and early resorption of excessive fat. It has a protective effect against breast and ovarian cancers as well. Mothers who exclusively breastfeed their babies are better adjusted with their babies as far as rearing and behavior adjustments are concerned.

### MILK PRODUCTION: PROLACTIN REFLEX

As the baby suckles on the breast it provides a sensory stimulus through nerve endings in the nipple and areola to the anterior pituitary glands resulting in the prolactin release through the prolactin reflex. This acts on glands in the breast for milk production. Prolactin is important determinant of milk volume. While baby suckles, milk is transferred under the influence of oxytocin. If a baby sucks the nipple and areola more, the milk production increases. If

a baby suckles less, milk production will fall. For the same reason, if a mother has twins, breastmilk production can double due to increased suckling. Relatively more prolactin is produced in response to suckling at night.

### MILK FLOW: OXYTOCIN REFLEX

Stimulation of sensory nerves in the nipple and areola by suckling also induces the secretion of oxytocin, from the posterior pituitary gland (the oxytocin reflex). Oxytocin acts on the muscle cells around the alveoli causing the ejection of milk. If it does not work well, the baby may have difficulty in getting the milk. It may seem that breast is not producing milk, although in fact it is there but not flowing. Oxytocin reflex may not be very prompt in some mothers, particularly preemies and may require 1–3 min of suckling for the response. Oxytocin also makes the uterus contract and controls postpartum bleeding. Oxytocin release is affected by the mother's emotional state. Positive emotions, particularly thinking lovingly of her baby and feeling confident of being able to breastfeed, can facilitate oxytocin reflex. The sight of the baby and the sounds made by the baby help augment the oxytocin reflex. Negative emotions like pain, worry, lack of confidence and doubt about her ability to produce milk inhibit the reflex. It is important that health professionals refrain from making adverse comments that could cause worry and undermine the self-confidence of the mother.

### SUCCESSFUL LACTATION

Breastfeeding should be initiated as soon as possible after birth, and definitely within 1 hour. In Cesarean section the breastfeeding should be initiated as soon as the mother recovers from the effect of anesthesia and mostly within 4 hours of birth. In the first 1–2 days the requirements of the babies are little, and are met with even a few minutes of suckling at the breast. The key to the successful initiation of lactation is frequent and regular suckling at the breast by the baby, on demand, and in the correct position. The baby should be kept with the mother to ensure good initiation of breastfeeding. No prelacteal feeds should be allowed as they inhibit the establishment of successful lactation. Measures to ensure successful breastfeeding are summarized in **Boxes 1 and 2**.

### NEONATAL REFLEXES THAT SUPPORT BREASTFEEDING

*Rooting reflex* When nipple is touched around the mouth of the baby, the baby turns its mouth towards the stimulus and opens it. This indicates the baby's readiness to accept the breast or its need for a feed. This is the method to initiate breastfeeding.

#### BOX 1 Ten steps to successful breastfeeding

1. Have a written breastfeeding policy that is routinely communicated to all health-care staff
2. Train health-care staff in skills necessary to implement these policies.
3. Inform all pregnant women about benefits and management of breastfeeding
4. Help mothers initiate breastfeeding within half an hour of delivery
5. Show mothers how to breastfeed, and how to maintain lactation even if they are separated from their mother
6. Give newborns no food or drink other than breastmilk, unless medically indicated
7. Practice rooming-in, allow mothers and infants to stay together 24 hours a day
8. Encourage breastfeeding on demand
9. Give no artificial teats or pacifiers to breastfeeding infants
10. Foster establishment of breastfeeding support groups and refer mothers to them on discharge from hospital, clinic.

#### BOX 2 Measures to establish and maintain lactation in very low birthweight or preterm and sick infants in NICU

- Mother should be allowed free access to her neonate in the nursery
- She should be provided with a bed as long as the baby is admitted in the nursery
- She should be encouraged to take part in the general care of her baby
- She should be taught the correct method of manual expression of milk with emphasis on correct site of pressure (at the areolar margin and not squeezing the nipple)
- Manual expression may be encouraged 10–12 times in a day including at night. Babies should be put on breast after manual expression for non-nutritive sucking if initiation of breastfeeding is delayed owing to baby's illness
- Building a mother's confidence should be high priority and all situations that undermine her confidence should be avoided
- Breastfeeding should be a precondition for discharge
- All health-care staff should be trained in managing breastfeeding problems including inverted, cracked and sore nipples.

*Sucking reflex* As the baby accepts the breast (nipple and areola), he starts sucking on the breast. Any touch on the palate induces this reflex.

*Swallowing reflex* As milk is transferred and collects in the mouth, it is swallowed. This swallowing reflex develops early in fetal life but its coordination with sucking occurs only by 32–34 weeks of gestation. The coordination can be enhanced by repeated exposure to suckling.

### PROCESS OF BREASTFEEDING

#### Position of the Mother and Baby

A mother can feed her baby in any comfortable position, such as lying (supine and lateral) or sitting. While feeding in the sitting position, the mother should sit comfortably leaning against a backrest. The baby should be held with the mother's palm under the buttock, and the leg and arm under the back of the baby, leaving the head free and at the level of the breast. Baby's body should be close, facing breast. Baby's body should not be away from the mother as that would twist his neck. Feeding in the lying down position does not cause otitis media.

#### Signs of Good Attachment

These include baby's chin is close to the breast and is sucking around the areolar circumference, baby's mouth is wide open and the lower lip turned outwards, more areola is visible above the baby's mouth than below it. There should be no pain in the nipple area during breastfeeding. The baby should take nipple as well as areola inside the mouth for transfer of maximal quantities of milk into the mouth. When a baby is well attached, he uses suction to pull out the nipple and areola to form a teat. Hence, he can effectively suck even if the size of the nipple is small.

#### Signs of Poor/Incorrect Attachment

These include baby sucking only at the nipple, mouth is not wide open, and most of the areola is outside the mouth. Chin is away from the breast.

#### Causes of Faulty Positioning (Attachment)

*Use of feeding bottles* If we offer bottle-feed to a baby before offering breastfeed, it may often lead to ineffective suckling due to nipple confusion. The mechanism of sucking from a bottle is different from that on the breast. Babies who receive some bottle-

feeds do not open the mouth fully and suck only at the nipple leading to sore nipple.

*Inexperienced mothers* Primipara mother may have difficulty in having her baby well attached.

*Functional difficulty* When a baby is small or sick or the mother has breast engorgement, attachment may be faulty. If skilled help is not available, baby may not be well attached. Due to ineffective suckling milk transfer is inadequate. It can further lead on to breast engorgement, baby is not satisfied and cries a lot, mother loses confidence in her breastmilk supply, leading to suppression of oxytocin reflex, incomplete emptying of breast further leads to decreased milk production.

### Duration and Frequency of Suckling

Babies can fulfill their requirements by suckling over 5–10 min. The baby should be allowed to decide the duration of the feed. Every mother should be advised to feed the baby from one breast completely and then put the baby to the other breast so that the baby gets the hindmilk also.

### Demand Feeding

The child should be fed on demand. Initially, the demands are very frequent but by 1–2 weeks the frequency decreases. The baby should be fed as frequently and for as long as it wants to, even at night. Breastfeeding at night helps maintain the milk supply as more prolactin is secreted during suckling at night.

## PROBLEMS DURING BREASTFEEDING AND LACTATION MANAGEMENT

Frequently encountered problems include those related to the nipple, like flat or inverted nipples, sore nipples, or breast engorgement, mastitis and not enough milk.

### Normal and Flat Nipple

Normal nipples may often appear flat. The protractility test helps in assessment. The mother rolls the nipple between index finger and thumb. If it protracts out, it is normal. The length of the resting nipple is not important for breastfeeding. However, the areola and the breast tissue beneath should be capable of being pulled out to form the teat. The nipple is just a guide to show where the baby has to take the breast.

### Inverted Nipple

Occasionally a nipple does not protract and on attempting to pull out the nipple it goes deeper into the breast—this is an inverted nipple. Fortunately, true inverted nipples are rare. The nipple usually becomes more protractile during pregnancy and mother should be reassured that she will be able to breastfeed.

*How to treat inverted nipples during postnatal period* The woman with inverted nipples needs help before every feed during postnatal period. Nipple exercises and shields are of limited value.

*Procedure to correct inverted nipple* Cut the nozzle end of the syringe. Introduce the piston from the ragged cut end side and apply the other end over the nipple and pull the piston. Nipple would protrude into the syringe. Put the baby to breast. It helps the nipple to erect out and baby is able to suckle in the proper position. Nipple may retract back subsequently but doing the procedure each time over a period of few days would help to solve the problem.

### Engorgement of the Breast

Fullness of the breast is a frequent problem. However, milk flow continues and the baby can feed normally. If enough milk is not removed, engorgement of breasts may result. The engorged breast

is tight, shiny (because of edema) and very painful. Also the milk may stop flowing. The common factors causing engorgement of breasts are: poor emptying of breasts due to infrequent suckling, prelacteal feeds, delayed initiation and long intervals between feeds, bottle-feeding, and any restrictions on breastfeeding. The baby cannot feed in the correct position because of engorged and painful breast, while the mother avoids feeding because of pain; this leads to inadequate emptying, decreased production of milk and sometimes infection. Once engorgement occurs, the baby should be breastfed frequently followed by expression of breastmilk. The commonest error in management is to stop breastfeeding, which aggravates the condition.

### Blocked Duct

If the baby does not suck well on a particular segment of the breast, the milk blocks the lactiferous duct, leading to a painful hard swelling. This *blocked duct* is not associated with fever. Tight clothing may also cause blocked duct. Treatment of a blocked duct includes: (a) improving suckling/position—the baby should be fed frequently on the affected breast and in various suckling positions so as to improve the emptying; (b) massaging the lump towards the nipple to promote emptying of the breast; and (c) encouraging the mother to take rest and wear loose clothes.

### Mastitis

If the blockage of the duct or engorgement persists, infection may supervene. The breast becomes red, hot, tender and swollen (mastitis). If untreated, an abscess may form as a hot, tender and fluctuant swelling, often associated with fever. A breast abscess may occur sometimes without preceding mastitis. Treatment consists of rest, and expressing the milk frequently. Antibiotics should be started and paracetamol administered for pain and fever. Warm water fomentation may help alleviate pain. Incision and drainage of the abscess may be needed in advanced cases. Breastfeeding should be restarted from the infected breast as soon as possible.

### Cracked/Sore Nipples

If a baby is not well attached to the breast, he sucks on nipple, causing sore nipples. If feeding continues in a poor position, it may lead to a cracked nipple and later stasis may lead to mastitis and breast abscess. Oral thrush in the baby is another important cause but it usually develops after a few weeks of breastfeeding. To prevent soreness and cracking of the nipples, attention should be paid to teaching correct feeding position to the mother.

*Treatment* Correct the attachment and positioning of the baby. This provides immediate relief to the mother. Breastfeeding should be continued on the affected breast as it heals readily after correcting the suckling position. Medicated creams are best avoided as they may worsen the soreness and draw the attention away from the main problem. For oral thrush, gentian violet should be applied over the nipple as well as inside the baby's mouth. For cracked nipples, treatment consists of feeding in correct position, washing the nipple once daily only with water, exposure of nipple to air and sun as much as possible, application of hindmilk drop on the nipple after each feed.

### Not Enough Milk

One of the commonest reasons for introducing supplementary milk early and terminating breastfeeding is that mothers feel that they are not producing enough milk. Mothers often worry about the amount of milk they produce. Sometimes relatives, friends or health workers casually comment that the mother may not have enough milk. The mother's confidence in her ability to meet the baby's needs is easily undermined. Almost all mothers can produce



enough breastmilk for one or even two babies, provided the baby suckles effectively as often as needed.

Often mother perceives that her milk is insufficient even though the baby is growing well on exclusive breastfeeding. The amount of milk produced is determined by the amount that the baby needs, it increases when the baby suckles more and empties the breasts completely. Milk volume is not affected by maternal diet.

Sometimes, however, a baby does not get enough breastmilk. Usually this is because the baby is either not suckling enough, or is not suckling effectively. Poor mammary gland development or hormonal disturbances are rare causes of decreased breastmilk production.

Mothers who believe that they do not have enough breastmilk need help and support. First, decide whether the baby is getting enough milk or not. If the baby is not getting enough breastmilk, decide why. Decide how to help the mother and baby. If a baby passes urine more than 6 times a day, and the urine is light-colored, the baby is probably getting enough breastmilk. This is a useful sign for monitoring the adequacy of breastmilk. If the baby is not getting enough breastmilk, the reason could be infrequent breastfeeding will produce less prolactin and hence reduced milk production; no night feeding leads to less prolactin. Use of bottles may lead to nipple confusion and psychological factors in the mother. Lack of confidence in the mother reduces secretion of oxytocin. Poor let down gives the mother an impression that she has no milk. Poor emptying of breasts leads to less milk production. Starting supplementary feeds further undermines mother's confidence leading to suppressed oxytocin reflex.

Explain to the mother why her baby is not getting enough breastmilk and reassure her that she can produce as much milk as the baby needs. Restore the mother's confidence. Help the mother to improve her baby's attachment at the breast. The baby should be allowed to suckle more frequently (12 times in 24 hours). The baby should be allowed to suckle at both the breasts.

If the baby is less than 6 months old and the mother gives supplementary milk feeds, help her to reduce them. Follow-up daily until the baby is exclusively breastfed. The advantages of exclusive breastfeeding and the dangers of unnecessary supplements should be clearly explained to the mother.

### Manual Expression of Breastmilk

All mothers should learn to express their breastmilk to feed a low birthweight or sick baby, relieve engorgement, maintain the milk supply when the mother is ill, relieve leaking breasts, and for storing milk for the baby when the mother goes out to work.

#### Method of Expression

The areolar circumference should be pressed between the index finger and thumb so that the lactiferous sinuses beneath the areola are compressed. If the procedure is painful, the technique is wrong. The fingers should not slide along the skin nor should the nipple itself be squeezed. Expression should be done all along the areolar circumference to ensure expression from all the segments of the breasts. The breast should be expressed for at least 5 min until the flow slows. To express milk adequately, it may take up to 20 min. It is important not to attempt hurried expression.

## FEEDING IN SPECIAL SITUATIONS

### Full Term Twins

Reassure the mother that she can produce enough milk for two babies and remind her that the increased suckling induces the production of more milk. Help her to discover the best method for

feeding. One method of breastfeeding twins together is by holding the babies with their bodies and legs under the mother's arms. Another useful position is to hold the babies in the mother's arms with the hands in front. The mother should ensure that weaker twin gets enough hindmilk. The family's support is absolutely essential.

### Low Birthweight Babies

Babies are able to suckle and swallow from about 24 weeks of gestation, but they may not be able to coordinate these movements completely until above 32–34 weeks. It is important for babies to start suckling at the breast as soon as they are able to and this exposure enhances the coordination. Manual expression of milk should be started as early as possible at intervals of 2 hours both in the day and night so as to ensure a good supply of milk.

### Cleft Lip or Palate

Breastfeeding is difficult in babies with cleft palate and counseling is required. Some babies with a partial cleft palate learn to breastfeed, especially if the mother is encouraged and the baby breastfeeds in an upright sitting position.

### Jaundice

Neonatal jaundice is not a contraindication for breastfeeding, in fact, it can help by clearing meconium early from the gut and reduces jaundice. Breastfeeding should not be temporarily stopped as a routine to find the cause of jaundice.

### Cesarean Section

As soon as the mother recovers from the effect of anesthesia (usually 4–6 hours after general anesthesia), the baby should be breastfed. The mother would need help in positioning the baby initially. The baby should be kept with mother. She should feed in the position she is comfortable with.

### Drugs and Breastfeeding

To stop breastfeeding is more likely to be harmful than the drugs themselves. Anticancer drugs, antithyroid drugs, radioactive substances and repeated doses of ergot (one dose postpartum is not harmful) must definitely be avoided. Diazepam, barbiturates, thiazide diuretics decrease milk supply. Most other drugs are safe.

### Environmental Pollutants

Household pollutants such as pesticides may be present in the breastmilk if these are present in the environment. Breastfeeding is safe in the presence of these in breastmilk as the other foods or animal milk would be more heavily contaminated.

## ANTENATAL COUNSELING

Preparations for breastfeeding should start in the antenatal period. Group discussions should be supplemented by individual talks on the advantages of breastfeeding, benefits of colostrum and dangers of animal milk feeding. Mothers should be shown how milk comes in, why the baby needs to suck even if the breast is empty and what is the correct attachment. The nipples should be examined and the mother reassured that she is fully capable of breastfeeding. The technique of breastmilk expression should be demonstrated.

All new mothers feel more emotional and sensitive than usual, and they should be explained that these feelings are normal and will pass. The mother should be encouraged to relax and should be handled calmly and gently. Her fears should be alleviated and her confidence boosted. If she looks miserable or is ignoring the baby, she might need extra counseling.



## CONCLUSION

There is ample evidence to suggest that group and individual counseling is an effective tool to achieve exclusive breastfeeding. A breastfeeding mother may easily lose confidence or give in to pressures from family members and friends to give artificial feeds. Situations which lower the mother's confidence should be avoided to protect exclusive breastfeeding. Hence, effective antenatal counseling, encouraging early initiation of breastfeeding, effective communication, baby-friendly hospital practices and management of common breastfeeding problems are keys to improving exclusive breastfeeding.

### IN A NUTSHELL

1. Breastmilk is the most optimum nutrition for the newborn babies and young infants.
2. Breastfeeding must be initiated within 1 hour of birth.
3. Good attachment on the breast, good sucking by the baby and frequent feeding (at least 8 times in 24 hours) are essential for successful lactation.
4. In every mother-baby dyad, it must be ensured that breastfeeding has been established before discharge from the health facility.
5. In low birthweight babies and those infants who cannot suck well, expressed breastmilk should be provided to the infant.

## MORE ON THIS TOPIC

- Black LS. Incorporating breastfeeding care into daily newborn rounds and pediatric office practices. *Pediatr Clin North Am.* 2001;48:299-319.
- Cusack L, Brennan M. Lactational mastitis and breast abscess—diagnosis and management in general practice. *Aust Fam Physician.* 2011;40:976-9.
- Gross RS, Fiermann AH, Mendelsohn AL, et al. Maternal perceptions of infant hunger, satiety and pressuring feeding styles in an urban Latina WIC population. *Acad Pediatr.* 2010;10:29-35.
- Jones G, Steketee RW, Black RE, et al. How many child deaths can we prevent this year? *Lancet.* 2003;362:65-71.
- Mathur NB, Dhingra D. Breastfeeding. *Indian J Pediatr.* 2014;81(2):143-9.
- Mathur NB, Dhingra D. Perceived breastmilk insufficiency in mothers of neonates hospitalised in neonatal intensive care unit. *Indian J Pediatr.* 2009;76:1003-6.
- Mathur NB, Seth A, Mishra TK. Physical growth and biochemical indicators of protein in exclusively breastfed neonates weighing less than 1500 grams. *J Trop Pediatr.* 2000;46:288-92.
- Mathur NB. Breastfeeding and Lactation Management. In: Mathur NB. *Essential Neonatology*. 1<sup>st</sup> ed. New Delhi: Noble Vision; 2012. pp.164-83.
- WHO/UNICEF. Breastfeeding counseling: a training course. WHO/CDR/93.4. Geneva: WHO; 1993.
- WHO/UNICEF. Ten steps to successful breastfeeding. From: [www.wholibdoc.int/publications/9241561300.pdf](http://www.wholibdoc.int/publications/9241561300.pdf). Accessed March 14, 2013.

# Section 13 DISORDERS OF WEIGHT AND GESTATION

**Section Editor** Siddarth Ramji

## Chapter 13.1

### Low Birthweight: Classification and Etiology

*Ruchi Nimish Nanavati*

The newborn health challenge faced by India is more voluminous, more diverse and more formidable than faced by any other country in the world as it contributes to the highest number of births and neonatal deaths in the world. India contributes to the largest number of low birthweight (LBW) infants born each year worldwide which is the single most important determinant of neonatal morbidity and mortality. The financial impact of LBW birth on the family and society is enormous in terms of the immediate neonatal intensive care and ongoing long-term health issues frequently experienced by this high risk group. Thus, LBW has emerged as a major public health concern worldwide and addressing it absolutely essential, if we hope to accelerate our progress toward Millennium Development Goal 4 as well as *Every Woman Every Child* initiative launched by UN Secretary General during the United Nations Millennium Development Goals Summit in 2010 aiming to save lives of 16 million women and children by 2015.

Newborn infant can be LBW (birthweight <2,500 g), because of suboptimal fetal growth commonly known as intrauterine growth retardation (IUGR) or fetal growth restriction (FGR), or due to prematurity (younger than 37 weeks of gestational age).

#### EPIDEMIOLOGY

*"Every Newborn"*, An Executive Summary for The Lancet's Series May 2014, highlights that worldwide annually 2.9 million newborn babies die and 2.6 million babies are stillborn. More than 75% of newborn deaths occur in south Asia and sub-Saharan Africa. In 2012, nine countries had a neonatal mortality rate (NMR) of more than 40 deaths per 1,000 livebirths; most countries were from sub-Saharan Africa. The day of birth is when 40% of all stillbirths and neonatal deaths occur. About three-quarters of all neonatal deaths occur during the first week of life, with 1 million babies dying on the day they are born. In 2012, complications from preterm births, intrapartum-related disorders or birth asphyxia, and infections (especially sepsis, meningitis, and pneumonia) were the main causes of neonatal deaths. Small babies face the highest risk of death in utero, during the neonatal period, and throughout childhood. More than 80% of neonatal deaths in sub-Saharan Africa and South Asia occur in small babies. Every year, an estimated 19 million newborn babies face life-threatening conditions, including preterm birth, intrapartum-related brain insults, severe bacterial infection, and pathological jaundice. At least 1.5 million newborn babies survive with long-term disabilities every year. Since 1990, under-5 deaths and maternal deaths have been halved worldwide owing to the Millennium Development Goals, however,

the average annual progress for reductions in NMR (2.0%) was much lower than the rate recorded for children aged 1–59 months (3.4%).

In India, 20% of world's infants, an awesome 27 million, are born every year. UNICEF's State of the World's children report cites 30% incidence of LBW in India. Overall estimates indicate that 8 million LBW infants are born in India every year or around 40% of the total of 20 million LBW babies born globally. The National Neonatal-Perinatal Database (NNPD) of the National Neonatology Forum of India reported data on 1,45,623 neonates born at 18 leading centers of the country for 2002–2003. The LBW incidence was 31.3%, 8.7% being less than 2,000 g and 3.4% less than 1,500 g. FGR incidence was 9.6%. Studies published by Bang et al. in 1999 and Rahmathullah et al. in 2003 revealed that over 80% of LBW neonates weigh between 2,000 g and 2,499 g, about 15% between 1,500 g and 1,999 g, and only 3% weigh less than 1,500 g. The Global Action Report on Preterm Birth 2012 states that worldwide 15 million babies were born preterm in 2010 and 1 million died as a result of their prematurity. Action report on Preterm Birth in India 2013 documents that the country accounts for 3.6 million, i.e., 24% of global preterm births and for 303,600 preterm deaths. India heads the list of 10 nations contributing to 60% of the world's premature deliveries. It is essential to recognize that in contrast to the high income countries, over three-fourth of LBW in India are full term. IUGR or FGR is the predominant cause of LBW in developing nations with higher LBW rates. Of preterm infants, 20–40% also have decreased growth for gestational age.

India also tops the list of 10 nations with highest neonatal death numbers. The LBW is the single most important etiology of neonatal morbidities and mortality. Nearly three-fourth of neonatal deaths and half of infant deaths occur amongst LBW infants. Complications of preterm birth are now single largest direct cause of neonatal deaths in the world responsible for 35% of the world's deaths a year, and the second most common cause of under-5 deaths after pneumonia. The NNPD reported 75% of neonatal deaths in infants less than 2,500 g. Various studies report that LBW infants between 1,500 g and 2,500 g contribute to a sizable proportion of total neonatal mortality. This group of infants is potentially salvageable in the home as well as in a first-level health facility using simple low-cost interventions. Even after the neonatal period, LBW remains vulnerable to malnutrition, recurrent infection, neurodevelopmental disabilities and death. The above facts highlight that LBW/preterm births are a major public health concern in our country. Research suggests that FGR results in anomalous programming of affected fetuses predisposing them to a variety of adult onset diseases such as obesity, diabetes, hypertension and coronary artery disease.

#### CLASSIFICATION OF LOW BIRTHWEIGHT

Low birthweight is a heterogeneous group consisting of infants born preterm (<37 completed weeks of gestation) and infants born at term but of reduced weight. Neonates can be classified as per birthweight or gestational age.

## Birthweight Classification

Birthweight is the first weight of a live or dead product of conception, taken after complete expulsion or extraction from its mother. This weight should be measured within 24 hours of birth, preferably within its first hour of life before significant postnatal weight loss has occurred.

- *Low birthweight*: Birthweight less than 2,500 g
- *High risk low birthweight (HRLBW)*: Birthweight less than 2,000 g
- *Very low birthweight (VLBW)*: Birthweight less than 1,500 g
- *Extremely low birthweight (ELBW)*: Birthweight less than 1,000 g
- *Micro premie*: Birthweight less than 800 g.

## Gestational Age Classification

The duration of gestation is measured from the first day of the last menstrual period. Gestational age is expressed in completed days or in completed weeks. This is considered physiologically more important than birthweight.

### Preterm

Neonates less than 37 completed weeks of gestation.

- *Extremely low gestational age neonate*: Neonates less than 28 weeks of gestation
- *Early preterm/very preterm*: Neonates less than 32 weeks of gestation
- *Moderate preterm*: Neonates between 32 weeks and 33 6/7 weeks of gestation
- *Late preterm*: Neonates between 34 weeks and 36 6/7 weeks of gestation.

### Term

Neonates from 37 completed weeks to less than 42 completed weeks of gestation.

- *Early term*: Neonates from 37 weeks to 38 6/7 weeks of gestation
- *Full term*: Neonates from 39 0/7 weeks to 40 6/7 weeks of gestation
- *Late term*: Neonates from 41 0/7 weeks to 41 6/7 weeks of gestation.

### Post-term

Neonates from 42 0/7 weeks of gestation and beyond.

## Birthweight and Gestational Age Classification Correlation

This has great clinical significance as it helps in anticipating immediate neonatal problems as well as in prognosticating short and long-term outcomes in neonatal population.

- *Small for gestational age (SGA)*: Birthweight less than 10th percentile for that period of gestation
  - *Appropriate for gestational age (AGA)*: Birthweight between 10th and 90th percentile for that period of gestation
  - *Large for gestational age (LGA)*: Birthweight more than 90th percentile for that period of gestation

Thus, a LBW baby could be preterm, term or post-term as well as AGA, SGA or LGA. For example, a baby born at 36 weeks of gestation weighing 1,400 g is described as late preterm VLBW SGA.

## ETIOLOGY

Fetal physiology and growth as well as maternal influence on the fetus are discussed in the earlier chapters. Fetal development is characterized by organized patterns of tissue and organ growth, differentiation, and maturation that are influenced by the maternal environment, uteroplacental function and the inherent genetic

growth potential of the fetus. The fetus depends on maternal nutrient intake and on maternal endogenous substrate stores as precursors for fetal tissue synthesis and as fuel for fetal oxidative metabolism. An adequate provision and effective placental transfer of substrates and oxygen, as well as an appropriate hormonal milieu are necessary for optimal fetal growth. Inherited regulatory factors within the fetal genotype affect nutrient use and thus influence fetal growth. Normally functioning placenta plays an important role for growing fetus being an organ of gaseous exchange and nutrition. Genetic potentials are usually determinants of early fetal growth. Nutritional and environmental problems affect the fetus when the requirements for tissue growth increase later in pregnancy.

The causes and origins of LBW seem much more complex and remain elusive. Although there seem to be differences in the relative incidence of IUGR and premature birth in different countries, risk factors associated with birth of an infant with LBW are similar. The LBW has been largely studied as single group only. The risk factors associated with LBW are given in **Table 1**.

## Maternal Factors

The prevalence of putative risk factors is very high in Indian population. Poor maternal nutrition, *too early, too frequent, and too many pregnancies* are the principle risk factors for LBW. Women with low income, prepregnancy weight less than 40–45 kg, a height less than 145 cm, insufficient nutrient intake, low weight gain during pregnancy and lack of antenatal care often produce LBW.

### Maternal Age

Extremes of maternal age are not conducive for optimum outcomes of pregnancies. In India, teenage pregnancy is an important public health issue. By the age of 15 years, 26% of females are married and by the age of 18 years, it rises to 54%. National Family Health Survey III data showed that 25–28% of women in Eastern India aged 15–19 years had already started childbearing. A study from Jabalpur revealed that adolescents accounted for 1.25% of total deliveries and most of them were shorter (<145 cm), lighter (<45 kg), anemic (Hb <9 g%) and had higher incidence of preterm deliveries, 27.7% compared to 13.1% in adult mothers.

### Maternal Education

National Family Health Survey II data showed that 58.2% of Indian mothers were illiterate. In the Bengaluru cohort study, a decreasing trend of IUGR was observed with increase in maternal education, ranging from 46% in women who had no schooling to 19% in women who had postgraduate education.

### Maternal Nutrition

Maternal weight before pregnancy and weight gain during pregnancy are two vital independent determinants of fetal growth. Appropriate weight gain during pregnancy is based on body mass index (BMI). A woman with a normal BMI of 19.8–26 may require a weight gain of 11.5–16 kg during pregnancy. A woman with lower BMI needs higher weight gain during pregnancy. Mean BMI values were lower in low per capita income households. Fetal requirements are easily met during the first trimester, however, as fetal growth accelerates in second trimester, the requirements increase and may not be met with if maternal diet is insufficient in calories. A mother who is deprived of calories, below critical caloric needs, and/or micronutrients during antenatal period is highly prone for LBW baby. Micronutrient deficiencies during pregnancy have serious implications on the developing fetus. The National Nutritional Monitoring Bureau reports that 50% of adult Indian rural population is suffering from some level of chronic energy deficiency (CED). Nearly 47% of adolescent women have BMI less

**Table 1** Etiology of low birthweight

<ul style="list-style-type: none"> <li>• <i>Maternal factors</i></li> </ul>
<ul style="list-style-type: none"> <li>• <i>Personal factors</i> <ul style="list-style-type: none"> <li>– Age (&lt;16 or &gt;35 years old)</li> <li>– Low weight for height</li> <li>– Short stature</li> <li>– Low educational status</li> <li>– Poor nutrition</li> <li>– Low birthweight of mother</li> <li>– Poor weight gain during pregnancy</li> <li>– No care or inadequate prenatal care</li> <li>– Short interpregnancy interval</li> <li>– Previous infant with low birthweight</li> <li>– Unmarried status</li> <li>– Low socioeconomic status</li> <li>– Smoking</li> <li>– Alcohol/drug abuse</li> <li>– Stress/heavy physical work</li> <li>– High altitude</li> </ul> </li> <li>• <i>Medical diseases</i> <ul style="list-style-type: none"> <li>– Anemia</li> <li>– Hypertension</li> <li>– Diabetes mellitus</li> <li>– Chronic renal disease</li> <li>– Heart and/or pulmonary disease</li> <li>– Maternal infection, urinary tract infection</li> <li>– Acute or chronic maternal illness</li> <li>– Collagen vascular disease</li> <li>– Autoimmune diseases</li> <li>– Thrombotic diseases</li> </ul> </li> <li>• <i>Obstetric diseases</i> <ul style="list-style-type: none"> <li>– Pregnancy induced hypertension, pre-eclampsia</li> <li>– Premature rupture of membranes</li> <li>– Chorioamnionitis</li> <li>– Uterine or cervical anomalies</li> <li>– Preterm cervical shortening</li> <li>– Uterine trauma</li> <li>– Bleeding</li> <li>– Assisted reproductive technology</li> <li>– Post-term delivery</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• <i>Placental factors</i> <ul style="list-style-type: none"> <li>– Placenta previa</li> <li>– Placental abruption</li> <li>– Infarction</li> <li>– Circumvallate placenta</li> <li>– Placental mosaicism</li> <li>– Vascular malformations</li> <li>– Velamentous umbilical cord insertion</li> <li>– Insufficient uteroplacental perfusion</li> <li>– Single umbilical artery</li> <li>– Chorioangioma</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• <i>Fetal factors</i> <ul style="list-style-type: none"> <li>– Constitutional</li> <li>– Multiple gestation</li> <li>– Congenital malformations</li> <li>– Chromosomal abnormality</li> <li>– Congenital infection</li> </ul> </li> </ul>

than 18.5, 11.4% are stunted. The odds ratio for LBW was found to be three times more in severe CED groups of mothers as compared to normal BMI groups. In one study, maternal weight gain during pregnancy was a critical determinant of birthweight; with every kilo weight gain during pregnancy, there was 8% reduction in LBW rate. Poor weight gain by 16 weeks' gestation is predictor of birth of a LBW infant. Poor nutrition may also reduce uterine blood flow, placental transport, and villus surface area. Analysis of the correlation matrix between the birthweight and maternal biosocial

and nutritional factors revealed that birthweight of a baby best correlated with the height and weight of the mother.

### Socioeconomic Status

It is a major determinant of and has a direct impact on maternal nutrition, hygiene, and antenatal care. Medical complications of pregnancy occur equally in all socioeconomic groups however many adverse practices, stress, misbeliefs that can hamper fetal well-being are more prevalent amongst the women of low socioeconomic strata of the society. A study from Chandigarh revealed that low per capita income in addition to low literacy level, birth order 2 and above and maternal age above 30 years were found to significantly increase LBW incidence.

### Lifestyle Factors

Stress and excessive physical work contribute to spontaneous preterm birth and are likely to be much higher in resource poor setting. A study from Odisha revealed that mothers who delivered preterm babies had significantly higher stressful life event scores. Excessive maternal activity during pregnancy was associated with smaller fetal size in rural population. Smoking, excessive alcohol consumption and drug addiction have been associated with increased risk of preterm birth. Cigarette smoking during pregnancy reduces eventual fetal birthweight, which is directly related to the number of cigarettes smoked.

### Medical and Obstetric Causes

The disease states which cause either uterine ischemia or hypoxia or both interfere with fetal growth. In India, 20% adolescent married females are moderately severe anemic which is an important risk factor for LBW. Chronic maternal hypertension adversely affects fetal growth especially if diastolic blood pressure is elevated. India has higher incidence of rheumatic heart disease, almost 17% of preterm births may be precipitated by such maternal illnesses. Women with pre-existing medical diseases such as kidney disease, asthma, interstitial lung disease or autoimmune disorders, may be unable to tolerate the pregnancy to term and premature delivery may be indicated for maternal safety. Pregnancy-induced hypertension adversely affects fetal well-being as well as growth through its action on uteroplacental circulation. It is important to note that clinical signs of edema, proteinuria, and hypertension may develop later. Abnormalities in Doppler flow velocity waveforms of the uterine artery are evident much before conventional fetal surveillance tests can detect fetal compromise. It affects 6–8% of pregnancies and has been reported to be responsible for 15–43% of preterm births. Mothers who have excessively low fasting blood glucose values and mothers whose blood glucose levels are insufficiently elevated after an oral glucose tolerance test are at risk of delivering an infant who is SGA. Advanced stages of maternal diabetes mellitus resulting in vascular insufficiency produce IUGR, despite the presence of maternal hyperglycemia. Mothers residing at high altitude have been described to have LBW. Drugs such as propranolol and other  $\beta$ -blocking agents and corticosteroids probably have a direct effect on the fetus. However, the mothers receiving these agents are expected to have chronic maternal illnesses which also can hamper fetal growth and well-being.

*Infection* plays an important role in preterm birth. Acute maternal illness, febrile illness, urinary tract infection, malaria, bacterial vaginosis, HIV are all associated with increased risk of preterm birth. Ascending intrauterine infection and inflammation causing cervical insufficiency and premature cervical shortening culminating into premature delivery is well-documented. Periodontal infection can be a reservoir for inflammatory mediators and increases the likelihood of preterm birth. Screening for urinary tract infection in antenatal clinic



followed by treatment of asymptomatic bacteriuria reduces the risk of LBW or preterm delivery by 40%.

### Placental Factors

Placental growth was poor in mothers who delivered LBW infants and was an independent risk factor for LBW in a community-based study. In maternal disorders, such as pregnancy-induced hypertension, pre-eclampsia, with compromised uteroplacental circulation, placental weight and volume also diminish. Significant additional amount of energy is needed for optimal metabolic, endocrine and gas exchanging functions of placenta essential for fetal growth and wellness. When placental insufficiency occurs, these functions are affected to a variable degree. Diminished placental growth adversely affects total nutrient transfer, whereas reduced placental production of chorionic somatomammotropin attenuates maternal mobilization of fuels to the fetus. Reduced placental energy production and protein synthesis limits active transport of amino acids and facilitative transport of glucose. Placenta previa, placenta accreta, vasa previa and placental abruption are associated with preterm births. Chronic abruption is frequently associated with FGR and cerebral palsy. The risk of recurrent abruption is significant ranging from 6% to 17% after first episode to 25% after second episode. Placental malformations are commonly seen in multiple gestations. As a result of arteriovenous interconnections in monochorionic twins, a twin who serves as the donor develops FGR.

### Fetal Factors

#### Genetic and Ethnic Factors

Genetic determinants of fetal growth are inherited from both parents. Maternal genetic factors influence fetus more as compared to paternal factors. Indian born women and women of Indian descent living in Western countries tend to have a lower mean birth weight and a higher LBW rate compared to their western counter parts. This effect persists into second generation even after adjusting for important confounders like socioeconomic status and literacy. This intergenerational effect partly explains the observation that mothers of infants of LBW were themselves neonates with LBW. It is known that fetuses with insulin resistance or decreased numbers of cells may be unable to grow despite adequate nutrient supply. Examples of fetuses with diminished cell numbers include fetuses affected by rubella embryopathy, autosomal trisomy, and other genetic causes of IUGR. Cytomegalovirus and rubella virus are the most important identifiable agents associated with marked FGR. After maternal viremia, both agents invade the placenta, producing varying degrees of villitis, and subsequently gain access to fetal tissues. Intracellular rubella virus inhibits cellular mitotic activity in addition to producing chromosomal breaks and subsequently cytotoxicity. In addition, this virus produces an obliterative angiopathy that compromises cell viability further. Cytomegalovirus also causes cytotoxicity, resulting in areas of focal tissue necrosis. These viral agents reduce cell number and subsequent birthweight by simultaneously inhibiting cell division and producing cell death. Chromosome disorders, such as trisomy 8, 13, 18, 21, are associated with FGR. Certain metabolic disorders, such as agenesis of pancreas, hypophosphatasia, phenylketonuria, etc., are associated with diminished birthweight. Cornelia de Lange syndrome, Meckel-Gruber syndrome, Potter syndrome, Prader-Willi syndrome, Rubinstein-Taybi syndrome, Williams syndrome as well as VATER/VACTERL anomalies are often associated with diminished birthweight.

### Multiple Gestations

The incidence of premature births in India is 21% and is still rising. Multiple pregnancies carry nearly 10 times the risk of preterm birth compared to singleton births. Approximately, 50–60% of twins, 90% of triplets are born preterm and virtually 100% of all higher multiple gestations result in preterm birth. Preterm birth can be classified into two broad subtypes: spontaneous preterm birth and provider-initiated preterm birth. Spontaneous preterm birth is a multifactorial process influenced by social and environmental factors, however the cause of spontaneous preterm labor remains unidentified in almost 50% cases. Maternal history of preterm birth is a strong risk factor driven by the interaction of genetic, epigenetic and environmental risk factors. A preterm first birth is the best predictor of a second preterm birth. Young or advanced maternal age, short interpregnancy intervals and low maternal BMI have been associated with an increased risk of spontaneous preterm birth. Another important risk factor is uterine over distension with multiple pregnancies. The uterus must have sufficient space for the fetus to grow. In multiple gestations, the uterine constraint seems to occur when combined fetal size approaches 3 kg. The number and causes of provider-initiated preterm birth are more variable. In a recent study in the USA, more than 50% of all provider-initiated preterm births at 34–36 weeks gestation were carried out in absence of a strong medical indication. Unintended preterm birth also can occur due to errors in gestational age assessment. Severe pre-eclampsia, placental abruption, uterine rupture, cholestasis, fetal distress and FGR with abnormal tests are some of the more important direct causes recognized. Both maternal and fetal factors are more frequently seen in pregnancies occurring after assisted fertility treatments, thus increasing the risk of both spontaneous and provider-initiated preterm births. Up to 24% of successful in vitro fertilizations result in multiple pregnancies. The levels of provider-initiated preterm births are increasing in part due to more aggressive policies for caesarean section for poor fetal growth and availability of advanced neonatal care for these tiny babies.

#### IN A NUTSHELL

1. Worldwide annually 2.9 million newborn babies die and 2.6 million babies are stillborn. More than 75% of newborn deaths occur in South Asia and sub-Saharan Africa.
2. In India, 8 million LBW infants are born every year or around 40% of the total of 20 million LBW babies born globally.
3. Newborn infant can be LBW (birthweight <2,500 g), because of suboptimal fetal growth commonly known as IUGR or FGR or due to prematurity (younger than 37 weeks).
4. India accounts for 3.6 million, i.e., 24% of global preterm births and for 303,600 preterm deaths. India tops the list of 10 nations contributing to 60% of the world's premature deliveries.
5. Poor maternal nutrition, *too early, too frequent, and too many pregnancies* are the principle risk factors for LBW. Women with low income, prepregnancy weight less than 40–45 kg, height less than 145 cm, insufficient nutrient intake, low weight gain during pregnancy and lack of antenatal care often produce LBW.
6. Low birthweight is the single most important determinant of neonatal morbidities and mortality. Nearly three-fourth of neonatal deaths and half of infant deaths occur amongst LBW infants.
7. Even after the neonatal period, LBW remain vulnerable to malnutrition, recurrent infection, neurodevelopmental disabilities and death as well as variety of adult onset diseases such as obesity, diabetes, hypertension and coronary artery disease.

## MORE ON THIS TOPIC

- Causes of preterm births in India. In: Indian Foundation for Premature Babies. *Delivered Too Soon: Action Report on Preterm Birth in India*. New Delhi: 2013. pp. 31-47.
- Every Newborn: An Executive Summary for The Lancet's Series. From: <http://www.thelancet.com>. Accessed May, 2014.
- Kliegman RM. Intrauterine growth restriction. In: Martin RJ, Fanaroff AA, Walsh MC. *Neonatal Perinatal Medicine: Diseases of the Fetus and Infant*. 9<sup>th</sup> ed. Missouri: Mosby; 2011. pp. 248.
- Newborn health issues. In: Dadhich JP, Paul V. *State of India's Newborns*. New Delhi. 2004. pp. 43-64.
- Preterm birth matters. In: Howson CP, Kinney MV, Lawn JE. *Born Too Soon: The Global Action Report on Preterm Birth*. Geneva: WHO; 2012. pp. 9-14.
- Smith VC. The high risk newborn: anticipation, evaluation, management and outcome. In: Cloherty JP, Eichenwald EC, Hansen AR, Stark AR. *Manual of Neonatal Care*. 7<sup>th</sup> ed. Philadelphia: Wolters Kluwer; 2012. pp. 74-90.
- Understanding and preventing preterm births. In: Indian Foundation for Premature Babies. *Delivered Too Soon: Action report on Preterm Birth in India*. New Delhi: 2013. pp. 1-13.

## Chapter 13.2

# Prematurity and Intrauterine Growth Restriction

Ashok Kumar, Sriparna Basu

Preterm and intrauterine growth retarded neonates share many common problems, but they also have distinct problems within each group. For convenience of the chapter the problems in each of these groups would be dealt with separately.

### PREMATURE NEONATES

Preterm birth is a major cause of morbidity and mortality in newborns and survivors have significant risks of long-term neurodevelopmental sequelae and functional impairments. The care of preterm infants imposes a heavy emotional and financial burden on families, the health-care system and the society. In recent years the incidence of preterm delivery has shown a steady rise globally, mainly due to indicated (or medically induced) preterm delivery, and multifetal pregnancy after artificial reproductive techniques and fertility-inducing drugs. In general, the risks of morbidity and mortality and long-term sequelae are inversely related to gestational age. The care of preterm newborns constitutes a major fraction of workload in any neonatal intensive care unit (NICU) and contributes disproportionately to the cost of care during initial hospitalization and subsequent period. Due to biologic immaturity, preterm infants are also highly vulnerable to iatrogenic complications.

### Complications of Preterm Neonates

Anatomical and physiological immaturity of different organ systems makes the preterm babies prone to different complications. Moreover, the need of various medical or surgical interventions also increases their risks of complications. The immediate and delayed complications of preterm birth are summarized in **Box 1** and discussed individually.

#### BOX 1 Complications of preterm birth

##### Immediate

- Increased mortality
- Perinatal asphyxia
- Hypothermia
- Hypoglycemia
- Fluids and electrolytes imbalance
- Respiratory distress syndrome
- Systemic hypotension
- Poor maintenance of nutrition and growth
- Patent ductus arteriosus
- Hyperbilirubinemia
- Infection
- Apnea of prematurity
- Necrotizing enterocolitis
- Intraventricular hemorrhage.

##### Delayed

- Retinopathy of prematurity
- Bronchopulmonary dysplasia
- Anemia of prematurity
- Metabolic bone disease
- Poor postnatal growth
- Hearing deficits
- Periventricular leukomalacia.

### Delivery Room Resuscitation and Perinatal Asphyxia

Preterm newborns have many handicaps which make transition from intrauterine to extrauterine life more difficult and challenging. The major handicaps include surfactant deficient lungs which makes ventilation difficult, immature brain with reduced capacity for spontaneous and sustained breathing, and inability to maintain normal body temperature in the absence of external heat. The need for delivery room resuscitation is more frequent in preterm newborns than in full-term babies. Great care should be taken to prevent hypothermia. While resuscitating newborns at less than 28 weeks' gestation, delivery room temperature should be at least 26°C and to reduce heat loss, babies should be covered with polyethylene wraps or bags up to the neck at birth without drying before putting under radiant warmer and starting resuscitation. Temperature of baby must be monitored closely when using these techniques in combination because there is a risk of hyperthermia which can potentiate the cerebral injury. In absence of polyethylene wrapping, exothermic mattresses can be used to maintain the temperature of newborn infants weighing less than 1,500 g within the normal range. Administration of supplementary oxygen should be cautiously regulated by blending oxygen and air since preterms are vulnerable to oxidative stress, and oxygen concentration should be guided by pulse oximetry. Measures for early respiratory support like continuous positive airway pressure (CPAP) and surfactant replacement therapy may be needed at birth and should be readily available in delivery room. In extremely premature infants, early endotracheal intubation may be needed for resuscitation. While assessing Apgar score in preterms, it should be remembered that Apgar score may be falsely low in preterm infants because of poor muscle tone and activity and should be interpreted with caution.

### Hypothermia

High body surface to body weight ratio, diminished subcutaneous fat, decreased brown fat reserve, thin nonkeratinized (permeable) skin, decreased glycogen store in liver, and limited metabolic response to thermal stress predispose preterm infants to hypothermia after birth. Hypothermia may result in hypoglycemia, apnea, infection, metabolic acidosis, disseminated intravascular coagulation, and death.

### Hypoglycemia

During pregnancy fetal blood glucose is maintained by the process of facilitated diffusion from the mother to the fetus via the placenta. Sudden cessation of maternal source of glucose along with insufficient glycogen stores in liver, poor gluconeogenesis, stress at birth and poor oral intake often lead to hypoglycemia. Hypoglycemia may be accompanied with hypothermia, apnea, infection, metabolic acidosis. Prolonged hypoglycemia may lead to brain damage. In extremely low birthweight infants, the incidence of hyperglycemia is also high, because of the poor ability of liver to handle glucose, increased secretion of stress hormones and use of drugs like aminophylline, adrenaline, etc.

### Fluids and Electrolytes Imbalance

In preterm infants, a larger proportion of body weight is contributed by water, with proportionally more fluid in the extracellular fluid compartment than the intracellular one. Physiological diuresis at 48–72 hours after birth, insensible water loss from skin and respiratory tract, and inadequate oral intake contribute to 10–15% weight loss after birth. This loss is further aggravated by use of radiant warmers, phototherapy, poor maintenance of temperature and humidity in NICU. On the other hand, excessive fluid administration is associated with opening of ductus arteriosus, pulmonary edema, intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD) and dilutional hyponatremia.

Hypernatremia and hyponatremia are common and are usually secondary to the disturbances of free water relative to total body sodium. Syndrome of inappropriate antidiuretic hormone secretion, secondary to disease conditions, may also lead to hyponatremia. Hyperkalemia secondary to acute kidney injury is also common.

### *Respiratory Distress Syndrome*

Respiratory distress syndrome (RDS) is the disease of immature lungs and occurs as a result of surfactant deficiency leading to atelectasis, ventilation-perfusion mismatch and alveolar hypoventilation causing hypoxemia and hypercarbia. The RDS is the most frequent cause of admission to NICU among preterm newborns. The incidence is inversely proportional to gestational age, about 50% of neonates born at 26–28 weeks develop RDS, whereas incidence drops dramatically after 34 weeks (<5%). Advances in the care of preterm newborns with RDS including antenatal corticosteroids, early surfactant use, and respiratory support (CPAP or mechanical ventilation) have greatly improved the outcome of these infants.

### *Systemic Hypotension*

Systemic hypotension is a very common diagnosis in preterm infants. An immature myocardium, poor peripheral vasoregulation, absolute volume depletion, shunts through fetal channels like ductus and foramen ovale, cytokine release causing vasodilatation, and the impact of positive pressure ventilation on venous return and cardiac output are the factors which contribute to inadequate systemic perfusion. Hypotension with evidence of inadequate tissue perfusion should be treated with fluid bolus and inotropes. The aim is to maintain mean arterial pressure above the gestational age of the infant in weeks. On the other hand, hypotension without any evidence of end organ perfusion abnormality may not warrant any therapeutic intervention (permissive hypotension).

### *Nutrition and Growth*

Initiation and maintenance of growth as expected in intrauterine life is often a challenge. The main contributing factor is inadequate caloric and protein intake along with breakdown of at least 1.2 g/kg/day of endogenous protein. Oral intake is poor because of incoordinated sucking and swallowing and feeding intolerance. Moreover, concern for necrotizing enterocolitis (NEC) and presence of systemic diseases often delays initiation and advancement of enteral feeding. The growth rate also defaults because of systemic diseases and sepsis. Prolonged use of parenteral nutrition to mimic intrauterine growth rates is also not free from complications and may result in hyperammonemia, cholestasis, sepsis and elevated triglyceride levels.

Extrauterine growth restriction, defined as growth rates less than or equal to 10th percentile of intrauterine growth expectation as per the postmenstrual age at the time of discharge from the hospital, is very common in neonates with birthweight less than 1,500 g. A recent study has estimated the incidence of extrauterine growth restriction to be 28%, 34%, and 16% for weight, length, and head circumference, respectively and for each growth parameter, the incidence increased with decreasing gestational age and birthweight.

### *Patent Ductus Arteriosus*

The ductus arteriosus is normally patent during fetal life and though functional closure of the ductus occurs within few hours after birth, anatomic closure needs several weeks to be complete. In preterm neonates, the ductus may remain patent because of immaturity of smooth muscles or may reopen secondary to disease conditions, like perinatal asphyxia, RDS, volume overload, methylxanthine therapy, etc. The incidence of patent ductus arteriosus (PDA) is

approximately 20% in infants more than 32 weeks and about 60% in less than 28 weeks. Availability of point-of-care echocardiography in the NICU has greatly improved the care of these infants and also avoided the unnecessary treatment of hemodynamically insignificant PDA.

### *Hyperbilirubinemia*

Most of the preterm infants develop significant hyperbilirubinemia requiring treatment. Increased red blood cell destruction, immature liver enzymes causing impaired conjugation and elimination of bilirubin, inadequate oral intake and reduced bowel motility with increased enterohepatic circulation lead to hyperbilirubinemia. Immaturity of blood-brain barrier (BBB) also makes the preterm infants prone for hyperbilirubinemia-induced complications like acute bilirubin encephalopathy, deafness, and kernicterus.

### *Infection*

Risks of infection are increased because of immunologic immaturity, use of different invasive procedures, such as, endotracheal tube, intravascular catheters, central venous lines, frequent handling, breach in mucosal and skin barriers, total parenteral nutrition, lack of breastfeeding, and prolonged stay in NICU. Indiscriminate use of broad spectrum antibiotics in NICU is associated with antibiotic resistant bacteria and fungal sepsis.

### *Apnea of Prematurity*

Apnea of prematurity, defined as cessation of breathing for more than 20s or apnea for less than 20s and accompanied by bradycardia or oxygen desaturation, is commonly seen in preterm infants. The incidence is inversely proportional to the gestational age. Approximately 70% of neonates born before 34 weeks of gestation have clinically significant apnea at least once during first 7 days of life and 50% or more of neonates weighing less than 1,500 g at birth need management with pharmacologic intervention or ventilatory support. Immaturity of the central respiratory center, vulnerability of the brainstem respiratory centers and peripheral chemo and mechanoreceptors to inhibitory mechanisms and mechanical obstruction due to poor muscle tone are the likely explanations for apneic episodes in preterm infants.

### *Necrotizing Enterocolitis*

Necrotizing enterocolitis is the most common gastrointestinal surgical emergency in preterm neonates. It usually occurs after a few days of birth and is characterized by inflammatory damage to the intestinal tract, ranging from mucosal injury to full-thickness necrosis and perforation. The NEC affects extremely preterm neonates with mortality or long-term complication rate above 50% or more depending on severity.

### *Periventricular-intraventricular Hemorrhage*

Periventricular-intraventricular hemorrhage (PVH-IVH) affecting the fragile capillary network of subependymal germinal matrix, is a significant cause of morbidity and mortality in preterm infants. Poor cerebral autoregulation and abrupt alterations in cerebral blood flow and pressure are the main causes of hemorrhage. PVH-IVH is often associated with long-term complications like posthemorrhagic hydrocephalus, neurological deficits, cerebral palsy, developmental delay, and seizures. Since PVH-IVH begins without obvious clinical signs, routine screening and serial cranial ultrasonography are necessary in sick preterm neonates for early diagnosis and management.

### *Retinopathy of Prematurity*

Retinopathy of prematurity (ROP) is a serious vasoproliferative disorder of immature retina which affects the tiniest and sick



premature infants and often leads to severe visual impairment or blindness. Approximately 50–70% of infants with birthweight less than 1,250 g at birth are affected by ROP. Prolonged exposure to supplemental oxygen, mechanical ventilation, PDA, intraventricular hemorrhage and shock are the common risk factors for ROP. Since there are no specific symptoms in neonatal period, routine screening should be done by 4 weeks of age in all infants with birthweight less than 1,500 g or gestational age of 32 weeks or less and selected larger infants with a birthweight of 1,500–2,000 g with an unstable clinical course.

### **Bronchopulmonary Dysplasia or Chronic Lung Disease**

Bronchopulmonary dysplasia or chronic lung disease, defined as the need for supplemental oxygen or ventilatory support at a postmenstrual age of 36 weeks or oxygen dependence after 28 days of life, is a major morbidity of preterm birth. Exposure to oxygen, barotrauma and volutrauma of mechanical ventilation, inflammatory agents, infection, vitamin A deficiency, etc., may lead to BPD in preterm neonates. A distinction has been made between old BPD and new BPD. Old BPD occurred in past in more mature preterm infants before the advent of antenatal steroids and surfactant. There was severe lung injury, characterized by prominent fibrosis, cystic changes, and inhomogeneous aeration of lungs. On the other hand, new BPD is observed in extremely preterm newborns who are exposed to antenatal steroids and receive surfactant replacement therapy. There is minimal fibrosis, more homogenous aeration of lungs, and histologically there is arrest of alveolarization. The developing pulmonary microvasculature can also be injured leading to pulmonary hypertension.

### **Anemia**

Anemia is commonly observed in preterm infants at 4–8 weeks of age. Contributing factors include frequent blood sampling, lower RBC mass at birth and shortened RBC survival, vitamin E deficiency, and rapid catch-up growth. Infant may manifest with poor growth, feeding problems, tachypnea and tachycardia, and pallor. Packed RBC transfusion is indicated in a symptomatic baby, or asymptomatic baby with hemoglobin below 7 g/dL.

### **Metabolic Bone Disease**

Metabolic bone disease is a common disease of preterm infants which generally manifests at 2–3 months of age and is characterized by a reduction in bone mineral content. It may occur in up to 55% of infants born with a birthweight less than 1,000 g and 23% of infants weighing less than 1,500 g at birth. The etiology is multifactorial and includes loss of intrauterine supply of minerals affecting bone mineralization, inadequate intake of calcium, phosphorus and vitamin D, total parenteral nutrition and prolonged immobilization. Since the disease can remain clinically silent for long time routine screening is recommended at 6–8 weeks of age. Low serum levels of phosphorus and high levels of alkaline phosphatase are suggestive. X-ray of long bones is not helpful because radiological changes become apparent only after considerable loss of bone mineral content (> 40%).

### **Hearing Deficits**

Hearing deficits are common in hospitalized premature infants due to immaturity of cochlea, exposure to hyperbilirubinemia, hypotension, ototoxic drugs like aminoglycosides, furosemide and infection and meningitis.

### **Periventricular Leukomalacia**

Periventricular leukomalacia (PVL) is the most common ischemic brain injury in preterm infants affecting the periventricular

region adjacent to the lateral ventricles. Neuropathologically, the lesion often extends beyond the periventricular area to involve the cerebral white matter diffusely. Therefore, the term white matter injury has been proposed to describe this disease entity. Developmental vulnerability of premature brain, hypoxia-ischemia, infection, and inflammation are believed to play central role in the pathogenesis of PVL. The PVL is characteristically a silent lesion in the neonatal period and manifests few months later when spasticity of legs is noticed. The diagnostic hallmarks of PVL are periventricular echodensities or cysts detected by cranial ultrasonography. A significant percentage of survivors develop CP, intellectual impairment, or visual disturbances.

### **Long-term Complications**

The long-term sequelae of preterm births are summarized in **Box 2**. Preterm babies are at 3–5 times higher risk of long-term growth impairment and significant long-term morbidity such as cognitive, visual, and learning impairments than children born at term. The increased risk of CP with decreasing gestational age is well documented. 10.8% of infants of gestational age 22–26 weeks and 6.3% of infants of gestational age 27–32 develop moderate to severe CP in western countries. Recent studies also highlight the range and severity of cognitive, sensory, language, visual-perceptual, attention and learning deficits in very preterm children. A recent meta-analysis has shown that mathematics, reading, and spelling are significantly poorer in very preterm infants. Verbal fluency, working memory and cognitive flexibility are significantly poorer in children born very preterm.

## **NEONATES WITH INTRAUTERINE GROWTH RESTRICTION**

Overall, perinatal mortality and subsequent morbidity have been found to be 8–10 times higher in intrauterine growth restriction (IUGR) fetuses compared to their age appropriate counterparts. Term IUGR neonates weighing between 1,500 g and 2,500 g have a 5–30 fold increase in perinatal morbidity and mortality whereas those less than 1,500 g at term have a 70–100 fold increase in poor perinatal outcomes. A 2013 analysis of pooled overall relative risks for mortality and postneonatal mortality in IUGR infants of low-income and middle-income countries like Asia, Africa, and Latin America were 1.83 [95% confidence interval (CI) 1.34–2.50] and 1.90 (1.32–2.73), respectively.

### **BOX 2 Long-term sequelae of preterm birth**

- **Neurodevelopmental impairments (5–10%):** Global developmental delay, cerebral palsy, cognitive impairments, specific learning disorders, dyslexia, attention deficit hyperactivity disorder, behavioral abnormality, increased anxiety and depression
- **Visual impairment secondary to retinopathy of prematurity (25%):** Blindness, high myopia, or hypermetropia
- **Hearing impairment (5–10%)**
- **Chronic lung disease (40%):** Exercise intolerance, need for home oxygen therapy, reduced lung function, increased rates of asthma and recurrent hospital admissions for respiratory tract infections
- **Cardiovascular complications:** Increased blood pressure
- Increased incidence of noncommunicable diseases
- Growth failure in early life
- Accelerated weight gain in adolescence
- Suboptimal physical productivity
- **Impact on family:** Psychosocial, emotional and economic burden, risk of preterm birth in offspring
- **Impact on health-care services:** High cost of care and utilization of health-care resources
- **Impact on society:** Increased disability and burden of disease.

Depending on fetal biometry, IUGR can be classified into two groups, symmetrical and asymmetrical. Approximately 20–30% of IUGR fetuses are symmetrically small, whereas 70–80% display asymmetric growth restriction. Asymmetric IUGR have a lower ponderal index and are at higher risk for perinatal asphyxia and neonatal hypoglycemia. But there may be a great deal of overlap between these two entities.

### Complications of IUGR

Chronic in utero hypoxia in IUGR fetus is associated with a variety of morphological and functional changes to compensate for the reduced oxygenation and hypoxia-mediated fetal tissue damage. At an initial stage, the human fetus tries to adapt to hypoxia by redistribution of blood flow towards brain and myocardium allowing preferential delivery of nutrients and oxygen to the most vital organs. Cerebral vasodilatation leads to a decrease in left ventricular afterload with systemic arterial vasoconstriction of lower body vessels to increase right ventricular afterload. With continued hypoxia, this protective mechanism is overwhelmed by the decline in cardiac output and the emergence of fetal distress. Finally, there is a decline in systolic and diastolic fetal cardiac function, secondary to myocardial ischemia.

Chronic fetal distress with hypoxia is associated with fetal Doppler arterial waveform velocities indicating reduced systemic flow in descending aorta and umbilical artery and normal or increased blood flow in middle cerebral artery. With progression of fetal cardiovascular compromise, abnormal pulsatility indices in the umbilical artery or middle cerebral artery are seen followed by abnormal peak systolic velocity in the middle cerebral artery with absent or reversed diastolic flow in the umbilical artery. In the most serious progression of fetal compromise, there is reversed flow in the ductus venosus or umbilical vein, indicating the need for an urgent delivery. The complications of IUGR neonates are summarized in **Box 3** and discussed individually.

#### BOX 3 Complications of intrauterine growth restriction infants

- Increased mortality
- Perinatal asphyxia
- Hypothermia
- Hypoglycemia
- Meconium aspiration syndrome
- Persistent pulmonary hypertension of newborn
- Poor maintenance of nutrition and growth
- Polycythemia
- Hyperbilirubinemia
- Infection
- Necrotizing enterocolitis
- Pulmonary hemorrhage
- Congenital malformations.

### Perinatal Asphyxia

Perinatal asphyxia is a potential complication of IUGR. There is high risk of fetal death and severe perinatal asphyxia if IUGR is caused by placental insufficiency with compromised placental perfusion, because during each uterine contraction, maternal placental perfusion further slows or stops by compression of the spiral arteries. When placental insufficiency is suspected, fetal heart rate should be monitored during labor. If fetal compromise is detected, rapid delivery, often by cesarean section, is indicated.

### Hypothermia

Intrauterine growth restriction infants are at risk of hypothermia due to a greater body surface area in relation to weight, less subcutaneous and brown fat reserves, less glycogen stores limiting their capacity of nonshivering thermogenesis.

### Hypoglycemia

Hypoglycemia occurs in 12–24% of IUGR infants, which is 7 times higher than appropriate for gestational age (AGA) infants. Severe IUGR and asymmetric IUGR are more commonly affected. Contributing factors include diminished hepatic and skeletal muscle glycogen, reduced alternate energy substrates such as free fatty acids due to the poor adipose tissue deposition, decreased concentration of lactate, hyperinsulinemia or increased sensitivity to insulin or both, decreased glycogenolysis and gluconeogenesis, and deficient counter-regulatory hormones. The risk of hypoglycemia is common during the first 3 days of life, maximum in the first 24 hours.

### Meconium Aspiration Syndrome

Hypoxia resulting from umbilical cord compression or placental insufficiency may cause the fetus to pass meconium into the amniotic fluid before delivery in about 10–15% of births. During delivery, 5% of neonates with meconium-stained amniotic fluid aspirate the meconium. Intrapartum aspiration of meconium may cause inflammatory pneumonitis and mechanical bronchial obstruction, causing respiratory distress, requiring mechanical ventilation, and high mortality.

### Persistent Pulmonary Hypertension of Newborn

Persistent pulmonary hypertension of newborn (PPHN) is commonly seen in IUGR neonates with perinatal asphyxia and MAS. In PPHN, there is persistence of or reversion to pulmonary arteriolar constriction, leading to a severe reduction in pulmonary blood flow and right-to-left shunting. Symptoms and signs include tachypnea, retractions, and severe cyanosis or desaturation unresponsive to O<sub>2</sub>.

### Polycythemia and Hyperviscosity

Intrauterine growth restriction infants are more prone to develop polycythemia, and the reported incidence is 15–17%. It is more common in asymmetric IUGR and after the gestation of 34 weeks. The increased red cell mass is the result of chronic in utero hypoxemia which increases the erythropoietin levels. Polycythemia can also contribute to hypoglycemia, hyperbilirubinemia and NEC in IUGR infants.

### Hyperbilirubinemia

It is common in IUGR neonates because of increase production of bilirubin from break down of red cell mass in polycythemia.

### Poor Immune Function and Sepsis

Intrauterine growth restriction infants have compromised humoral and cellular immunocompetence, including decreased IgG concentration, phagocytic function and lysozymes. Intrauterine infections commonly result in IUGR.

### Necrotizing Enterocolitis

Necrotizing enterocolitis occurs in IUGR infants secondary to hypoxia, poor superior mesenteric arterial blood flow, polycythemia and infection.

### Pulmonary Hemorrhage

Intrauterine growth restriction infants have significantly lower levels of coagulation factors V and VII and platelet counts. Massive pulmonary hemorrhage has been reported as a cause of sudden unexpected death in severe IUGR infants.

### Congenital Malformations

The risk of congenital malformations or genetic abnormalities is increased 2–3 fold in IUGR infants.

## Long-term Complications

### Poor Growth

Majority (90%) of healthy, term IUGR infants have catch-up growth during first 2 years of life, premature IUGRs may take longer to catch up. The recovery is considered complete when the children reach their mid-parental height. 10–15% of IUGR infants remain short statured with height less than 2 SD during childhood and adult life. These children generally have an adequate endogenous growth hormone secretion in response to pharmacological tests. However, they often have low serum insulin-like growth factor-1 (IGF-1) levels and altered physiological growth hormone secretion and may respond to growth hormone supplements.

For pubertal growth spurt, the age of initiation of puberty is normal in most of the cases. However, an earlier or late puberty has been reported. A decrease in pubertal growth has been observed, especially in females with earlier menarche, suggesting gender-dimorphic susceptibilities.

### Metabolic Risks

Intrauterine growth restriction infants are at significantly increased risk of developing hypertension, dyslipidemia, obesity and type 2 diabetes during adulthood. Several hypotheses have been put forward to explain the association between low birthweight and increased metabolic risks. Barker and colleagues proposed the hypothesis of *fetal programming* to explain the developmental origins of adult diseases. Barker's theory postulated that physiologic adaptations that enable a fetus to survive a period of intrauterine nutritional deprivation result in permanent reprogramming of the development of key organs in the body which have pathological consequences in later life.

The fetal cortisol hypothesis postulated that maternal nutrient restriction may act to reprogram the development of the pituitary-adrenal axis, resulting in excess glucocorticoid exposure and adverse health outcomes in later life. Another hypothesis was fetal insulin hypothesis which proposed that genetically determined insulin resistance results in impaired insulin-mediated growth in the fetus, as well as insulin resistance in adult life.

Obesity is also potentiated by alterations in appetite regulation and increased adipogenesis. Leptin, a primary satiety factor which reduces food intake in a normal child, has been shown to be one of the factors influenced by fetal programming. In IUGR fetuses, cord blood leptin levels are decreased. In addition, IUGR individuals may also demonstrate abnormal activation of adipocytes, leading to obesity.

Hypertension occurs by alterations in renal and blood vessel development. Reduced numbers of nephrons are associated with elevations in arterial blood pressure and changes in postnatal renal function. Diabetes is associated with decreased beta cell number and function along with alterations in cellular insulin signaling.

## PROBLEMS OF PRETERM IUGR

Approximately 30–50% of extremely preterm neonates are born as IUGR. These infants have higher mortality rates than their AGA counterparts and are at significant risk for reduced postnatal growth and development as well as acute and chronic morbidities, such as RDS, BPD, hyperglycemia, NEC, sepsis, ROP and IVH. Contrary to the common belief that the intrauterine stress associated with IUGR may enhance lung maturation, an increased incidence of RDS has been reported in preterm IUGR infants. Postulated underlying mechanisms include delayed metabolic adaptation,

systemic inflammatory response due to chronic hypoxia and free oxygen radical mediated injury. Very preterm IUGR infants have developmentally low insulin secretion and plasma insulin levels leading to hyperglycemia. The risk of NEC in premature IUGR infants is also increased secondary to in utero bowel ischemia due to redistribution of blood flow. Preterm IUGR can also be implicated in the genesis of ROP due to intrauterine hypoxia, altered levels of growth factors, and diminished antioxidant capacity. Neutropenia in extremely preterm IUGR infants, which occurs frequently in those born to pre-eclamptic mothers, adds substantially to the risk of sepsis. Some studies have reported an increased incidence of IVH in preterm IUGR infants though no increased risk for PVL has been found.

### IN A NUTSHELL

1. Preterm birth and intrauterine growth restriction (IUGR) are major causes of morbidity and mortality in the neonatal period as well as in later life.
2. The rates of preterm births have risen worldwide in recent years, mainly due to medically induced preterm delivery, and the global incidence stands at 11.1%.
3. The etiology of preterm births and IUGR is multifactorial with numerous maternal, fetal and uteroplacental factors responsible for these conditions.
4. The major immediate complications encountered in preterm newborns are difficult delivery room resuscitation, respiratory distress syndrome, apnea, hypotension, hypothermia, hypoglycemia, necrotizing enterocolitis, intracranial hemorrhage, feeding difficulties, and vulnerability to infections and iatrogenic complications.
5. Late sequelae in preterm newborns include retinopathy of prematurity, bronchopulmonary dysplasia, periventricular leukomalacia, metabolic bone disease, anemia of prematurity, poor growth and neurodevelopmental impairments.
6. Approximately two thirds of IUGR newborns have asymmetrical phenotype manifesting as reduced weight and length with sparing of brain growth.
7. Immediate complications in IUGR newborns include perinatal asphyxia, hypothermia, hypoglycemia, meconium aspiration syndrome, persistent pulmonary hypertension, pulmonary hemorrhage, polycythemia, infections, and poor growth.
8. IUGR infants are also at higher risk of developing lifestyle disorders in later age such as type 2 diabetes mellitus, hypertension, and obesity due to fetal programming as a consequence of nutritional insult during critical periods of fetal development.

### MORE ON THIS TOPIC

- Boguszewski MC, Mericq V, Bergada I, et al. Latin American consensus: children born small for gestational age. *BMC Pediatr*. 2011;11:66.
- Chang HH, Larson J, Blencowe H, et al. Preventing preterm births: analysis of trends and potential reductions with current interventions in 39 countries with very high human development index. *Lancet*. 2013;381:223-34.
- Kramer MS, Papageorgiou A, Culhane J, et al. Challenges in defining and classifying the preterm birth syndrome. *Am J Obstet Gynecol*. 2012;206:108-12.
- Lawn JE, Kinney MV, Belizan JM, et al. Born too soon: accelerating actions for prevention and care of 15 million newborns born too soon. *Reprod Health*. 2013;10:56.
- Rosenberg A. The IUGR newborn. *Semin Perinatol*. 2008;32:219-24.



## Chapter 13.3

# Feeding of Low Birthweight

Kanya Mukhopadhyay

Providing optimal nutrition to very low birthweight (VLBW) babies is an essential part of preterm newborn care as extrauterine growth retardation (EUGR) remains a major concern for neonatologists. Preterm babies develop significant calorie and protein deficit during first few weeks of life without adequate nutrition which subsequently becomes difficult to compensate and remains a major cause of postnatal growth retardation.

Though the early aggressive nutrition policy has reduced the initial weight loss and birthweight regain earlier but it is still not optimal. Poor postnatal growth is a predictor of abnormal long-term neurodevelopment. Hence there is a need for a comprehensive nutrition policy for VLBW neonates to improve their postnatal growth.

The concerns and risks of feeding preterm babies include gut immaturity, delayed enteral feeding due to sickness, metabolic immaturity, feed intolerance and risk of necrotizing enterocolitis (NEC), and immature feeding reflexes which delay spontaneous breastfeeding.

## GOAL OF GROWTH

A preterm neonate loses weight initially up to 10–15% and regains birthweight by 2–3 weeks though the regain may be delayed in a sick neonate especially with inadequate nutrition. The initial weight loss is presumed to be predominantly extracellular fluid loss but the contribution by protein, glycogen and lipid losses are not known. The gold standard for growth of preterm neonates is considered to match intrauterine growth rate (~15 g/kg/day) however the body composition acquired in utero is different as compared to postnatal accretion of composition. In utero it is predominantly protein and glycogen while fat accretion occurs mainly during third trimester whereas ex utero major source of nutrients are fat and glucose and less protein, hence body composition differs in the fetus and the newborn infant.

## NUTRITIONAL REQUIREMENTS

### Energy Requirements

Preterm infants have higher nutritional requirements than term infants as they would have missed the rapid period of growth and nutrient accretion during third trimester. In addition postnatal sickness adds to catabolism and leads to higher need of calorie. Energy requirements in preterm babies are approx. 110–130 kcal/kg/day (**Table 1**) and 96–120 kcal/kg/day in a term neonate. Preterm babies lose protein (approx. 1 g/kg/day), lipids and glycogen (approx. 2–5 g/kg/day), and incur a significant energy deficit if adequate nutrition is not provided specially in first few days of life. It has been suggested that small for gestational age (SGA) babies probably have a higher energy need than appropriate for gestational age (AGA) neonates, but data is conflicting. The focus should be achieving an optimal lean mass rather than fat mass which happens with excess calorie and without adequate protein intake.

### Protein

Protein intake has a direct linear relationship with weight gain. In utero accretion of protein during second half of gestation is ~2 g/kg/day and postnatal obligatory protein losses are ~1 g/kg/day. Hence to match in utero protein accretion rate, ~3 g/kg/day

protein is required after birth. In the first few days of postnatal life providing 1 g/kg/day will prevent catabolic loss but there will be no positive nitrogen balance. In a growing preterm baby, extra protein is required to compensate for initial losses and weight gain during growth period. Protein to energy ratio (> 3–3.6 g/100 kcal) also must be considered to ensure adequate growth as significant amount of energy is required for synthesis of new tissue. As per ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology And Nutrition) recommendation, ELBW (extremely low birthweight) neonates require 4–4.5 g/kg/day and 3.5–4 g/kg/day is required for babies between 1 kg and 1.8 kg to sustain adequate growth (**Table 2**). Only high calorie intake may match in utero growth rate but leads to more fat growth than lean body mass.

### Lipid

Lipids are required not only as one of the major source of energy but also to provide essential components for cell membrane functions and bioactive eicosanoids. Considering in utero accretion of 3 g/kg/day and postnatal 10–40% loss from fat malabsorption and 15% unavoidable oxidation and for tissue triglyceride deposition, the fat requirement is about 3.8–4.8 g/kg/day. In babies with restricted fluid intake up to 6.6 g/kg/day may be allowed. Long chain polyunsaturated fatty acids (LCPUFA) are essential requirements for preterm infants for visual and neurodevelopment which is mainly acquired transplacentally during the third trimester. Breastmilk contains all the essential fatty acids but infant formulas contain only precursors linoleic acid and linolenic acid and infants need to synthesize docosahexaenoic acid (DHA) and arachidonic acid. A Cochrane review on LCPUFA supplementation in preterm babies did not show any long-term benefit on growth or visual or neurodevelopment.

### Carbohydrate

This is the main source of energy and ~10.5–12 g/kg/day is recommended for a growing preterm baby. A minimum amount of glucose is required to maintain brain and other glucose dependent organs as well as to prevent protein by preventing gluconeogenesis. Initially a glucose infusion rate of 4–8 mg/kg/min is required to maintain euglycemia which can be increased subsequently to a maximum of 11–12 mg/kg/min.

### Calcium and Phosphorus

Calcium absorption depends on calcium and vitamin D intake and retention depends on absorbed phosphorus. Hence with the aim of retention of 60–90 mg/kg/day and absorption rate of 50–60%, an intake of 120–140 mg/kg/day of calcium is required. Adequate calcium intake is required to ensure adequate bone mineralization in preterm infants. Maintaining calcium to phosphate ratio of 2:1 which is present in human milk, an intake of 65–90 mg/kg/day of phosphate is required. Phosphate absorption is quite efficient in those who are fed human milk or preterm formula but also depends on bioavailability of calcium and nitrogen retention.

**Table 1** Energy requirements for growing preterm infants

Parameter	kcal/kg/day
Resting metabolic rate	50
Energy for activity	5
Thermoregulation	10
Total energy expenditure	65
Energy excreted	15
Energy stored	30–50
Recommended total intake	110–130



**Table 2** Recommended nutritional intake for LBW (ESPGHAN, 2010)

Nutrient	Minimum-maximum (per kg/day)
Fluid, mL	135–200
Energy, kcal	110–135
Protein, g	
Birthweight < 1 kg	4–4.5
Birthweight 1–1.8 kg	3.5–4
Lipids, g	4.8–6.6
Carbohydrate, g	11.6–13.2
Sodium, mg	69–115
Calcium, mg	120–140
Phosphate, mg	60–90
Iron, mg	2–3
Zn, mg	1.1–2
Vitamin A, mcg RE, (1 mcg ~3.33 IU)	400–1,000
Vitamin D, IU/day	800–1,000
Vitamin E, mg ( $\alpha$ -tocopherol equivalent)	2.2–11

Abbreviation: ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology and Nutrition.

### Vitamin D

Vitamin D is important for bone mineralization and neuromuscular function and also improves calcium absorption. Preterm babies are born with low vitamin D stores and quite often born to vitamin D deficient mothers. An intake of 800–1,000 IU/day is recommended in preterm infants. Target level of 25 hydroxyvitamin D (25OHD) is 75–80 nmol/L. Metabolic bone disease or osteopenia of prematurity can arise if there is inadequate intake of calcium, phosphate and vitamin D in VLBW babies. This biochemically manifests as low serum phosphate (< 3.5–4 mg/dL) and high alkaline phosphatase (> 800 IU) and calcium may be low or normal. Rapid mineralization in a growing preterm also can cause increase in alkaline phosphatase but this is not associated with low phosphate. Early enteral feeding and adequate supplementation can prevent this condition.

### Vitamin A

Vitamin A is required for various cellular growth and differentiation. It is required for vision, immune system, normal lung growth and respiratory tract epithelial system. Routine supplementation of 400–1,000  $\mu$ g RE is recommended. Preterm infants have low vitamin A and this has been associated with development of chronic lung disease (CLD). A systematic review showed that vitamin A supplementation reduced the risk of developing CLD.

### Iron

Poor neurodevelopmental outcome has been reported in iron deficiency anemia, however excess dose may be associated with increased risk of infection, poor growth, and disturbed other mineral metabolism. Iron is a pro-oxidant and excess non-protein bound iron produces free radicals which is harmful and can increase the risk of retinopathy of prematurity. A daily intake of 2–3 mg/kg/day is recommended (not more than 5 mg/kg/day) and to be started at 2–6 weeks of age (2–4 weeks in ELBW) and to be continued at least till 1 year of age depending on diet later on. In babies who received multiple blood transfusions, supplementation can be delayed.

## WHEN TO START FEEDING?

All stable preterm babies should be started on feeds as soon as possible after birth preferably with mother's milk. There is no evidence that delaying feeds decreases the risk of NEC whereas risk of delayed feedings are inadequate enzymatic and gut hormone response, delay in establishing full feeds and risk of hepatic dysfunction and sepsis.

### Minimum Enteral Nutrition

Minimum enteral nutrition (MEN) or trophic feeds is a non-nutritive use of a small amount of milk to prime the gut before full feed is provided to a preterm baby. There are several advantages of MEN (**Box 1**). MEN can be initiated in a stable preterm baby irrespective of gestation at the volume of 20–25 mL/kg/day. Breastmilk should be used preferably. MEN is not attempted in severe hemodynamic instability, suspect NEC, paralytic ileus, and any other intestinal pathology. Presence of patent ductus arteriosus (PDA) and presence of umbilical artery catheter are not contraindications for trophic feeds.

### Volume to Start and Rate of Advancement

The ideal volume to start with and the rate of advancement are debatable. The rate of increase depends on weight, gestation, postnatal age, clinical status and tolerance of oral feeds. In most of the babies a maximum volume of 180–200 mL/kg/day can be achieved. There is no evidence that slow advancement prevents NEC but decision should be taken cautiously in ELBW neonates. **Table 3** provides a suggested approach for initiation and hike in stable preterm neonates while transiting from intravascular fluid to enteral feeds.

## METHOD OF FEEDING

Standard method of feeding in less than 32 weeks GA is intermittent orogastric route. There is no evidence that continuous feeding is better than intermittent feeding with regard to time to achieve full feeds, somatic growth and incidence of NEC and babies on continuous feeding needed longer time to achieve full feeds. Babies on nasojejunal feeds are on continuous feeds as jejunum is not capable of handling large volume at a time.

Babies who are less than 32 weeks are started on initially orogastric feeding and then transition to spoon and breastfeeding done. Babies more than 32 weeks can be directly started on spoon feeding. Babies more than 34 weeks can be tried on direct breastfeeding though some babies may need supplemental spoon feeding. Bottle-feeding is strongly discouraged.

### Non-nutritive Sucking (NNS)

All preterm babies who are on orogastric feeding and not on continuous positive airway pressure or ventilator, should be allowed to do non-nutritive sucking on mother's empty breast.

#### BOX 1 Advantages of minimum enteral nutrition (MEN)

- Improves release of gut hormones
- Improves gut motility
- Stimulates cell proliferation, decreases permeability
- Decreases complications associated with gut starvation like villi atrophy, mucosal thinning and bacterial translocation
- Better feed intolerance and earlier full feeds and less days on TPN
- Improved weight gain and reduction in hospital days
- Better calcium and phosphate retention
- Early feeds reduces rate of sepsis and do not increase in NEC.

Abbreviations: TPN, total parenteral nutrition; NEC, necrotizing enterocolitis.

**Table 3** Feeding volume and frequency of feeding for low birthweight babies

Birthweight	Starting volume (mL/kg/day)	Volume increment/day (mL/kg/day)	Max volume (mL/kg/day)	Frequency of feeds
< 1,200 g/GA < 29 weeks	10–20	20	180–200	2 hourly
*1,200–1,500 g/GA 30–32 weeks	20–30	30	180–200	2 hourly
**> 1,500–2,000 g/GA > 32–34 weeks	30	30–40	150–180	2–3 hourly
> 2 kg/> 34 weeks	Full breastfeeds can be tried		Ad lib	2–3 hourly

\*If the baby is well then feed can be started at 50% of total requirement and increased rapidly to full feeds by end of day 1.

\*\*If the baby is well, full feed can be given from the beginning (60 mL/kg/day).

Oromotor stimulation enhances oral feeding skills of preterm infants specially the one with prolonged illness requiring orogastric feeding. There is evidence of earlier attainment of oral feeding, reduction of hospital stay and better breastfeeding rate at discharge in those babies who practiced NNS.

### Feed Intolerance

Feed intolerance is a very common symptom in preterm neonates mostly due to gut pathology, sepsis and electrolyte disturbances. Clinical symptoms of feed intolerance include increased aspirates; vomiting; altered aspirates (bile or blood); abdominal distension (>2 cm from previous or baseline in 6h gap); abdominal wall discoloration (may suggest underlying necrosis); bleeding per rectum; and increase in stool frequency.

## CHOICE OF MILK

### Expressed Breastmilk

Expressed breastmilk remains the choice of feeding in all babies. The benefits of breastmilk are well documented and these are:

- Immunological benefit due to presence of several immunoglobulins, lactoferrin, prebiotics and probiotics and thereby reducing sepsis and NEC. The mortality in ELBW babies with NEC is 35–50% and in VLBW babies 10–30%. Almost 20% VLBW babies die due to sepsis and even the survivors postsepsis are likely to have significant long-term complications like bronchopulmonary dysplasia (BPD) and developmental delay.
- Better bioavailability of nutrients (calcium, iron, fatty acids, etc.) as compared to formula milk.
- Less feed intolerance and early attainment of full feeds (presence of gut hormones, enzymes and growth factors which help in gut growth and thereby establishing full feeds earlier than formula fed babies.
- Possibly better neurodevelopment outcome.
- Improved long-term adult outcome in the form of coronary artery disease, hypertension, type 2 diabetes, etc.

### Donor Expressed Breastmilk

Donor breastmilk through human milk bank is the next best option when there is inadequate lactation of baby's own mother. However the processing causes some loss of immune function and nutritional composition. As pasteurization causes loss of bile salt stimulated lipase, fat absorption is less with donor milk and causes slow growth but still it is associated with long-term advantage. Donor human milk is preferred over preterm formula as risk of gut associated problem is less with human milk. Donor milk should be used only during transition to full enteral feed and all attempts should be made to get baby's own mother's milk. Breastmilk alone or with some formula feed as compared to formula alone is protective against NEC. Donor human milk also probably has similar protective role when compared to formula though poor weight gain is a concern with donor milk.

### Fortified Human Milk

Multicomponent human milk fortifier provides extra calories, proteins, minerals and vitamins. In cases of inadequate growth on full volume milk (180–200 mL/kg/day), especially in babies less than 1,250 g, fortified human milk can be considered to improve weight gain. According to Cochrane systematic review fortification improves short-term weight, length and head circumference (HC) in VLBW babies though no long-term benefit has been documented yet. There is no increased NEC with fortification. Fortifier can be added to breastmilk once the baby reaches 150 mL/kg/day. There no increased risk of NEC with various fortifiers.

### Preterm Formula

In absence of donor breastmilk or inadequate breastmilk, preterm formula is the next choice of feeding in growing preterm infants. They provide nearly adequate calorie, protein, vitamins and minerals if fed in full volume. They contain protein which is predominantly whey based rather than casein based which is more digestible, contains a carbohydrate mixture of 40–50% lactose and 50–60% glucose polymers to compensate for relative lactase deficiency in preterm babies. The fat content is a mixture of 50% medium chain triglycerides (MCT) to compensate for limited pancreatic lipase and bile salt pool which are required for fat absorption and rest 50% is long chain triglycerides which supplies essential fatty acids. In short-term it improves weight gain though no long-term benefit is proven. However risk of NEC is 6–10 times more than those fed exclusive breastmilk and 3.5 times more who are fed combined breastmilk and formula.

**Table 4** provides a comparison of various nutrients in human milk, fortified human milk, preterm formula and when fed at the rate of 150 mL/kg/day.

### Animal Milk

Though animal milk is used very frequently in our country after discharge, there is no study on their impact on growth and neurodevelopment. All components are not equally suitable in growing preterm infants. **Table 5** provides a comparison of various components in animal milk.

## WHEN TO START SUPPLEMENTS?

Babies who are not on fortifier or preterm milk should receive multivitamins, calcium, phosphate and vitamin D supplements as per recommended doses. Supplements can be started after the baby tolerates a volume of 150 mL/kg/day. Fortification can also be initiated at this stage. Iron can be started at the age of 2–4 weeks. Term formula and other animal milk are not suitable for growing preterm babies due to either lack of or excess of certain components as given below. Term human milk fed at the rate of 200 mL/kg/day may meet calorie requirements but still falls short of protein requirements. There is no role of prelacteal feeding in the form of water or dextrose as it has a negative impact on breastfeeding.

**Table 4** Macronutrient and mineral composition of preterm milk, fortified milk and preterm formula per 100 mL and @ 150 mL/kg/day

Nutrients	<sup>#</sup> Recommended intake (per kg/day)	<sup>§</sup> Preterm milk (per 100 mL)	Preterm milk fed @ 150 mL/kg/day	Fortified preterm milk* (per 100 mL)	Fortified preterm milk fed @ 150 mL/kg/day	Preterm formula** (approx) (per 100 mL)	Preterm formula fed @ 150 mL/kg/day
Energy (kcal)	110–135	69	103	82	123	80	120
Protein (g)		1.6*	2.4	2	3	2	3
< 1 kg	4–4.5						
1–1.8 kg	3.5–4						
Fat (g)	4.8–6.6 of which MCT < 40%	3.5	5.25	3.7	5.5	4	6
Carbohydrate (g)	11.6–13.2	7.2	10.8	8.9	13.3	9.1	13.6
Calcium (mg)	120–140	28	42	128	192	128	192
Phosphorus (mg)	60–90	14	21	64	96	64	96
Sodium (meq)	2.8–4.8	0.8	1.2	1.6	2.4	1.3	1.95
Iron (mg)	2–3	0.09	0.135	0.9	1.35	0.8	1.2
Vitamin A (IU)	400–1,000 mcg	48	72	1510	2262	241	361
(1 mcg~3.33 IU)	RE = 1332–3330 IU						
Vitamin D (IU)	800–1,000/day	8	12	88	120	72	108
Zinc (mg)	1.1–2	0.6	0.9	0.8	1.2	0.5	0.75
Osmolality		290		392		390	

\*As per ESPGHAN (2010)

<sup>§</sup>Preterm milk composition changes with time. It has higher protein, sodium and calorie during first 2–3 weeks and later it changes like term human milk.

\*Fortified with Lactodex—HMF (till now this is the only available fortifier in Indian market), 2 g added in 50 mL of breastmilk. Approximate composition per 2 g: protein—0.2 g, fat—0.1 g, carbohydrate 1.46 g, calcium—50 mg, phosphorus—25 mg, sodium 1.75 mg, zinc—0.1 mg, vitamin A—730 IU, vitamin D—40 IU, energy—7.54 kcal

\*\*Composition of preterm formula is variables.

Abbreviation: MCT, medium chain triglycerides.

**Table 5** Composition of term human milk, term formula milk, cow's milk and buffalo's milk

Per 100 mL	Term human milk	Term formula milk	Cow's milk	Buffalo's milk
Cal	67	67	67	117
Protein (g)	1.1	1.7	3.2	4.3
Fat (g)	4.5	3.3	4.1	6.5
Carbohydrate (g)	7.1	7.5	4.4	5.1
Calcium (mg)	33	62	120	216
Phosphorus (mg)	15	47	90	—
Iron (mg)	0.03	0.8	0.2	0.2
Vitamin A (IU)	250	200	—	—
Vitamin D (IU)	2.2	40	—	—
Sodium (mEq)	0.8	1.3	—	—

## HOW LONG TO CONTINUE SUPPLEMENTS?

Multivitamins are continued at least till 6 months of life and calcium supplements are given till at least 40 weeks postconceptional age in larger preterm neonates. In small preterm babies who could not be started on adequate calcium or phosphate early, supplements are continued for a longer time along with monitoring of metabolic parameters. Vitamin D is initially given at a dose of 800–1,000 IU which can be reduced subsequently. Iron is continued at least till the age of 1 year and to be stopped depending on adequacy of complementary feeding.

## How Long to Continue Fortification or Preterm Formula?

Fortification should be continued till the baby reaches at least 2.5–3 kg or able to take breastfeeds directly. Preterm formula should

also be continued for the similar duration. Once the babies are off fortification or changed over to term formula or other types of milk, supplements to be provided.

## FEEDING IN SPECIAL SITUATIONS

### Absent/Reversed End Diastolic Flow (AEDF/REDF)

The fetuses who had AEDF or REDF are frequently growth retarded and have less blood flow to gut in order to maintain flow in more vital organs like brain. Hence these babies are more likely to develop feed intolerance and NEC. There is significant controversy regarding initiation and advancement of feeding in these babies. The recent evidence shows that early initiation of feeding by day 2 as compared to day 6 resulted in no higher incidence of NEC. In this study the babies who were less than 29 weeks gestation took significantly longer time to reach full feeds and incidence of NEC was 3 times than babies more than 29 weeks gestation. Use of breastmilk was associated with decreased risk of NEC in these babies. In these cases feeding can be initiated within first 24 hours and may be within 4–6 hours of birth if abdomen is clinically ready for feeds namely:

- No distension or redness
- No altered or increased aspirate
- Passed meconium or bowel sound appeared
- No other contraindication

Feeding should preferably with expressed breastmilk or donor human milk.

### Bronchopulmonary Dysplasia

Babies with bronchopulmonary dysplasia (BPD) require higher energy, 130–150 kcal/kg/day. Though there is no strong evidence of fluid restriction in BPD, as a matter of practice they receive restricted fluid 150–160 mL/kg/day but they should be provided

calorie rich food (fortified or preterm formula) so that energy expenditure along with growth can be taken care. Restriction of fluid may decrease oxygen consumption and improve lung function.

### Patent Ductus Arteriosus

Babies with significant patent ductus arteriosus (PDA) who failed medical therapy and show signs of congestive cardiac failure, need fluid restriction till ligation of the duct can be conducted; though there is no strong evidence whether fluid restriction helps or not.

### GROWTH MONITORING

Growth must be monitored in all preterm babies till discharge and subsequently during follow-up. In the initial phase baby is weighed daily but subsequently during growing period it can be done on alternate days. Length and HC are measured weekly. There are various growth charts intrauterine as well as postnatal growth charts which can be used during hospital stay and till 40 weeks corrected age and after 40 weeks WHO growth charts can be used.

Desired gain till 40 weeks corrected age—for weight 15 g/kg/day, length 0.7–1 cm/week, HC 0.7–1 cm/week. After 40 weeks till about 3 months, weight gain of 20–30 g/day, length and HC 0.5 cm/week are desirable. Inadequate growth is indicated by reduction in growth velocity or failure to gain adequate weight or loss of weight. In a growing baby, weekly serum sodium, calcium, phosphate and alkaline phosphatase should be done till discharge and then monthly till 40 weeks corrected age.

*Failure to thrive* If a growing baby fails to gain weight, following causes should be looked at: adequacy of calorie and protein intake; anemia; cold stress; chronic illness like BPD, postsurgical conditions; fungal infection; urinary tract infection; fluid restricted conditions with inadequate calorie intake in BPD and PDA; and late hyponatremia of prematurity.

*Early aggressive nutrition and outcome* Early aggressive nutrition is aimed at providing high energy and protein supplements as soon as possible after birth in order to prevent significant weight loss. In a preterm baby, especially in ELBW babies, it is not possible to provide required nutrition orally and quickly. Hence to bridge the gap, total parenteral nutrition (TPN) to be provided in the initial days till full enteral nutrition can be established. Early parenteral high protein intake has not been associated with any significant side effects though adequate calories (~3.3 g/100 kcal) also need to be provided along with for growth. Enteral nutrition must be started as soon as the baby is hemodynamically stable at 20 mL/kg/day and in bigger preterms at 30 mL/kg/day with human milk. Feeds can be increased depending on tolerance and TPN needs to be continued till at least 2/3rd of feed volume is achieved.

Early aggressive nutrition policy decreases extra-uterine growth retardation. A comparison of cohort before and after implementation of aggressive feeding protocol showed babies regained birthweight earlier, reached full feeds earlier, discharged home earlier and discharge Z score improved significantly in new feeding protocol. Another study showed that every 10 kcal/kg intake improves mental developmental index by 4.2 points and extra protein intake of 1 g/kg improves MDI 8.4 points at 18 months corrected age.

### Prebiotics and Probiotics

Probiotics are good bacteria and used to colonize premature gut and prebiotics are their substrates. There have been several randomized controlled trials and meta-analysis on use of probiotics and reduction in sepsis and mortality in VLBW infants. However, the settings in which these studies have been conducted

are different from our country. There is also no consensus on best combination or dosages. It is also unknown about their long term immunological effects and rarely infection by probiotic agents has been reported. Hence before recommending routine use of probiotics in our country, some country specific trials are required and long term safety needs to be established. Breastmilk contains several probiotics and more than 130 prebiotics and a combination of both exert a favorable effect in the preterm gut. Hence breastmilk is a better option than commercially available prebiotics or probiotics.

### POSTDISCHARGE NUTRITION

Most of the babies are significantly growth retarded at the time of discharge and continue to have poor catch-up growth. Hence the enriched feed should be continued for some more period postdischarge. In absence of a proper postdischarge formula, fortification and/or preterm formula can be continued till at least the baby is 2.5–3 kg. If the baby is completely breastfed, then maximization of breastmilk intake should be ensured with continued supportive care of mother and her lactation. Supplements should be continued. Continuation of kangaroo mother care may help in maintaining longer lactation period.

#### IN A NUTSHELL

1. Preterm babies need early and adequate nutrition.
2. Adequate protein along with adequate calorie required for optimum growth.
3. Early aggressive nutrition improves discharge weight and reduces postnatal weight loss.
4. Poor postnatal growth is associated with abnormal neurodevelopment which can be improved with early aggressive nutrition.
5. Breastmilk remains the choice of feeding along with mineral and vitamin supplements though some ELBW (extremely low birthweight) babies and those in whom fluids are being restricted may need fortification.

### MORE ON THIS TOPIC

- Agostoni C, Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants: commentary from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr.* 2010;50:85-91.
- Bertino E, Di Nicola P, Giuliani F, et al. Benefits of human milk in preterm infant feeding. *J Pediatr Neonatal Individual Med.* 2012;1:19-24.
- Bombell S, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database Syst Rev.* 2008;1:CD001970.
- Morgan J, Bombell S, McGuire W. Early trophic feeding versus enteral fasting for very preterm or for very low birth weight infants. *Cochrane Database Syst Rev.* 2013;3:CD000504.
- Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database Syst Rev.* 2013;3:CD001241.
- Pinelli J, Symington AJ. Non-nutritive sucking for promoting physiologic stability and nutrition in preterm infants. *Cochrane Database Syst Rev.* 2005;(4):CD001071.
- Quigley M, McGuire W. Formula versus donor breastmilk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev.* 2014;4:CD002971.
- Senterre T, Rigo J. Optimizing early nutritional support based on recent recommendation in VLBW infants and postnatal growth restriction. *J Pediatr Gastroenterol Nutr.* 2011;53:536-42.



## Chapter 13.4

### Long-term Outcome of Low Birthweight

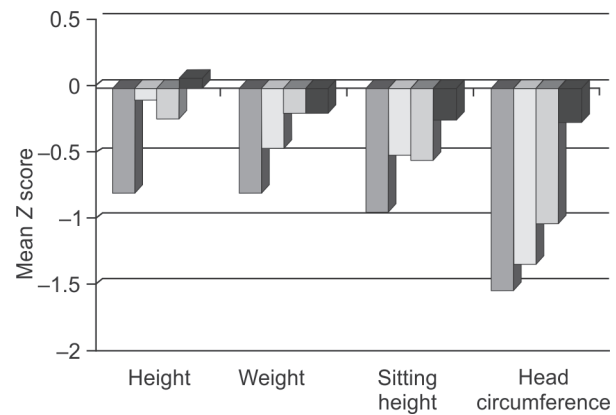
Suman Rao PN, Nikhil Kulkarni

With advanced medical care, low birthweight (LBW) survival has been steadily improving in the past years. The consequence of LBW extends throughout childhood, adolescence and into adulthood. They are not only at risk of higher postneonatal mortality but also are at risk for poor growth, recurrent hospitalizations, neurosensory impairment, cognitive deficits and behavioral problems (**Box 1**). Hence the needs for special multidisciplinary follow-up services to be set-up as an integral extension of a good neonatal intensive care unit.

#### GROWTH

Low birthweight newborns have poor growth in the neonatal period. There is a decline in the Z score from birth to discharge for weight, length and head circumference. This is followed by *catch-up growth*—an accelerated period of growth in LBW. Catch-up growth is usually first noted in the infant's head circumference, followed by the infant's weight and length. This usually occurs during the first 2–3 years of life. The catch-up growth however may not be complete. Lower gestation, LBW, intrauterine growth restriction (IUGR) and severity of neonatal illness are risk factors for poorer catch-up growth. The Z scores remain low in infancy and early childhood. In a follow-up study of very low birthweight (VLBW) infants from AIIMS, Delhi, it was noted that at 18 months, 30.9% were undernourished, 50.9% were stunted, 14.5% were wasted and 25.4% had microcephaly. The extremely low birthweights (ELBW) were significantly more affected.

The catch-up growth continues during childhood and adolescence; however persistence of height disadvantage into adulthood is common. The COHORTS study includes birth



**Figure 1** Pune LBW cohort study: Growth at 18 years by weight for gestational age with Agarwal, et al standards

Source: Chaudhari S, Otiv M, Khairnar B, Pandit A, et al. Pune low birth weight study, growth from birth to adulthood. Indian Pediatr. 2012;49:727-32.

cohorts from five low income-middle income countries including India. Adults born preterm were 1.11 cm shorter and term small for gestational age (SGA) were 2.35 cm shorter. Growth failure in the first 2 years is most consistently associated with adult stature emphasizing the need for interventions in intrauterine life or infancy. The Pune LBW study is a birth cohort study of LBW less than 2,000 g born between 1987 and 1989. The preterm SGA infants remained shorter and had smaller head circumference as adults (**Fig. 1**). Other studies from South India (Nair et al., Trivandrum and Christian Medical College Vellore birth cohort study) have also found lower growth parameters on follow-up to adolescence and adulthood. Postnatal growth failure is associated with poor cognitive outcomes and academic achievement. This emphasizes the need for growth monitoring.

The data on effect of LBW on pubertal development, sexuality and fertility is still scarce. Children born SGA have an earlier onset of puberty, smaller amplitude of pubertal spurt and a reduced final height. Girls have an advanced menarche. In the Pune LBW study, sexual maturity and menarche was similar in the LBW groups. In a few follow-up studies, ELBW girls have grown up and have given birth. A transgenerational effect of LBW is seen with the offspring of ELBW infants being smaller.

#### NEUROLOGIC OUTCOMES

Preterm and LBW infants are at risk of variety of developmental problems, psychological and intellectual functioning (**Box 2**). Most Indian studies have used the DASII (Developmental Assessment Scale for Indian Infants), and the Indian adaptation of Bayley Scale of Infant Development (BSID) II for assessment. Mukhopadhyay et al. from Chandigarh followed up a cohort of VLBW infants that included a significant number of ELBW infants. The mean mental and motor quotients at 18 months, were 80.4 (±10.7)

#### BOX 1 Long-term outcome of low birthweight (LBW)

##### Growth

##### Neurologic outcomes

###### Neuromotor

- Cerebral palsy
- Transient neurologic abnormalities
- Developmental coordination disorders

###### Cognitive

- Intelligence quotient
- Speech and language
- School and academic achievement

###### Behavior

- ADHD
- Autism spectrum disorders
- Depression
- Self-esteem

##### General health

- Hospitalizations
- Respiratory
- Bone

##### Developmental origin of diseases

- Obesity
- Diabetes mellitus
- Hypertension
- Dyslipidemia.

Abbreviation: ADHD, attention deficit hyperactive disorder.

#### BOX 2 Cognitive abilities affected in preterm LBW IUGR

- General cognitive ability
- Processing speed
- Attention
- Visual and perceptual skills
- Memory and learning
- Language
- Executive function
- Educational outcomes.

Abbreviations: LBW, low birthweight; IUGR, intrauterine growth restriction.

and 77.2 ( $\pm 13.3$ ), respectively. A score of less than 70 was found in 17% (mental DQ) and 25.7% (motor DQ) VLBW babies.

**Correction for prematurity** Neuromotor and developmental assessments are done and compared after correcting for prematurity. This is known as corrected age (adjusted/post-conceptional age).

Corrected age = Chronological age – (40–gestational age) in weeks

The correction is generally applied till 2 years. But it is suggested that the correction be extended till 3 years for less than 32 weeks, till 5 years for less than 28 weeks and till 7 years for less than 24 weeks.

## NEUROMOTOR OUTCOMES

Preterm children have a different trajectory of motor development. Cerebral palsy (CP) is inversely related to birthweight and gestational age. Neonatal problems such as shock, infection, severe illnesses, and lack of antenatal steroids and use of postnatal steroids are associated with motor disorders. The VLBW infants do not completely outgrow their motor problems which persist into school age and adulthood. Even as adults they have poorer fine and gross motor skills. They are slower than peers. Factors affecting neurodevelopment in LBW are summarized in **Table 1**.

### Cerebral Palsy

The commonest type of CP seen in preterm infants is spastic diplegia. Cystic periventricular leukomalacia (PVL) highly predictive of CP in preterms has decreased but diffuse non-cystic central white matter abnormalities referred to as diffuse PVL occurs in 30–50% of very preterm infants. The preterm SGA is at highest risk for CP. Half of all CP in preterm are mild CP. The CP rate

in Mukhopadhyay's study was 3% despite including a large number of ELBW. This lower rate could be due to the higher gestational age of the ELBW babies and high incidence of IUGR. Early sequential neuroassessment in infancy (by methods such as Amiel-Tison, Voita, Infant Neurological International Battery) is mandatory if CP is to be identified and managed. Spasticity at 3–4 months and persistence of primitive reflexes are early signs of CP.

### Transient Neurologic Abnormalities (TNA)

These are more common in preterm babies with incidence from 40% to 80%. TNA refers to the tonal abnormalities seen in LBW infants during infancy, that peaks at about 7 months but the tone normalizes by 1–2 years. They may be associated with learning disabilities in school age. They are probably a result of milder neurological insults like mild PVL. The follow-up should therefore extend at least to school age if not into adulthood.

### Developmental Coordination Disorder

Developmental coordination disorder is defined as impairment in motor performance sufficient to produce functional impairment that cannot be otherwise explained by the child's age, cognitive ability, or neurologic or psychiatric diagnosis. Developmental coordination disorder is found in 31–34% of VLBW and 50% of ELBW infants. In preterm LBW infants without CP, deficits are reported in motor coordination, balance, visuospatial skills, and hand-eye coordination. This results in developmental dyspraxia, clumsiness, hand writing problems.

## COGNITIVE OUTCOMES

Low birthweight is a risk factor for lower intelligence scores. Assessment can be done using tests such as Wechsler Intelligence Scale for Children-IV, Raven's progressive matrices or Stanford-Binet Intelligence Scales. The preterms are 2.5–3.5 times more likely to have memory impairment. The core deficits of working memory, perceptual-organizational skills, processing speed lead to poor performance on executive function and intelligence tests. Though significantly lower most LBW have intelligence quotient (IQ) within normal limits. Studies have shown that the IQ scores reduce 1.5–2.5 points for each week decrease in gestational age. It is the preterm ELBW IUGR neonates who have the poorest cognitive outcomes. It is also important to highlight that even moderate and late preterms have significantly lower scores on BSID.

The debate on the relative effects of *nature versus nurture* continues. Apart from the biologic variables of birthweight and gestational age, maternal education, home environment, two parent family, type of school and socioeconomic status strongly influence cognitive outcomes. High-risk infants in good environment have the potential for recovery of cognitive and academic performance with improved age. This forms the basis for early interventional programs.

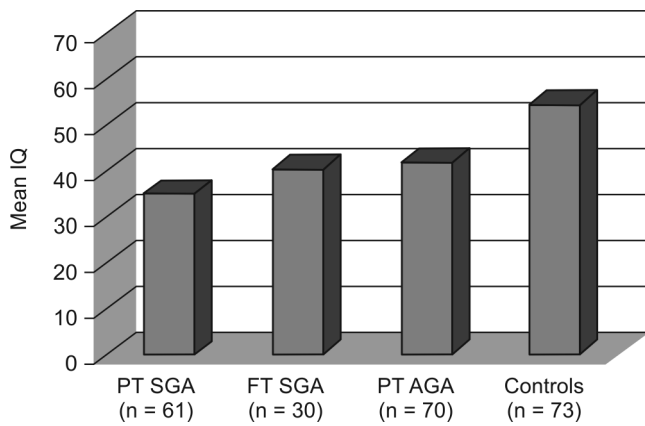
In the Pune LBW study, the intelligence and academic performance of LBW cohort though within normal limits was significantly lower than controls at 12 years (**Fig. 2**). They also had poor visuomotor perception, motor incompetence, reading and mathematics learning disability. The preterm SGA and VLBW children had the poorest cognitive abilities. This continued into adulthood. Nair et al. found low performance scores on intelligence tests in 51.4% LBW versus 41.7 % normal weight adolescents. 14% of LBW and 19% of ELBW had below average IQ.

**Speech and language** Problems of speech and language are common in LBW. They score poorly on language tests even in the absence of a major disability and independent of socioeconomic status. Screening with only IQ tests may therefore not be enough. This impairment continues to adolescence and adulthood

**Table 1** Factors affecting neurodevelopment in low birthweight (LBW)

	Adverse factors	Protective factors
<i>Antenatal</i>	Lower gestational age Lower birthweight Multiple gestation MCMA TTTS Death of co-twin Chorioamnionitis Intrauterine infection	Higher gestational age Higher birthweight Singleton Female sex Antenatal corticosteroids Antenatal magnesium sulphate
<i>Natal</i>	Asphyxia-ischemia	Prompt and adequate resuscitation
<i>Postnatal</i>	Neurobiologic risk score Hypothermia Bronchopulmonary dysplasia Brain injury—PVL/IVH Severe sepsis Severe ROP Shock Necrotizing enterocolitis Poor postnatal growth Postnatal steroids	Exclusive breastfeeding Kangaroo mother care Early intervention therapy Massage therapy Strict SaO <sub>2</sub> target 90–94% Caffeine Restrictive transfusions Nutrition Zinc supplementation Early iron supplementation Early salt supplementation DHA
<i>Social</i>	Poor care givers IQ Single parent Lower socioeconomic status	Maternal education Two parent family High socioeconomic status Parent based early intervention

**Abbreviations:** MCMA, monochorionic monoamniotic; TTTS, twin-to-twin transfusion syndrome; PVL, periventricular leukomalacia; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; DHA, docosahexaenoic acid.



**Figure 2** Pune LBW study. Mean IQ (by Raven's progressive matrices) according to weight for gestation. Normal is between 25th and 75th percentiles.

Abbreviations: SGA, small for gestational age; AGA, appropriate for gestational age; FT, full term; PT, preterm.

Source: Chaudhari S, Otiv M, Khairnar B, et al. Pune low birth weight study—birth to adulthood—cognitive development. *Indian Pediatr.* 2013;50:853-7.

particularly for complex language functions. Early language interventions improve outcome.

**Educational outcomes and academic achievement** LBW are at risk of poor school performance, repeating a grade, not completing school or college education. The LBW may experience major difficulties in executive functioning, mathematics and spelling (7.2–11.4 point decrement). Moderate preterm and late preterm infants too have a 50% and 34% adjusted risk of needing special education services respectively.

**Head circumference** A predictor of neurodevelopment: It is long known that head circumference is a surrogate marker for brain growth. The earlier in gestation the head circumference begins to slow, poorer is the neurodevelopmental outcome. Among SGA infants, symmetrical SGA have poorer head growth compared to asymmetrical SGA infants. Even asymmetrical growth restricted newborns may have abnormal brain development despite the external physical appearance of *brain sparing*. Poor head growth postnatally rather than growth restriction at birth is most associated with poor outcome. Those with catch-up growth fare better neurologically.

## BEHAVIOR

Low birthweight infants are at increased risk for behavioral problems such as attention deficit hyperactive disorder (ADHD) and autism spectrum disorders (ASD). The LBW have inattention rather than hyperactivity as the main feature of ADHD and poor social communication rather than stereotype or repetitive behavior as the predominant feature of ASD. Internalizing problems (withdrawn behavior, symptoms of depression) may also be present. This cluster of ADHD, peer relationship problems and emotional disorders has been termed the *preterm behavior phenotype*. Screening for behavioral problems should start at 2 years. This neurocognitive, neurobehavioral sequelae affects even late preterm infants. A new problem that has emerged is *victimization* of premature infants in school. This is in the form of verbal, psychological and physical abuse. As adults, LBW have higher risk of depression, bipolar affective disorders and non-affective psychosis. On the positive front, LBW have been found to have lower risk taking behavior such as smoking, alcoholism, criminality, high-risk sex behavior and drug abuse. Mukhopadhyay reported a high incidence of behavioral disorders in her cohort of

VLBW infants. Most (84.4%) VLBW and all ELBW had a high score for behavioral problems—stressing the need for monitoring for behavioral problems.

**Self-esteem** It is reassuring to know that generally LBW are satisfied with life as adults and have comparable self-esteem as normal weight controls despite their poor growth and health status. Though the preschool child may have lower quality of life scores; this diminishes over time. There is a definite discrepancy between self-reporting and parents or teachers proxy reporting. This could be due to denial or recalibration of expectations. However some studies such as by Nair et al. found lower self-esteem scores among LBW adolescents.

## NEUROSENSORY OUTCOMES

**Ophthalmologic outcome** Impaired vision in VLBW could be due to sequelae of retinopathy of prematurity (ROP). Blindness due to ROP has reduced from 8% to 10% to less than 2% with introduction of cryo-laser therapies. Visual acuity, contrast sensitivity, strabismus, stereopsis, convergence and visual perception are affected in preterm. Preterm brain injury involving the reticulo-geniculate visual pathways can lead to cerebral visual impairment in the absence of ROP. ELBW have 4 times the risk of abnormal acuity, double the risk of errors of refraction, accommodation and 3–9 fold the risk of retinal detachment in adult life. In one study, 64% of ELBW adults required prescription glasses versus 37% of term controls.

**Audiologic outcomes** LBW have higher incidence of hearing impairment (up to 7%) versus 2% in controls. Auditory processing may also be affected. This leads not only to speech impairment but also poorer intellectual, academic and behavior progress. Hearing loss due to otitis media is also common.

## NEUROIMAGING

One review by Voss and on prognosticating cognitive outcomes describe that early testing is generally unreliable (only 49% correct) for later outcome; with the exception of the most severely and obviously affected children. They suggest that follow-up must be at least up to the age of 6 years to make a reliable cognitive diagnosis.

The prognosis may be better determined by newer modalities of neuroimaging. MRI diffusion tensor imaging, voxel-based morphometry and functional MRI demonstrate microstructural evidence of injury and changes in neural connections and cortical maturation that could predict long-term outcomes. Two major findings are decreased white matter volumes and lower fractional anisotropy in specific regions such as posterior limb of internal capsule. Volumetric MRI of the IUGR infant shows reduced cortical gray matter volume, particularly in the hippocampus. PVL is another common feature. MRI is recommended for preterm at term gestation for prognostication.

## GENERAL HEALTH

Low birthweight are at higher rates of health concerns. There is a gradient effect of poorer health outcomes with decreasing gestational age from term to extreme preterm including general health, hospitalizations and chronic illnesses. The most frequently occurring medical conditions are respiratory illness (asthma and recurrent bronchitis), gastrointestinal illness (gastroenteritis and gastroesophageal reflux), viral fever and epilepsy.

Upper and lower respiratory infections are the most frequent cause for rehospitalizations during infancy and early childhood. Asthma and wheezing are more prevalent later in life. The risk factors for repeated hospitalizations due to respiratory illnesses are decreasing gestational age, bronchopulmonary dysplasia, parental smoking, and living with school age siblings. These hospitalizations reduce from early childhood to adolescence.



Respiratory health in adulthood is inversely related to birthweight. Size at 1 year, is a predictor of mortality from respiratory illness in adulthood. Prematurity is associated with airway obstruction, reduced forced expiratory volume in 1 second (FEV1), low forced expiratory flow (FEF) 25–75% and air trapping. Pulmonary functions correlate with high resolution CT scan.

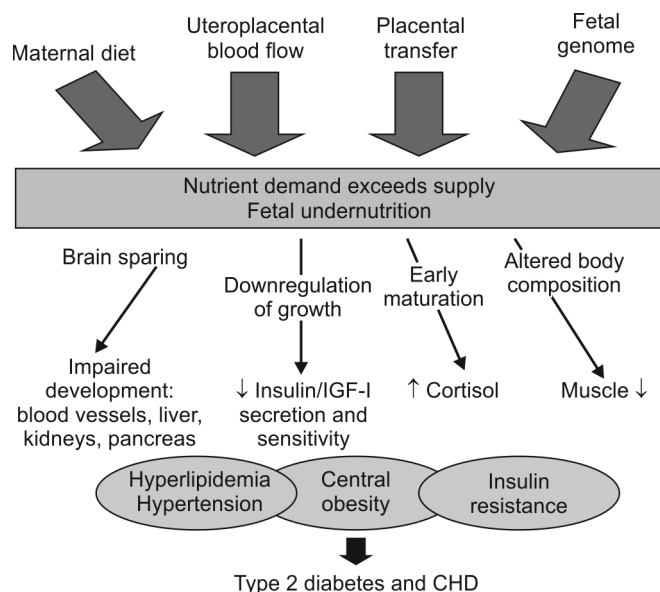
Preterms and IUGR have reduced exercise capacity, and oxygen consumption as young adults even with normal pulmonary function. This may be related to physical fitness. ELBW also have decreased bone mass, osteopenia with risk of pathological fractures.

## THE ADULT FUNCTIONAL OUTCOMES

The LBW does result in residual limitations and challenges extending into adulthood. This affects life achievements, social functioning and socioeconomic status. School completion, higher education, employment is lower in extreme preterm babies, though some studies have shown comparative outcomes. Most ELBW follow-up studies have shown that they are still dependant on their parents, less likely to be married, or be a parent. Female premature babies are at risk for recurrent premature deliveries as adults. Due to functional limitations, former premature adults live a more sedentary life style with less participation in strenuous physical exercise. Despite residual limitations, they report a fairly high quality of life. This phenomenon of discordance between functional limitations and perceived quality of life has been termed *disability paradox*.

## DEVELOPMENT ORIGINS OF HEALTH AND DISEASES

Nutrition deprivation during critical periods of intrauterine life *programs* the fetus to exhibit a *thrifty phenotype*. This programming results in alterations in various fetal organs (**Fig. 3**). Maternal and early postnatal nutrition alters the state of the fetal genome and imprints gene expression by epigenetic mechanisms. The epigenetic alterations explain the transgenerational effects of the thrifty phenotype. Altered appetite regulation results in increased fat deposition. Lipid profile shows elevated cholesterol, triglycerides and low-density lipoprotein. Renal and blood vessel development is altered resulting in hypertension. Alterations in



**Figure 3** Developmental origins of health and disease DOHaD

Abbreviations: DOHaD, developmental origins of health and disease; IGF, insulin-like growth factor; CHD, congenital heart disease.

Source: Adapted from Fall CH. The fetal and early life origins of adult disease. Indian Pediatr. 2003;40:480-502.

cellular insulin signaling and reduced  $\beta$ -cell function results in diabetes. The final result is the full *metabolic syndrome*. Though this is particularly described for the IUGR newborn, it is also seen in preterm LBW neonates with poor nutrition in the first few weeks followed by rapid catch-up growth. Screening blood pressure, glucose tolerance, lipid profiles, should be part of follow-up services for VLBW IUGR children.

In the Pune LBW study at 4 years, LBW had higher insulin-like growth factor-1 and higher blood pressures. After a glucose load, the glucose and insulin concentrations were higher in LBW. However in adults, central obesity or hypertension was not found. Nair et al. found that LBW adolescents at 16 years had higher triglyceride levels and obesity. In the Christian Medical College Vellore cohort, LBW young men had higher blood pressure and a tendency to insulin resistance. The COHORTS study group confirmed that the metabolic syndrome was associated with rapid weight gain in infancy and childhood and an increase in body mass index. Greater weight gains at any age and not just infancy increased the risk of hypertension. Hypertensive adults born preterm have higher systolic and diastolic blood pressure by 4.2 and 3.6 respectively. These differences are considerable given that, at the population level, a 2 mm Hg reduction in diastolic pressure is estimated to result in a 6% reduction in the risk of coronary heart disease and a 15% reduction in risk of cerebrovascular events.

## INTERVENTIONS TO IMPROVE NEURODEVELOPMENTAL OUTCOME

Early interventions to target improvement in neurodevelopment take advantage of the *plasticity* of the newborn brain. Compensatory mechanisms exist in the preterm brain and this plasticity is encouraged by stimulation of neurons. *Cells that fire together wire together*. The mother is the key instrument for all interventional programs. Early interventions include individualized developmentally supportive care [Newborn Individualized Developmental Care and Assessment Program (NIDCAP)], multi-sensory stimulation, physiotherapy, occupational therapy, home-based programs and interventions to improve mother-child interaction. Early interventional programs improve neurodevelopment, but their benefits into late childhood and adulthood are not consistently seen. IQ scores may improve by as much as 10 points. Early intervention programs result in greater school achievements, less grade retention and special education. One of the common and simple comprehensive interventions is kangaroo mother care (KMC).

**Kangaroo mother care** Kangaroo mother care has consistently shown improvement in growth parameters. The benefits of KMC extend beyond the immediate neonatal period into adolescence and adulthood. Bera et al. from Kolkata have documented better growth and DASII scores in KMC group at 1 year corrected age. In another study, KMC had benefits at 10 years in the form of better organized sleep, autonomic functioning, cognition, executive functions, maternal behavior and mother-child reciprocity. As adolescents, transcranial migration stimulation studies were comparable between term controls and LBW receiving KMC and significantly higher than those did not receive KMC.

**Nutritional supplementation** Breastfeeding with mineral supplementation is the *best* food for the LBW. Zinc supplementation in first 2 months may improve linear growth. Docosahexaenoic acid supplementation could improve visual and cognitive outcomes. Iron supplementation improves behavioral outcome. Salt supplementation of 4–5 mmol/day from day 4–14 have better neurodevelopmental outcome. Approximately 10% IUGR do not display catch-up growth. This group has been targeted for growth hormone therapy. Growth hormone may also improve IQ, social acceptance, and feelings of self worth. This is independent of



the weight gain achieved. Lifestyle changes are important from early life to balance developmental origins of health and disease (DOHaD). Blood pressure monitoring should start in early life.

There is a need for development of a dedicated long-term follow-up program up to middle age and beyond to assess the long term impact of LBW. Such a program can be incorporated into already existing newborn follow-up programs like *Rashtriya Bal Swasthya Karyakram*.

### IN A NUTSHELL

1. Catch-up growth in low birthweight (LBW) may not be complete. Lower the gestational age and birthweight, poorer is the catch-up growth.
2. Developmental assessment should be done as per corrected age. Correction for prematurity may have to be continued beyond 2 years in extreme preterm babies.
3. Low birthweight babies are at risk for motor abnormalities ranging from transient tonal abnormalities to cerebral palsy; poorer cognitive outcomes such as lower IQ and poorer academic achievements; behavioral problems such as attention deficit hyperactive disorder (ADHD) and autism spectrum disorders (ASD); and neurosensory problems like retinopathy of prematurity (ROP) and hearing loss.
4. LBW babies continue to be compromised in general health in adulthood as witnessed by recurrent respiratory illness and are also at risk for metabolic syndrome [developmental origins of health and disease (DOHaD)].
5. Kangaroo mother care (KMC), nutritional supplementation and early intervention with good maternal child interaction are known to improve neurodevelopmental outcome of LBW babies.

### MORE ON THIS TOPIC

- Chaudhari S, Otiv M, Khairnar B, et al. Pune low birth weight study, growth from birth to adulthood. *Indian Pediatr.* 2012;49:727-32.
- Chaudhari S, Otiv M, Khairnar B, et al. Pune low birth weight study - birth to adulthood - cognitive development. *Indian Pediatr.* 2013;50:853-57.
- Doyle LW, Anderson PJ. Long term outcome for the tiniest or most immature babies. *Semin Fetal Neonatal Med.* 2014;19:71-136.
- Mukhopadhyay K, Malhi P, Mahajan R, Narang A. Neurodevelopmental and behavioral outcome of very low birth weight babies at corrected age of 2 years. *Indian J Pediatr.* 2010;77:963-7.
- Myers E, Ment LR. Long-term outcome of preterm infants and the role of neuroimaging. *Clin Perinatol.* 2009;36:773-89.
- Nair MK, Chacko DS, Paul MK, et al. Low birthweight babies—outcome at 13 years. *Indian Pediatr.* 2009;46 Suppl:s71-4.
- Nair MK, Nair L, Chacko DS, et al. Markers of fetal onset adult diseases: a comparison among low birthweight and normal birthweight adolescents. *Indian Pediatr.* 2009;46 Suppl:s43-7.
- Sharma PK, Sankar MJ, Sapra S, et al. Growth and neurosensory outcomes of preterm very low birth weight infants at 18 months of corrected age. *Indian J Pediatr.* 2011;78:1485-90.
- Stein AD, Barros FC, Bhargava SK, et al. Birth status, child growth, and adult outcomes in low- and middle-income countries. *J Pediatr.* 2013;163:1740-6.
- Thomas N, Grunnet LG, Poulsen P, et al. Born with low birth weight in rural Southern India: what are the metabolic consequences 20 years later? *Eur J Endocrinol.* 2012;166:647-55.

## Chapter 13.5

### Postmaturity

Reeta Bora, Pranay Phukan

Postmaturity or post-term pregnancy is not an infrequent problem in clinical practice and is associated with increased perinatal and neonatal mortality and morbidity. For proper management to reduce these complications, the condition needs a combined effort of obstetrician and pediatrician.

#### DEFINITION

WHO defines post-term birth as a birth occurring at a gestational age of 42 weeks (294 days) or greater assuming a menstrual cycle of 28 days. Post-term babies who have begun to lose weight but have normal length and head circumference are said to be postmature. In 2013, The American College of Obstetrics and Gynecology's Society of Fetal and Neonatal Medicine has redefined term pregnancy to improve neonatal outcome and expand efforts to prevent non-medically indicated termination of pregnancies before 39 weeks of gestation. A series of more specific labels have been proposed for use. The terminologies used to redefine delivery at term and beyond are:

- *Early term*: Between 37 weeks 0 days to 38 weeks 6 days.
- *Full term*: Between 39 weeks 0 days to 40 weeks 6 days.
- *Late term*: Between 41 weeks 0 days to 41 weeks 6 days
- *Post-term*: Between 42 weeks 0 days and beyond.

#### INCIDENCE

The overall incidence of post-term pregnancy has been reported in western literature to be approximately 3–12% of all pregnancies. In the United States the incidence has been reported as 5.6% whereas in Europe it has been found to be as high as 8.1%. No data could be found published from India mentioning incidence of post-term pregnancy.

The definition of normal human gestation is itself open to discussion. Mean duration of pregnancy may vary among different population and under different conditions. For example gestations ending in summer months may be longer than those ending in winter, pregnancy with male fetus may be longer than with female fetus. Race, ethnicity and country of origin of mother are associated with differences in average duration of pregnancy. It has been mentioned in the literature that perinatal complications seem to increase in some population starting as early as 38 weeks of gestation. However, overall risk of perinatal mortality increases with pregnancy beyond 41 weeks of gestation.

Although last menstrual period (LMP) has been traditionally used to calculate gestational age and expected date of delivery (EDD), it may be inaccurate many a times in women who have had irregular menstrual cycles, who have cycle length other than 28 days, who have been on hormonal birth control pills, women who have inconsistent ovulation times and those who had 1st trimester bleeding. Hence not only LMP but also other important factors needs to be considered while calculating EDD or gestational from LMP, so as not to overestimate incidence of post-term pregnancy. Obstetric ultrasonography (USG) at 1st trimester can improve estimation of gestational age but it is important to understand that there is a margin of error of +3–5 days. Second and third trimester USG are not reliable for assessing gestational age as they have wide margin of error (7–10 days in 2nd trimester and 3 weeks in 3rd trimester.)

The importance of determining by what method a pregnancy is dated cannot be overemphasized because this may have significant

consequences on the neonatal outcome. There are risks to the neonate both if the physician delivers a so-called term pregnancy that is not or observes a so-called term pregnancy that is very post-term.

#### RISK FACTORS

Maternal factors like genetic predisposition, primiparity, prior post-term delivery are risk factors for post-term delivery. Recently maternal obesity (maternal body mass index of more than 29 kg/m<sup>2</sup>) has been mentioned as a risk factor for post-term delivery. Elevated pre-pregnancy weight as well as weight gain during pregnancy, both have been found to increase risk of post-term delivery. Maintaining maternal weight gain in a recommended range can prevent post-term pregnancy.

Placental sulfatase deficiency may be another factor leading to post-term pregnancy. Fetal factors like chromosomal abnormalities, e.g., trisomy 16 and 18, anencephaly, fetal pituitary adrenal axis anomalies have been mentioned as fetal causes of post-term pregnancy but with modern obstetric care these causes are rare (Table 1).

**Table 1** Risk factors associated with post-term pregnancy

Maternal factors	Fetal factors
Genetic predisposition	Trisomy 16, 18
Primipara mother	Anencephaly
Prior post-term delivery	Fetal pituitary adrenal axis anomaly
Maternal obesity	Seckel syndrome (bird headed dwarfism)
Placental sulfatase deficiency	

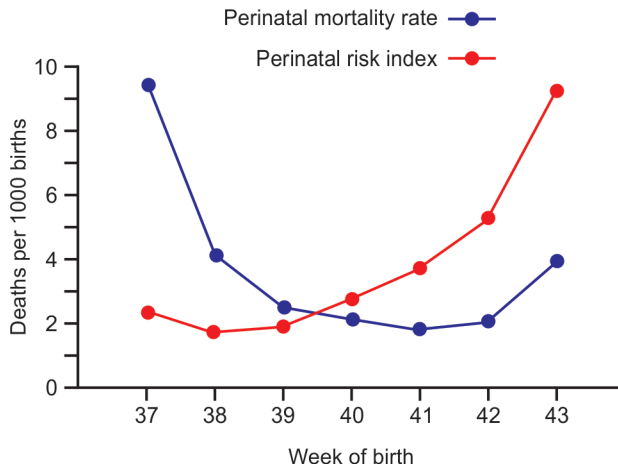
#### PERINATAL OUTCOME

Several population based studies have shown that the risk for fetal death is higher in post-term pregnancy than those with term gestation. The risk has been found to be increased by a factor of 1.5 in nulliparous women as compared to multiparous women. This risk has been calculated traditionally as rate of fetal loss per 1000 livebirths, however this risk may increase further if calculated as proportion of ongoing pregnancies. The stillbirth rate has been cited in a population based study to be, 1.27/1000 ongoing pregnancies at 41 weeks, 1.55/1000 at 42 weeks of gestational age and 2.12/1000 ongoing pregnancies at 43 weeks of gestational age.

It is well established that post-term pregnancy is associated with labor dystocia, severe perineal injury in mother and is also associated with increased incidence of cesarean delivery. The incidence of intrauterine fetal demise plus neonatal deaths, meconium aspiration, infectious morbidity, birth trauma, low Apgar score and low umbilical cord pH level increases in post-term pregnancy as compared to term. Occasionally macrosomia (defined as birthweight more than 4,500 g) and associated birth injury is also seen to be associated with post-term pregnancy. The low Apgar score in post-term pregnancy has been found to be related to postmaturity and meconium aspiration syndrome. At 42 weeks the stillbirth rate and early neonatal death rate have been found to be twice as that of at 40 weeks and the risk trebles at 43 weeks. Due to the maternal and neonatal morbidity associated with post-term pregnancy, the American Academy of Obstetrics and Gynecology recommends initiation of antenatal surveillance between 41 weeks and 42 weeks of gestation. Induction may be indicated after discussion of risks and benefit of induction with mother.

The risk for fetal demise has been found to be higher in recent studies compared to those mentioned in older studies, the reason being many pregnancies which were termed post-term in older studies were probably term pregnancies as dating was done traditionally by using LMP rather than using 1st trimester USG.

The perinatal morbidity and mortality in post-term pregnancy may be related to the slow deterioration of placental blood flow and function and progressive increase in size of the fetus. These changes as occur over a period of time after term, the risk of perinatal complications might be expected to increase with advancing gestational age in a continuous rather than threshold fashion. Studies have shown that the risk of maternal and neonatal complications increase as pregnancy progresses beyond 40 weeks of gestation (**Fig. 1**).



**Figure 1** Perinatal risk index and perinatal mortality rate for birth between 37 weeks and 43 weeks

Source: Adapted from Am J Obstet Gynecol Vol 184, 2001.

## POSTMATURITY SYNDROME

Ballantyne (1902) first reported this syndrome and Clifford (1954) described it as a recognizable clinical syndrome. 20% of post-term neonates have a risk for postmaturity syndrome. These post-term neonates have begun to lose weight due to poor placental blood supply leading to progressive reduction of oxygen supply, but have normal length and head circumference. The outcome of postmaturity includes oligohydramnios, cord compression, fetal distress and meconium aspiration. Many authors prefer to use the term *dysmaturity syndrome* for such babies rather than using *postmaturity syndrome* as although in the past the clinical features suggestive of this syndrome was attributed to prolonged pregnancy and was thought to be seen only in neonates delivered after prolonged pregnancy, recent work has shown that the constellation of signs may be found in neonates of any gestation with placental insufficiency (**Fig. 2**).

**Classification** Postmaturity syndrome is further classified traditionally into three stages:

**Stage I** includes those postmature infants who have dry crackled skin, loose and wrinkled skin with malnourished appearance, decreased subcutaneous tissue with alert eyes.

**Stage II** includes infants with all features suggestive of stage I with meconium staining of amniotic fluid and perinatal depression.

**Stage III** babies have all features of stage I and II and meconium staining of skin, nails suggestive of long standing meconium staining of amniotic fluid. Neonates with stage III condition have high risk for fetal, intrapartum and neonatal death.

Recent evidence suggests that the risk of meconium staining, asphyxia and mortality increases beyond 41 weeks and 42 weeks by itself is not a threshold below which risk is low. There is also evidence that nulliparous women have a higher risk of perinatal mortality if pregnancy is postterm compared to multiparous women. Post-term neonates with postmaturity syndrome are



**Figure 2** Neonate with postmaturity syndrome

also known to be at risk of persistent pulmonary hypertension, neonatal seizures, metabolic derangements like hypoglycemia and hypocalcemia.

## LONG-TERM OUTCOME

Postmaturity syndrome has also been found to be associated with long-term neurological and developmental consequences including lower social quotient at 12 months of age and lower Bayley mental developmental score at 8 months of age. Mortality in 1st year of life seems to be increased in this group of babies as compared to those delivered at term. Behavioral and emotional abnormalities, specially attention deficit or hyperactive disorder have also been reported in infants who were delivered post-term. In one study in long-term post-term boys were found to have accelerated weight gain during adolescence leading to obesity. It has been proposed that prolonged gestation may lead to suboptimal fetal environment through inadequate fetal nutrition and physiological stress, resulting in long-term abnormal postnatal body composition. **Box 1** summarizes the outcomes of post-term births.

### BOX 1 Outcomes associated with post-term delivery

1. Increased perinatal mortality
2. Perinatal morbidity
  - Low Apgar score and perinatal asphyxia
  - Meconium aspiration syndrome
  - Increased NICU admission
  - Persistent pulmonary hypertension
  - Hypoglycemia, polycythemia
3. Long-term morbidity
  - Delayed and abnormal development
  - Decreased social quotient
  - Increased rate of hospitalization in 1st year of life
  - Childhood obesity.

Abbreviation: NICU, neonatal intensive care unit.

**Maternal risk** Higher incidences of perineal injury (third and fourth degree perineal laceration), cesarean section, hemorrhage and infection are seen in mothers with post-term pregnancy compared to those with term pregnancy.

## MANAGEMENT

**Antenatal** Gestational age should be assessed carefully including 1st trimester USG data. Antenatal assessment should be done by

antenatal fetal monitoring from 41 weeks onwards by twice weekly. The first decision that must be made when managing a post-term pregnancy is whether to deliver or to wait expectantly. A non-reassuring fetal surveillance result, oligohydramnios, fetal growth restriction, or certain maternal diseases like pregnancy induced hypertension makes the decision for delivery straightforward. However, frequently several options can be considered when determining a course of action in the low-risk pregnancy. The certainty of gestational age, cervical examination findings, estimated fetal weight, patient preference, and past obstetric history must all be considered when mapping a course of action. Elective induction of labor has been used increasingly for management of such pregnancies. Recent systematic reviews and meta-analysis of randomized controlled trials comparing routine induction with expectant management of mothers with post-term pregnancy concluded that labor induction may reduce perinatal and neonatal mortality but without increasing risk of cesarean delivery.

**Intrapartum** As perinatal asphyxia and meconium aspiration are common in such pregnancies, the delivery of the fetus should be attended by a person expert in neonatal resuscitation including intubation. Delivery of such pregnancies should ideally be conducted in a health set-up with facility for managing neonates with complications like meconium aspiration syndrome, persistent pulmonary hypertension, etc. Procedures like amnioinfusion, suction of oropharynx at perineum, etc. have not been found to be effective in reducing meconium aspiration syndrome contrary to popular belief. Undiagnosed fetal chromosomal abnormality remains a probability in such pregnancies, hence neonates should be closely examined after delivery for such abnormality.

**Postpartum management** This includes close monitoring of the neonate for conditions like persistent pulmonary hypertension, hypoglycemia, hypocalcemia, neonatal seizure, neonatal encephalopathy and polycythemia to which these babies are prone to. If such conditions are detected they should be managed

accordingly. Meconium aspiration and persistent pulmonary hypertension will indicate need for ventilator care. Neonatal seizure may be there in these babies because of neonatal encephalopathy or metabolic derangements like hypoglycemia, hypocalcemia, etc. These conditions if present would indicate need for secondary or tertiary level care for the baby.

### IN A NUTSHELL

1. Post-term delivery with an incidence of 2–5% is not rare and is consistently associated with small risk of rise in perinatal death and neonatal morbidity.
2. Duration of normal human gestation may vary in different population.
3. Careful assessment of duration of gestation is necessary before intervention.
4. Twenty percent of post-term pregnancy may be associated with postmaturity syndrome.
5. Close monitoring of pregnancies after 40 weeks of gestation and careful antepartum, intrapartum management may prevent many of the mortality and morbidities.

### MORE ON THIS TOPIC

- Bel-Ange A, Harlev A, Weintraub AY, Sheiner E. Waiting for post-term in healthy women, is it an accident waiting to happen? *J Matern Fetal Neonatal Med.* 2013;26:779-82.
- Cheng YW, Nicholson JM, Nakagawa S, et al. Perinatal outcomes in low-risk term pregnancies: do they differ by week of gestation? *Am J Obstet Gynecol.* 2008. p. 370.
- El Marroun H, Zeegers M, Steegers EA, et al. Post-term birth and the risk of behavioural and emotional problems in early childhood. *Int J Epidemiol.* 2012;41:773-81.
- Halloran DR, Cheng YW, Wall TR, et al. Effect of maternal weight on post-term delivery. *J Perinatol.* 2012;32:85-90.



## Chapter 13.6

# Large for Gestational Age

Rhishikesh Thakre

Large for gestational age (LGA) is an abnormal growth descriptor used as a diagnostic tool and a prognostic marker. The LGA neonates are defined as having weight for gestation above the 90th percentile on the growth chart. However, it seems the optimal birthweight percentile in defining LGA is 2 standard deviations (> 97th percentile) above the weight for gestation as this identifies neonates at highest risk for perinatal morbidity and mortality. *Macrosomia* is a clinical term used to describe an abnormally large fetus regardless of gestational age (birthweight > 4500 g). The LGA are at high risk for perinatal morbidity and potentially long-term metabolic complications.

## EPIDEMIOLOGY

Large for gestational age affects 1–10% of all pregnancies. There is racial and ethnic variability in the incidence of LGA infants. A steady rise in the prevalence of LGA newborns over a few decades has been noted in many parts of the world including developing countries due to increasing prevalence of diabetes, gestational diabetes, obesity and lifestyle changes.

## ETIOLOGY

Birthweight is influenced by many factors, many of which are known (**Table 1**) and some unknown (idiopathic). The majority of large babies are due to large mothers (constitutional). Excessive fetal growth can occur because of genetic factors or increased supply of nutrients. Maternal body mass index (BMI), diabetes, and weight gain during pregnancy are known to be positively associated with infant size at birth. There are many risk factors which predispose a mother in having large for gestational age birth, however, the extent to which each of these factors influence birthweight is unclear (**Table 2**).

## PATHOPHYSIOLOGY

The growth of the fetus is complex and dependent upon numerous factors like maternal uterine environment, functioning of the

placenta, and availability of nutrients to mother and fetus. One of the commonest causes of LGA is maternal diabetes. Un-controlled maternal diabetes, leads to fetal hyperglycemia stimulating the beta cells of pancreas resulting in fetal hyperinsulinemia. Because insulin is an anabolic hormone the fetal hyperinsulinemia stimulates protein, lipid and glycogen synthesis causing increased fetal body fat, excessive adipose deposition, visceral organ hypertrophy, and acceleration of body mass accretion to cause macrosomia. Macrosomia leads to complications of delivery, such as shoulder dystocia, obstructed labor, perinatal asphyxia and birth injury. Fetal hyperinsulinemia also causes elevated metabolic rate, leading to increased oxygen consumption and fetal hypoxemia predisposing to intrapartum complications (fetal distress, still births), inhibition of the normal maturational effect of cortisol on the lung leading to delayed pulmonary maturation processes required for surfactant production (RDS), and persistence into neonatal life contributes to the propensity to develop neonatal hypoglycemia.

Not all LGA fetuses are due to hyperinsulinemia. Parents of large stature (weight or height), obese mothers and those who gain excessive weight during pregnancy lead to excessive delivery of nutrients to the fetus and contribute to increased fetal growth. Possibility of one of the rare syndromes associated with accelerated fetal growth should be considered, particularly in the presence of one or more fetal structural anomalies (**Table 3**). Limited data suggest that placental epigenetic alterations may contribute to increased fetal growth.

## CLINICAL FEATURES

### Delivery Room

The classical appearance of LGA is large, plethoric baby due to increased body fat in the abdominal and scapular regions (**Fig. 1**). The higher the weight greater is the risk of complications of delivery, such as shoulder dystocia, obstructed labor, perinatal asphyxia and birth injury (e.g. brachial plexus injury (**Fig. 2**) or fractured clavicle or humerus (**Fig. 3**). The rate of birth injury is more in vaginal compared with cesarean deliveries. The extremity may appear swollen, tender with minimal movement because of pain (pseudoparalysis) due to underlying bone fracture. Physical findings of brachial plexus injury are distinctive. Erb's palsy (C5–7) has classical waiters tip hand, i.e., forearm is pronated and the wrist flexed with asymmetrical Moro reflex. Klumpke palsy (C8–T1) affects small muscles of the hand, wrist and finger flexors (claw hand deformity) with absent grasp reflex. Horner syndrome (30% in Klumpke palsy, involves T1), causes ptosis, miosis on affected

**Table 1** Etiology of large for gestational age (LGA) infants

• Constitutional
• Maternal obesity/overweight
• Prepregnancy/pregnancy diabetes
• Hydrops fetalis
• Genetic (Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome, Perlman syndrome, Sotos syndrome, Weaver syndrome, Costello syndrome)

**Table 2** Risk factors for LGA infants

• Multiparity
• Advanced maternal age (≥30 years)
• Post-term pregnancy (≥ two fold risk)
• Previous history of large baby
• Excessive weight gain in pregnancy (≥20 kg)
• Maternal birthweight > 4000 g
• Male sex



**Figure 1** Large for gestational age infant

**Table 3** Genetic syndromes with large for gestational age (LGA) neonates

Condition	Characteristic
Beckwith-Wiedemann syndrome (BWS) (AD)	Macroglossia, linear fissure in ear lobule, visceromegaly, neonatal hypoglycemia, hemihypertrophy, cryptorchidism
Perlman syndrome (AD)	Hypotonia, mental retardation, depressed nasal bridge, anteverted upper lip, mild micrognathia, nephromegaly, bilateral cortical hamartomas, increased risk for Wilms tumor
Sotos syndrome—Cerebral gigantism (Sporadic)	Macrocephaly, dolichocephaly, ventriculomegaly, downslanting palpebral fissures, hypertelorism, prognathism, high narrow palate, premature eruption of teeth, large hands and feet, kyphoscoliosis, mental deficiency
Weavers syndrome (Sporadic)	Mental retardation, hypertonia, hoarse voice, macrocephaly, round face, ocular hypertelorism, downslanting palpebral fissures, long philtrum, large ears, micrognathia, camptodactyly, thin deep-set nails, prominent fingertip pads
Simpson-Golabi-Behmel syndrome (XLR)	Macrocephaly, coarse facies, macrosomia, hypertelorism, macroglossia, cleft lip, nail hypoplasia, macrostomia, postaxial polydactyly, umbilical/inguinal hernias, visceromegaly, skeletal abnormalities, increased risk for embryonal tumor
Costello syndrome	Coarse facies, loose skin, diffuse hypotonia, joint laxity, sparse fine hair, failure to thrive, increased risk for malignant solid tumors

Abbreviations: AD, autosomal dominant; XLR, X-linked recessive.

**Figure 2** Brachial plexus injury of right hand**Figure 3** Note the fullness of right arm with paucity of movement suggesting underlying fracture humerus due to shoulder dystocia

side. Minor congenital anomalies are more common in LGA than AGA infants. The most common anomalies associated are talipes calcaneovalgus, hip subluxation, hydrocephaly and nonbrown pigmented nevi. Two-thirds of the anomalies in infant of diabetic mother (IDM) involve the cardiovascular or central nervous system. Poor feeding is a major problem; it occurs in almost one-third of infants and is often present in the absence of other problems.

### Neonatal Unit

The most common diagnoses in LGA infants, which account for nursery admission, are respiratory distress syndrome (19%, due to surfactant immaturity in diabetes), transient tachypnea of the newborn infant (16%, due to increased cesarean section delivery), hypoglycemia (9%), and meconium aspiration (9%). Almost half of the IDM need admission to neonatal intensive care unit (NICU). Up to 15% of all LGA infants and 50% of IDM develop hypoglycemia which may be symptomatic (irritability, lethargy, apnea, grunting, respiratory distress, tachypnea) or asymptomatic. The highest risk is between 1–4 hours and unlikely beyond 48 hours of birth. Hence all LGA need monitoring for blood sugar. Unrecognized hypoglycemia can lead to seizures (0.3%), encephalopathy, and brain damage. Initial jitteriness hypotonia followed by increased tone, and seizures are signs and symptoms of brain injury secondary to perinatal asphyxia. Prematurity, increased RBC destruction contribute to development of indirect jaundice. Polycythemia can lead to poor circulation and exacerbate hyperbilirubinemia.

### DIFFERENTIAL DIAGNOSIS

Large for gestational age infants may be due to overweight or obese mothers (constitutional), maternal diabetes, hydrops fetalis or genetic syndromes. The characteristic features of each are in **Tables 3** and **4**. An infant with hydrops has an abnormal accumulation of excess fluid leading to generalized edema with effusions in multiple body cavities.

### Approach to Diagnosis

Identification and evaluation of neonate at risk for LGA should begin during pregnancy, and such neonates should be followed up postnatal. A thorough family and pregnancy history shall help to identify *at risk* mothers and provide appropriate anticipatory care to prevent complications. Fetal well-being is commonly assessed through the use of maternal glucose tolerance testing, nonstress testing, and biophysical profiles. Trend in maternal weight gain

**Table 4** Characteristics of LGA and infant of diabetic mother (IDM)

Features	LGA	IDM
Macrosomia	+	+
Asphyxia	+	+
Birth trauma	+	+
Hypoglycemia	+	+
Hyperbilirubinemia	+	+
RDS, MAS, diaphragmatic palsy, air leak	–	+
Polycythemia	–	+
Congenital anomalies	–	+
Hypocalcemia, hypomagnesemia	–	+
Organomegaly	–	+
Neurologic sequelae	–	+

is monitored. Causative factors for LGA neonates are investigated antenatally. Prenatal management is aimed at determining the ideal time and mode of delivery depending on obstetric factors.

At least one person capable of neonatal resuscitation should be present at the time of birth. In the well infant, routine care should be provided. A rapid assessment is done for presence of any birth injury, congenital malformations, and evidence of macrosomia, hypoglycemia, respiratory distress or genetic syndrome. All babies should have weight, length, and head circumference plotted on the growth chart [e.g. modified Fenton's chart for preterm, WHO (2005) chart for term infants]]. Weight more than the 90th percentile for gestational age confirms the diagnosis of LGA. A focused physical examination from head to toe should be done (**Table 5**).

## MANAGEMENT

### Delivery

For the majority of pregnant women who are not diabetic, a policy of elective cesarean delivery for ultrasonographically diagnosed fetal macrosomia is medically and economically unsound. In pregnancies complicated by diabetes, such a policy appears to be more tenable, although the merits of such an approach are debatable. Most recent studies do not show any advantage to induction before the due date. Early neonatal complications such as asphyxia, birth trauma and hypoglycemia must be anticipated. In absence of any complications, routine care should be provided and baby handed over to the mother for skin-to-skin contact and early breastfeeding.

### Supportive Care

Infant of diabetic mothers with asphyxia, congenital malformations, history of maternal insulin administration, unstable vital parameters and hypoglycemia should be admitted to nursery and should receive supportive care while being evaluated for hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia. All LGA newborns are nursed in thermoneutral environment. Vital parameters are continuously monitored using pulse oximetry. State of well-being, sensorium, tone, cry and activity and perfusion is assessed periodically. Every attempt is made to ensure early supervised feeding. Gavage feeding may be started if there is poor oral-motor coordination. Those unable to tolerate enteral feeding are initiated on IV fluids.

### Glucose Control

Glucose sampling is usually accomplished during the first 2 hours after birth and monitored as per unit policy. Glucose value less than 45 mg% identifies hypoglycemia. Asymptomatic LGA with blood glucose 25–45 mg% are offered additional supervised oral feeds and reassessed. Sick infants, blood glucose less than 25 mg%, inability to tolerate enteral feeding, or those who remain hypoglycemic

**Table 5** Evaluation of LGA infants

Appearance	Plump, well-nourished, proportionately large head and body
Activity	Irritable (asphyxia, fracture, pain), drowsy (asphyxia, intracranial hemorrhage, hypoglycemia), lethargy (hypoglycemia, spinal cord injury), jitteriness, poor feeding (hypoglycemia, trauma)
Cry	High-pitched cry, inspiratory stridor, dysphonia (difficulty crying), or dysphagia (difficulty swallowing) may indicate unilateral or bilateral vocal cord paralysis
Head	Small fontanel (overlapping sutures), large fontanel, metopic suture (Beckwith-Wiedemann syndrome (BWS), caput succedaneum, cephalhematoma, subgaleal hemorrhage)
Face	Bruises, abrasions, nasolabial fold-drooping mouth-open eye (facial nerve palsy), hairy pinna (IDM), pinna abnormalities—macroglossia (BWS)
Skin	Increased subcutaneous fat, increased muscle mass, meconium staining (MAS), jaundice (increased bilirubin production due to macrosomia, polycythemia, adrenal hemorrhage), pallor and poor perfusion (shoulder dystocia), bruises, abrasions, plethora, nonbrown pigmented nevi
Limbs/bones	Movements, symmetry, swelling, tenderness, crepitus (fracture, dislocation, trauma), Talipes, DDH, Erb palsy, Klumpke palsy
Respiration	High respiratory rate, work of breathing (RDS, MAS, asphyxia, TTNB, phrenic nerve palsy, CHD)
Abdomen	Mass, organomegaly (adrenal hemorrhage or subcapsular hematoma of liver, BWS), umbilical hernias, omphalocele and diastasis recti (BWS), single umbilical artery (genitourinary-cardiac anomalies), Non-passage of meconium (hypoplastic left colon)
Heart	Murmur, abnormal pulses, cyanosis (CHD, PPHN)
Tone	Hypotonia-apnea-areflexia (spinal cord injury),
Reflexes	Moros for symmetry (fracture clavicle or humerus, brachial plexus injury), Suck (facial palsy), Grasp (absent in Klumpke palsy)
Genitalia	Inguinal hernia, cryptorchidism, clitoromegaly (BWS)

despite full enteral feeds, should receive an intravenous infusion of glucose at an initial rate of 6 mg/kg/min and increasing rapidly if indicated by repeat blood glucose monitoring. The blood glucose is maintained above 45 mg%. 2 cc/kg of 10% glucose bolus followed by glucose infusion is restricted to symptomatic hypoglycemic newborns. Seizures are most commonly due to hypoglycemia and comorbid conditions like sepsis, asphyxia, hypocalcemia, electrolyte imbalance, intracranial hemorrhage should be considered if seizures persist despite glucose control.

### Respiratory Care

Respiratory distress assessment is made by SA score (preterm) or Downes score (term). Oxygen is started if there is respiratory distress and the SpO<sub>2</sub> is not maintained. Sepsis screen, blood culture, blood sugar are done on admission as indicated. Chest X-ray defines the underlying cause of respiratory distress. ABG is done to assess the metabolic and respiratory status. Apnea, worsening sensorium, irregular breathing and inability to maintain oxygen saturation despite oxygen supplementation warrants initiation of artificial respiratory support. 2D echo and cardiology consult may be indicated if there is murmur, refractory hypoxia, unexplained shock or differential cyanosis. Paradoxical breathing pattern should raise suspicion of diaphragmatic paralysis which can be confirmed by fluoroscopy or ultrasound. Blood pressure is supported with fluid bolus, inotropes as needed. Bilirubin levels



should be measured if the infant appears to be jaundiced and hematocrit in first few hours and managed as hospital protocol.

### Birth Injury

X-ray long bones detect fractures, dislocation or humeral epiphyseal separation. Many fractures (clavicle or long bones) require no special treatment other than the simple measure of immobilization by slings, using paracetamol for pain control and advising parents not to grab the neonate or attempt to pick newborn up by the affected limb. For facial nerve palsy, patching the affected eye and lubricating eye drops are used. Facial nerve palsy generally improves within days after birth, but full recovery may take weeks to months and surgery restricted to cases with no full spontaneous recovery. In case of brachial plexus injury, protect the affected arm of the neonate is protected from dangling when moving or holding the neonate and parents told not to lift the neonate under the axillae. Physical therapy may be initiated with passive range of motion exercises at 1 week of age and no later than 3 weeks of age. Surgery may be necessary after 3 months if there is extensive damage to the nerve. EMG, nerve conduction, myelography, MRI may help define lesion at 1–4 months of age, but physical exam remains the ultimate guide to assess recovery and decide on surgical interventions.

### Counseling

The risk of obstetric and neonatal complications increases with rising birthweight. These risks need to be addressed during pre- and postdelivery counseling. Most genetically affected infants are diagnosed during pregnancy on ultrasound. The counseling should include a discussion on confirmation of diagnosis, survival, quality of life and risk of recurrence.

### OUTCOME

Neonatal morbidity and mortality is higher in LGA than in AGA infants for term and post-term but not for preterm babies. The risk increases as the birth percentile rises (**Table 6**). Large for gestational age pregnancies are associated with an increased rate of cesarean section, PPH, shoulder dystocia and neonatal hypoglycemia, as well as longer hospitalization. Simple fractures generally heal without complications. Majority of brachial plexus palsy recover on their own, but it depends on the degree of damage. Traumatic facial nerve palsy may improve within days,

with full recovery potentially taking months, possibly even years, depending on the severity. The most dismal prognosis associated with LGA neonates is for spinal cord injury.

Adverse outcomes are likely with prolonged or severe hypoglycemia and moderate to severe asphyxia requiring close neurodevelopmental follow-up. LGA neonates continue to grow longer and heavier and longitudinal data from developed countries convincingly associates macrosomia with long-term metabolic complications, including childhood obesity and the metabolic syndrome in adulthood. However no cognitive function differences compared to normal weight babies have been noted.

### PREVENTION

No intervention has been proven to significantly reduce the risk of macrosomia. Potentially useful strategies include prevention of maternal obesity before pregnancy with appropriate education and lifestyle modification, essential obstetric care, early assessment for gestational diabetes, tight glucose control during pregnancy, institutional delivery and skilled perinatal care, routine glucose screening, early recognition and prompt intervention for complications like asphyxia, hypoglycemia. It is possible that macrosomia is genetically programmed and cannot be altered by antepartum interventions.

#### IN A NUTSHELL

1. Large for gestational age (weight > 90th percentile) is an important risk factor for obstetric, neonatal and long-term metabolic complications. The risk increases as the birth percentile rises.
2. The use of risk factor information to identify mothers at risk of having large for gestational age births is an important clinical tool to meet individual needs by *anticipating* and providing the appropriate perinatal care.
3. Accurate anthropometric measurements and plotting them on appropriate growth charts is must. A focused physical assessment is vital.
4. Early identification and prompt management of feeding, traumatic birth injury, asphyxia, hypoglycemia, jaundice and polycythemia helps improve outcomes.

### MORE ON THIS TOPIC

- Chauhan SP, Grobman WA, Gherman RA, et al. Suspicion and treatment of the macrosomic fetus: a review. *Am J Obstet Gynecol*. 2005;193:332-46.
- Elizabeth J. Lawrence. Evaluating the Large-for-Gestational-Age Neonate. *Advances in Neonatal Care*. 2007;7:187-97.
- Gilleen JR, Coonrod DV, Russ R, Bay RC. Big infants in the neonatal intensive care unit. *Am J Obstet Gynecol*. 2005;192:1948.
- Groenendaal F, Elferink-Stinkens PM. Hypoglycaemia and seizures in large-for-gestational-age (LGA) full-term neonates. *Acta Paediatr*. 2006;95:874.
- Koyanagi A, Zhang J, Dagvadorj A, et al. Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. *Lancet*. 2013; published online Jan 4.
- Lapunzina P, Camelo JS, Rittler M, Castilla EE. Risks of congenital anomalies in large for gestational age infants. *J Pediatr*. 2002;140:200.
- Whincup PH, Kaye SJ, Owen CG, et al. Birth weight and risk of type 2 diabetes: a systematic review. *JAMA*. 2008;300:2886-97.

**Table 6** Outcome risk of LGA infants

Maternal	Neonatal	Long-term
<ul style="list-style-type: none"> <li>• Prolonged or arrested labor</li> <li>• Assisted vaginal delivery</li> <li>• Cesarean delivery</li> <li>• Genital tract lacerations</li> <li>• Postpartum hemorrhage</li> <li>• Uterine rupture</li> </ul>	<ul style="list-style-type: none"> <li>• Birth trauma</li> <li>• Asphyxia</li> <li>• Hypoglycemia</li> </ul>	<ul style="list-style-type: none"> <li>• Obesity</li> <li>• Metabolic syndrome</li> <li>• Impaired glucose tolerance</li> <li>• Abnormal lipid profile</li> <li>• Increase in aorta intima-media thickness, left ventricular mass</li> </ul>



## Chapter 13.7

# Multiple Gestations

Mamta Jajoo

The human female is programmed to ovulate once during every menstrual cycle and results in fertilization of a single ovum, to take care of one fetus and one neonate at a time. This happens in 99.2% of the cases, but in the remaining 0.8%, more than one zygote is ovulated resulting in twins or rarely high-order multiple gestations (MGs).

Multiple gestations became more common because of increasing maternal age and implementation of induction ovulation therapy and assisted reproductive technologies (ARTs). Studies from developed countries show that, because of ARTs, the rate and number of twins and higher-order multifetal births have increased with frequencies approaching 50% for twins and more than 75% for high-order MGs. No exact data showing the effect of ARTs on the rate and number of MGs is available from India, probably due to lack of registry in infertility clinics.

Multiple gestations are associated with increased maternal, fetal, and neonatal complications. It has been found, that compared to singletons, risk of pre-eclampsia, postpartum hemorrhage and maternal deaths were 2–3 times more in MGs. MGs are also at increased risk of preterm and very low birthweight delivery. Multifetal pregnancies generate a medical, psychological and economic burden to families and society, especially in developing countries, due to scarcity of human resources and proper health infrastructure.

### PATHOPHYSIOLOGY

Twin fetuses can be monozygotic (MZ) or dizygotic (DZ). Most MZ conceptions result in singleton births but in 0.4% cases, the zygote splits to form MZ or identical twins. The mechanism of zygotic splitting is unclear but is also increased with methods of assisted reproduction. The outcome of MZ twinning process depends on the time of division. If zygote divides within the first 3 days of fertilization, two embryos, two amnions and two chorions develop, that is diamniotic dichorionic pregnancy evolves. Approximately, 30% of MZ twins have dichorionic (DC) diamniotic placenta. If division occurs between 4 days and 8 days, it results in a diamniotic monochorionic twin pregnancy. If division occurs after 8 days of fertilization, it results in monoamniotic and monochorionic twin pregnancy. Embryonic division after 13 days results in conjoined twins.

Dizygotic or fraternal twins result from multiple ovulations and the subsequent fertilization of two ova by two different spermatozoa. DZ twins have two placentas with two chorions and two amnions called DC placenta. If twins are of a different sex, they are DZ; however, if they are of the same sex, they can be MZ or DZ. The ratio of MZ and DZ twins varies from population to population.

### Higher Multiples

Multiple pregnancies with higher number of fetuses can arise from fertilization of one, two or more ova and division of one or more fertilized ova, which results in multiple pregnancies that can be simultaneously dizygous and monozygous.

### Superfecundation and Superfetation

*Superfecundation* is fertilization of second ova within the same menstrual cycle when one ovum has already being fertilized. *Superfetation* is fertilization and subsequent development of an embryo during the course of an established pregnancy.

### INCIDENCE

Estimates of incidence of MGs are incomplete in the developing countries where the frequencies of twin deliveries are high with poor birth registrations, unknown number of abortions and early fetal death. The incidence of spontaneous twins is approximately 1 in 80 pregnancies. For spontaneous triplets, the estimated incidence is 1 in 8,000 and for quadruplet births, approximately 1 in 600,000 births. Differences in twinning rates among countries are mostly due to variation in DZ twinning. The MZ twinning is approximated to occur at a relatively constant rate of 3.5–4 per 1,000 births across human population.

Dizygotic comprises of 67% of spontaneous twins and they have the same genetic similarities as between any two siblings. The overall DZ twin's rate varies from 4 to 50 per 1,000 worldwide: minimum 1.3% in Japan, and maximum 49% in Nigeria and 8.1% in India. According to a recent retrospective analysis of Demographic and Health Survey data of 76 developing countries, done over a period of 14 years, the average of the natural twinning rate in these countries was 13.1 per 1,000 and in India, incidence of twinning was about 9 per 1,000, a huge variation was found in twinning rates across the different regions of the countries surveyed.

According to this survey, in India, the increase in incidence of twinning over a period of 14 years was no more than 0.84 per 1,000 births, which is very small and nonsignificant. This suggests that influence of infertility treatment is still low in India.

### ETIOLOGY

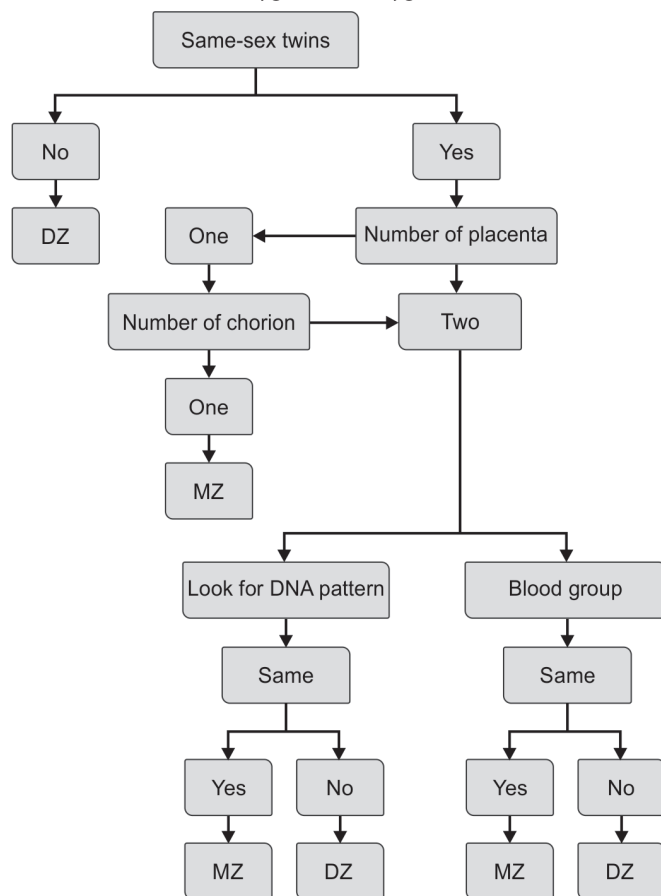
There are no known factors affecting the rate of MZ twinning but following ovarian stimulation or effect of assisted reproduction technology, it is 6–12 times more common. Many factors affect the rate of DZ twinning, like maternal age, race, ethnicity, heredity, parity, maternal nutrition level, infertility treatment and ovulation induction therapies. Important factor associated with twinning is maternal age. The number of twin pregnancies increases substantially with maternal age due to overstimulation by follicle-stimulating hormone and the luteinizing hormone surge.

### DETERMINATION OF ZYGOSITY AND CHORIONICITY

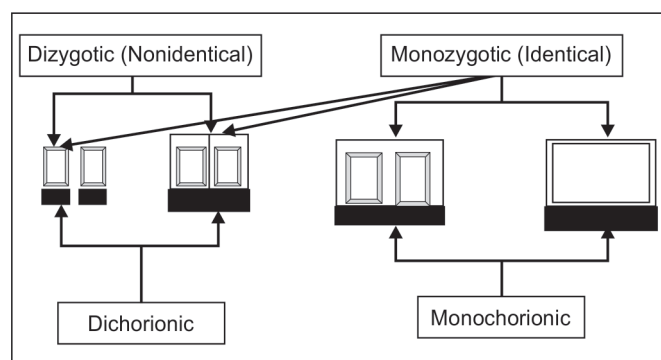
It is necessary to determine zygosity not only for epidemiological, genetic, obstetric and pediatric reasons but also because of the difference in prognosis between MZ and DZ twins as most of the complications occur in monochorionic MZ twins. It should be done routinely in all multiple pregnancies. Diagnosis of zygosity and chorionicity in antenatal period is important for the antepartum management of associated potential complications of twins like twin-to-twin transfusion, congenital anomalies, intrauterine growth restriction (IUGR) and demise of one fetus. It can be diagnosed by using ultrasound markers including the number of placental sites, thickness of dividing membrane, the lambda sign and fetal gender. At 10–14 weeks of gestation, ultrasound criteria correctly diagnose chorionicity in 99.3% of cases which is confirmed by postpartum placental examination.

Careful examination of placenta, physical similarity questionnaires, detail blood typing, tissue typing and human leukocyte antigen typing can also be used for determination of chorionicity (**Flow chart 1**). In twins of same sex, zygosity should be determined and recorded at birth. If the twins are of unlike sex, they are DZ and when a monochorionic placenta is found, they are MZ. DZ twins with same gender cannot be distinguished with MZ twins with DC placenta. In half of the DZ twins with same sex and one third of MZ twins with DC placenta, we are blind to zygosity (**Fig. 1**).

**Flow chart 1** Approach to diagnosis of monozygotic and dizygotic twins



Abbreviations: DNA, deoxyribonucleic acid; MZ, monozygotic; DZ, dizygotic.



**Figure 1** Relationship between zygosity and chorionicity

### Examination of Placenta

A careful placental examination after delivery establishes zygosity and chorionicity in approximately two-thirds of cases. Placenta should be carefully delivered to preserve the attachment of amnion and chorion. In DC placenta, dividing septum appears thicker and includes two amnions and two chorionic layers. In contrast, in monochorionic placenta the dividing septum consists of two thin amnions. One placenta, same-sex fetuses, and absence of a dividing septum suggests monoamniotic twins, but absence of a dividing septum may also be due to septal disruption.

## DIAGNOSIS OF MULTIPLE FETUSES

Early diagnosis is important for optimal antepartum management of fetuses. Taking a careful history and physical examination is useful in detecting multiple pregnancies. Family history or maternal personal history of twins, advanced maternal age, high parity and history of ingestion of clomiphene citrate, gonadotropins or pregnancy achieved by ARTs are more associated with MGs. Uterine size, and auscultation of two fetal hearts are helpful for a clinical diagnosis. Prenatal ultrasonography is used to confirm multifetal pregnancy and to monitor intrauterine fetal growth. It also helps in knowing the correct location of placenta and number of sacs. Without ultrasonic screening, the diagnosis is missed in 50% of the cases until the beginning of labor or delivery of one twin. Elevated maternal serum  $\alpha$ -fetoprotein and increased human chorionic gonadotropins in plasma and urine are present with MGs. Differential diagnosis of the large-for-date pregnancy includes inaccurate dating, hydramnios, hydatiform mole, uterine leiomyoma, fetal macrosomia or adnexal masses.

## PREGNANCY OUTCOMES

### Maternal Complications

Maternal mortality and morbidity increase many fold in a multifetal gestation. MGs are at increased risk for maternal complications like anemia, pregnancy-induced hypertension, polyhydramnios, hyperemesis gravidarum, acute fatty liver of pregnancy, venous thromboembolism, postpartum hemorrhage, malpresentations, premature rupture of membranes, hypertensive disorders, gestation-induced diabetes mellitus, preterm labor and abnormal placentation.

### Fetal and Neonatal Complications

Spontaneous abortions are three times more in twins than singletons. The incidence of congenital malformation is 2-3 times more in multiples; this increase is primarily related to MZ twinning. Malformation rates of DZ twins are similar to singletons. Malformations in twins are categorized under four subheadings:

1. *Due to twinning:* Neural tube defects, congenital heart defects, holoprosencephaly, esophageal and anorectal atresia, genitourinary tract anomalies are more common.
2. *Due to MZ twins:* This is because of reversal of blood flow in vascular anastomosis. Examples include twin reversed arterial perfusion (TRAP) sequence, amniotic band syndrome, conjoined twins and twin embolization syndrome.
3. *Due to placental malformations:* Particularly more in monochorionic placenta, resulting in twin-to-twin transfusion and velamentous cord insertion.
4. *Due to fetal crowding:* Defects include congenital hip dislocation, talipes equinovarus.

## COMPLICATIONS UNIQUE TO TWINNING

### Monoamniotic Twins

Monoamniotic twins account for 1% of MZ twin pregnancies. Monoamniotic twins are at increased risks of morbidity and mortality of one or both twins because of cord compression as a result of cord entanglement.

### Twin Reversed Arterial Perfusion Sequence

Vascular anastomosis between fetuses are frequent in monochorionic twin which may be from artery to artery, vein to vein, vein to artery. They are usually hemodynamically balanced but sometimes significant shunts develop between fetuses. In TRAP sequence, one twin transfuses its co-twin via an arterioarterial shunt; hence transfused twin receives blood by an artery instead

of vein giving rise to reversed perfusion. The donor twin is usually normally formed fetus, who has heart failure, and a recipient twin who lacks heart (acardius) and other structures, called acephalic-acardiac twin. Without treatment, the death rate of donor twin ranges from 50% to 75%. TRAP is very rare and occurs in 1 out of 35,000 births.

### Twin-to-twin Transfusion Syndrome

Twin-to-twin transfusion syndrome occurs in 20% of monochorionic twins. It is thought to occur secondary to placental vascular anastomoses. This leads to increased blood flow to one fetus (recipient fetus) and reduced blood flow to the other one (donor fetus). It is usually diagnosed by ultrasound in the second trimester with the appearance of oligohydramnios in the donor and polyhydramnios in the recipient twin. In the classic twin-to-twin transfusion syndrome, there is difference of 5 g/dL in hemoglobin levels and birthweight discrepancy of at least 20% can be present between two twins. There are other associated signs, such as plethora and hydrops in the recipient twin and pallor, malnourishment, and hypoxic damage in the donor twin. Perinatal mortality in twin-to-twin transfusion syndrome is as high as 70%. Several therapies have been used including serial amnioreduction and laser coagulation of the communicating vessels. Laser treatment is more effective than amniocentesis. In neonatal period, the donor shows signs of anemia, hypoproteinemia and intrauterine growth retardation whereas the recipient twin is polycythemic, heavier, and has complications of hyperviscosity, intravascular thrombosis and hyperbilirubinemia. Postnatal treatment is same as of polycythemia or anemia for singleton with the same problems. Risk of brain damage and periventricular leukomalacia is high in a recipient twin.

### Conjoined Twins

It is very rare and occurs approximately in 1 in 50,000 pregnancies. It occurs in MZ twins in which the division of the zygote is incomplete. Good visualization with two-dimensional or three-dimensional ultrasound and color Doppler assessment in antenatal period helps in delineating the site and extent of the fusion.

### Chromosomal Anomalies

Heterokaryotypes and misdistributions of chromosomes occur more during the twinning process which lead to a higher frequency of chromosomal anomalies in twins. The risk in MZ twins is equivalent to that of a singleton. The risk in DZ twins is independent for each fetus, so the risk of chromosomal abnormality in at least one DZ twin is twice that of a singleton fetus. Advanced maternal age also increases the risks of chromosomal anomalies in MG fetuses.

### Fetal Brain Damage

Neurological damage like cerebral palsy, microcephaly, porencephalic cysts more common in fetus of MG pregnancies, and is most likely caused by ischemic necrosis secondary to blood pressure instability and episodes of severe hypotension.

### Discordant Twins

It is the most common growth aberration in multiples. Discordance in growth is defined as the percent definition, when the larger fetus weighs 20% more than the smaller fetus. Etiology of discordant twin is unclear, but it is different in monochorionic and DC twins. In monochorionic twins, it is caused by placental vascular anastomosis that causes hemodynamic instability and in DC twins; it is mainly due to different genetic growth potential. Mortality is 11 times higher in highly discordant (>30%) twins. Birthweight discordance has been associated with increased risk of intrauterine and malformations related deaths.

### Intrauterine Growth Restriction

Intrauterine growth restriction is defined as an estimated fetal weight below the tenth percentile for singleton gestation. The growth restriction is more in MZs than DZs, compared to singletons; twins develop IUGR after 32 weeks of gestation and triplets after 29 weeks of gestation. Approximately, 14–25% of twin gestations and 50–60% of triplet or higher-order gestations are affected by growth restriction. Growth restriction in MGs is likely to be secondary to uteroplacental insufficiency but can also be secondary to structural anomalies, umbilical cord abnormalities, ultrasound error, infections, or genetic abnormalities.

### MANAGEMENT

Aim of the antenatal care is to prevent fetal growth retardation, premature delivery and to decrease the maternal complications. Antenatal care should be done every 2–3 weeks, monthly cranial ultrasonography after 24 weeks of gestation to assess fetal growth and weight and early detection of complications related to monochorionic placenta is required.

### Nonstress Test

A nonreactive nonstress test should be done; the results of an abnormal biophysical profile should be interpreted as for singleton pregnancy. The nonstress test may be impractical in all instances because of the difficulties of simultaneous assessment in three or more fetuses.

### Maternal Nutrition

Needs special care because of increased requirement of calories, minerals and vitamins in women with multiple fetuses.

### Prevention of Preterm Delivery

There is no evidence showing definite role of bed rest, cerclage and prophylactic tocolytics in prevention of preterm labor, but decreased physical activity after 20–24 weeks, helps in prevention of preterm labor.

### Timing of Delivery

Twins should be delivered by 36–37 weeks of gestational age (GA) because of two reasons. First, neonatal mortality and morbidity are increased after 37 or 38 weeks of GA and second, the fetal systems of MGs get matured by these dates. At present, there is great controversy exists regarding elective preterm delivery of monochorionic twins.

### Mode of Delivery

Due to increased maternal and neonatal complications in twins and high-order MGs, the delivery of higher-order MGs presents great challenges to obstetricians. Many clinicians preferred to deliver them by cesarean section. The decision depends on many other factors, e.g., fetal size, uterine discordance, prior uterine surgery and the experience and skills of obstetrician.

### OUTCOME

There is significant gap in the literature on the outcome of twin deliveries in developing countries where frequency of twin is high and research on multiple births is challenging.

### Perinatal Mortality

The perinatal mortality is over four times higher in twins and 4–9 times higher in triplets. According to a secondary analysis of the WHO global survey to analyze maternal and perinatal outcome in 23 low- and middle-income countries on twin gestation, it has been found that perinatal mortality is higher (7.1%) in twins than

singleton (2%). Increased perinatal mortality in twins may be due to increased intrauterine growth retardation, premature rupture of membrane, preterm deliveries and low birthweight and low Apgar scores. Stillbirth rate in twins is much higher than singleton mainly because of twin-to-twin transfusion syndrome. If one fetus dies in case of MZ twin, there is 20% risk of intrauterine death of co-twin. Mortality in MZ twin is higher than in DZ twins.

### Neonatal Mortality

Rates of neonatal mortality are GA specific and are similar for singletons, twins, and triplets. Prematurity and low birthweight are the predominating factors that increase the rates of mortality for multiple births. An increase in mortality rate was associated with monochorionic twin, especially after intrauterine fetal demise of one twin.

### Neonatal Morbidity

These complications are mainly related to prematurity and IUGR. As the gestation age decreases, incidence of respiratory distress syndrome increases. Compared with first-born twin, the second twin is at increased risk for respiratory distress syndrome, asphyxia and death. They are also associated with an increased risk of morbidities such as bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity and intraventricular hemorrhage.

### Long-term Morbidity

Neurological outcomes also appear to be worse in multiple births. When matched for GA at delivery, infants born from multifetal pregnancies have an approximately threefold increase in cerebral palsy. The prevalence of cerebral palsy in twins is 7.4%, compared with 1% in singletons. This is primarily because of increased risk of prematurity and low birthweight in multiple births and high risk for cerebral injury in twins with monochorionic placentation and in those with twin-to-twin transfusion syndrome.

### Counseling of Parents

Parents need special counseling because of emotional, financial as well as practical issues involved with MGs. They are often not only associated with problems of caring of two babies but also with the problems of MGs like prematurity, low birthweight and other related neonatal morbidities. In situations where one baby is more demanding, and needs more attention than other, mother should not feel guilty and should be reassured.

Physicians should try to discharge both the babies together; otherwise baby left behind may suffer in his relationship with parents. Mothers should be encouraged to exclusively breastfeed both the neonates, she should be educated about proper positioning and attachment and technique to feed two babies simultaneously. Simultaneous feeding is time efficient and stimulates the let-down reflex for weaker infant.

### Prognosis

Most of the multiple neonates are at high-risk, they need regular follow-up in high-risk follow-up clinic for routine screening of hearing, vision, growth and development. Early stimulation therapy should be started at term corrected gestation age.

#### IN A NUTSHELL

1. Multifetal pregnancies generate a medical, psychological and economic burden to families and society.
2. Increase in multiple pregnancies is a public health concern; they have 5–10 times higher risk of complications than do singletons.
3. There is higher incidence of maternal, fetal and neonatal mortality.
4. Frequent prenatal visits should be advised. Serial ultrasound examinations (every 3–4 weeks) must be done to detect any growth abnormalities. If diagnosed, additional antenatal ultrasonography is important to monitor the pregnancy, to detect growth discrepancies, zygosity, and the fetofetal transfusion.
5. Early diagnosis and management of maternal and fetal morbidities are most important for the better outcome of MGs.
6. Providing care to women and neonates with multiple pregnancies constitutes a challenge especially in developing countries to the obstetricians, and neonatologists because of limited resources and infrastructure.
7. Education and counseling of parents are very important for a better long-term outcome of MGs neonates.

#### MORE ON THIS TOPIC

- Blickstein I, Shinwell ES. Obstetric management of multiple gestation and birth. In: Martin RJ, Fanaroff AA, Walsh MC (Eds). *Fanaroff and Martin's Neonatal and Perinatal Medicine: Diseases of the Fetus and Infant*. 9<sup>th</sup> ed. Elsevier Mosby; 2011. pp. 343-50.
- Marquard K, Moley K. Multiple gestation and assisted reproductive technology. In: Gleason CA, Devaskar SU (Eds). *Avery's Diseases of the New Born*. 9<sup>th</sup> ed. Philadelphia: Saunders; 2012. pp. 60-6.
- Murdoch E, Smith G. Twins. In: Rennie JM (Ed). *Robertson's Textbook of Neonatology*. 5<sup>th</sup> ed. China: Churchill Livingstone Elsevier; 2012. pp. 395-404.
- Smits J, Monden C. Twinning across the Developing World. *PLoS One*. 2011;6:e25239.
- Vogel JP, Torloni MR, Seuc A, et al. Maternal and perinatal outcomes of twin pregnancy in 23 low- and middle-income countries. *PLoS One*. 2013;8:e70549.
- Wingate MS, Alexander GR, Boulet S, et al. Population based risk of perinatal mortality and morbidity among multiple births. In: Kurjak A, Chervenak FA (Eds). *Textbook of Perinatal Medicine*. 2<sup>nd</sup> ed. Informa UK Ltd; 2006. pp. 1560-8.



# Section 14 HIGH-RISK NEWBORN

**Section Editor** Siddarth Ramji

## Chapter 14.1

### Recognition of High-Risk Neonate

Niranjan Thomas, Vijay Gupta

*Who are high-risk neonates?* Neonates with an increased likelihood of mortality or morbidity because of any preconceptional, prenatal, natal or postnatal condition that interferes with normal birth process, impairs extrauterine transition or impedes postnatal growth and development are called high-risk newborns.

Anticipation and early intervention will prevent the development or progression of more serious illness and will minimize the risk of morbidity and mortality in this vulnerable group. Most high-risk infants can be identified before birth based on maternal history (e.g., maternal diabetes, multiple gestations, preterm labor, etc.), while others are identified in the delivery room based on clinical assessment (e.g., small for gestational age, large for gestational age, congenital malformations, respiratory distress syndrome, asphyxia, etc.) or in the postnatal wards/homes because of certain symptoms and signs (e.g., cyanosis, jaundice, poor feeding, etc.).

Risk factors (antenatal, intranatal and postnatal) that increase neonatal morbidity and mortality, making a newborn high-risk, and their effects on the fetus/newborn are summarized in **Tables 1 to 3**.

## ASSESSMENT AND DIAGNOSIS

### Antenatal Risk Factors

It is essential to obtain a complete maternal history to anticipate and prepare for a high-risk delivery. The prenatal record, current hospital chart and laboratory studies should be reviewed for known risk factors (**Table 1**). Maternal age of conception, nutritional status, personal social status, systemic diseases and infections predispose the fetus to preterm delivery, intrauterine growth restriction (IUGR) or intrauterine fetal demise. During the antenatal period, a high-risk fetus can be identified by several assessments and screening tests as discussed below:

#### Gestational Age Assessment

Gestational age assessment is important as prematurity contributes significantly to neonatal mortality and morbidity. This is usually based on the last menstrual period (LMP) or an early scan. Early ultrasound scan between 10 weeks and 12 weeks have the best predictive value (92%), while dating based on scans less than 20 weeks measuring the crown rump length (CRL) and biparietal diameter (BPD) provides a better estimate of gestational age as compared to LMP (predictive value 89–92%). However, after 24 weeks, reliable LMP provides a better estimate as compared to ultrasound. Early ultrasound scans using CRL precisely estimate

the gestational age with accuracy of  $\pm 5$  days and  $\pm 7$  days at 10 and 12 weeks, respectively. BPD estimates the gestational age with accuracy of  $\pm 10$  days,  $\pm 14$  days and  $\pm 21$  days at 20 weeks, 30 weeks and 40 weeks of gestation, respectively.

#### Ultrasound Screening

Ultrasonography is a useful tool in the assessment of the high-risk fetus and can be used at different times during the pregnancy as given below:

*First-trimester nuchal translucency screening* Ultrasonographic assessment of the fluid collected at the nape of the fetal neck is a sensitive marker for aneuploidy which can identify 76.8% of fetuses with trisomy 21, with false-positive rate of 4.2%.

*Anomaly screening* Ultrasound screening is performed at 20–22 weeks of gestation to rule out structural malformations in the fetus. In the absence of structural malformations, the markers associated with an increased risk of fetal growth restriction/IUGR and aneuploidies include bright or echogenic fetal bowel, single umbilical artery, isolated short femur (where the femur length is below the fifth percentile for gestational age but the abdominal circumference measurements and the estimated fetal weight are within the normal range).

*Doppler velocimetry* Umbilical artery Doppler evaluation after 16 weeks of gestation is useful in monitoring the pregnancy that is associated with maternal disease (hypertension or diabetes), uteroplacental insufficiency, and fetal growth restriction. The development of absent (AEDF) or reversed end-diastolic flow (REDF) (**Figures 1A and B**) in the umbilical artery is regarded as an ominous finding and is associated with fetal hypoxia and fetal acidosis with subsequent adverse perinatal outcome. The odds of increased perinatal mortality in pregnancies complicated by AEDF and REDF are 4.0 and 10.6, respectively. These indices in the umbilical artery will rise when 60–70% of the vascular tree has been altered. Fetal middle cerebral artery Doppler is presently the best tool for evaluating for the presence of fetal anemia in at risk pregnancy like Rh isoimmunization.

#### Serum Markers

Alteration in the levels of various serum and amniotic fluid markers (**Table 4**) during first and second trimester of pregnancy individualizes a woman's risk of carrying a high-risk fetus. Women carrying fetus with trisomy 21 can be identified using first- and second-trimester serum screen. In the first trimester (11–14 weeks) it is marked by decreased levels of pregnancy-associated plasma protein-A (PAPP-A) and increased levels of free beta-human chorionic gonadotropin ( $\beta$ -hCG). In the second trimester (15–20 weeks), triple test [ $\uparrow\beta$ -hCG,  $\downarrow$ alpha-fetoprotein and  $\downarrow$ unconjugated estriol (uE3)] has a sensitivity of about 60%, and the quadruple test ( $\uparrow\beta$ -hCG,  $\downarrow$ AFP,  $\downarrow$ uE3 and  $\uparrow$ inhibin A levels) has a sensitivity of approximately 67–76% in diagnosing a fetus with trisomy 21 in women less than 35 years of age. The sensitivity of triple test increases to more than 75% when performed in women more than 35 years.

**Table 1** Antenatal risk factors

<i>Maternal risk factors</i>	<i>Risk to fetus/newborn</i>
<i>Age at delivery</i>	
Age <16 years	IUGR, prematurity
Age >40 years	Chromosomal abnormalities, macrosomia, IUGR, blood loss (abruption or previa)
<i>Personal/social factors</i>	
Lower socioeconomic status	Prematurity, IUGR, infection
Illiteracy	Low birth weight
Smoking	Increased perinatal mortality, IUGR
Drug abuse and alcohol use	IUGR, fetal alcohol syndrome, withdrawal syndrome, sudden infant death syndrome
Physical or psychological stress	IUGR, low birth weight, prematurity
<i>Maternal nutrition</i>	
Poor diet/maternal malnutrition	IUGR, fetal demise in severe malnutrition
Obesity	Macrosomia, birth trauma, hypoglycemia
Vitamin D deficiency	Neonatal hypocalcemia, rickets
<i>Assisted reproductive technology</i>	
In vitro fertilization, intracytoplasmic sperm injection	Increases the risk of perinatal mortality, infant morbidity, prematurity, low and very low birth weight, increased risks for birth defects and cerebral palsy
<i>Obstetric history</i>	
Poor weight gain during pregnancy	IUGR
Short interpregnancy interval	Prematurity
Bleeding in early pregnancy	Stillbirth, prematurity
Uterine bleeding (abruption, placenta previa)	Premature delivery, asphyxia
Uterine or cervical anomaly	Prematurity
Trauma (acute, chronic)	Abruptio placentae, fetal demise, prematurity
Premature rupture of membranes	Infection/sepsis
Polyhydramnios	<i>Neurological anomalies:</i> Anencephaly, hydrocephalus, spina bifida and other central nervous system (CNS) disorders and Neuromuscular disorders. <i>Other congenital anomalies:</i> Duodenal atresia, cystic adenomatoid lung malformation, chylothorax, diaphragmatic hernia, omphalocele, gastroschisis, tumors (teratoma) <i>Problems with swallowing</i> (e.g., agnathia, any mass in the mouth, cleft lip or palate, esophageal atresia with tracheoesophageal fistula) <i>Other causes:</i> Hydrops fetalis, isoimmunization, anemia, cardiac failure, polyuric renal disease, large for gestational age, Infant of diabetic mother, Twin-twin transfusion (recipient), Syndromes (e.g., Achondroplasia, Klippel-Feil, trisomies 18 and 21), intrauterine infection e.g., TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex)"
Oligohydramnios	Fetal demise, placental insufficiency, IUGR, deformations, intrapartum distress, post-term delivery, fetal anomalies, twin-twin transfusion (donor), renal agenesis (Potter syndrome), urethral atresia, prune belly syndrome, pulmonary hypoplasia, amnion nodosum, intestinal pseudo-obstruction
Hyperthermia	Fetal demise, fetal anomalies
Previous pregnancy with intrauterine fetal demise, neonatal death, prematurity, respiratory distress syndrome, IUGR, congenital malformation, incompetent cervix, blood group sensitization, neonatal jaundice, neonatal thrombocytopenia, hydrops, inborn error of metabolism	Same with current pregnancy
<i>Medical disease: Systemic</i>	
Systemic cardiovascular or respiratory problems	Stillbirth, IUGR, prematurity
Hypertension (chronic or pregnancy-related)	Stillbirth, IUGR, prematurity, asphyxia
Cholestasis/liver disease	Preterm delivery, intrauterine fetal demise
Inflammatory bowel disease	Prematurity, IUGR
Renal disease	Stillbirth, IUGR, prematurity
Renal transplantation	Intrauterine growth restriction (uteroplacental insufficiency)

Contd...

Contd...

<b>Maternal risk factors</b>	<b>Risk to fetus/newborn</b>
Urinary tract infection	Prematurity, sepsis
Chronic periodontal disease	Preterm labor
Myotonic dystrophy	Neonatal myotonic dystrophy, congenital contractures, respiratory insufficiency
<i>Medical disease: Endocrinal</i>	
Diabetes mellitus	Congenital anomalies like: Congenital heart disease, limb abnormalities, CNS anomalies, small left colon syndrome, femoral hypoplasia-unusual facies syndrome, caudal regression syndrome Fetal macrosomia, birth trauma, stillbirth, hypoglycemia, hyperbilirubinemia, polycythemia, cardiomyopathy Respiratory distress syndrome (RDS) and growth restriction
Hypoparathyroidism	Fetal hypocalcemia, neonatal hyperparathyroidism
Hyperparathyroidism	Neonatal hypocalcemia and hypoparathyroidism
Graves' disease	Fetal and neonatal hyperthyroidism, intrauterine growth restriction, prematurity
Endemic goiter/hypothyroidism	Goiter, hypothyroidism, hyperthyroidism
Herpes gestationis (noninfectious)	Bullous rash, intrauterine fetal demise
<i>Medical disease: Hematological</i>	
Anemia (Hb < 6 g/dL)	Stillbirth, IUGR, hydrops, prematurity, asphyxia
Iron deficiency anemia	Lower mental and developmental scores in follow-up
Sickle cell anemia	Prematurity, IUGR, stillbirth
Idiopathic thrombocytopenic purpura	Thrombocytopenia, CNS hemorrhage
Alloimmunization (fetal platelet antigen sensitization)	Thrombocytopenia, CNS hemorrhage, stillbirth
Isoimmune neutropenia	Neutropenia
Isoimmunization (red cell antigens)	Stillbirth, hydrops, anemia, jaundice, hypoalbuminemia
Maternal hypercoagulable states	Fetal demise
Thrombocytopenia	Stillbirth, bleeding
<i>Medical disease: Autoimmune</i>	
Autoantibody against folate receptors	Neural tube defects
Myasthenia gravis	Transient neonatal myasthenia
Systemic lupus erythematosus	Congenital heart block, rash, anemia, thrombocytopenia, neutropenia, neonatal lupus
<i>Medical disease: Inborn errors of metabolism</i>	
Phenylketonuria (poorly controlled)	Microcephaly, retardation, congenital heart disease
<i>Medical disease: Neoplastic</i>	
Cervical neoplasia	Preterm premature rupture of membranes
Malignant melanoma	Placental or fetal tumor (metastasis)
<i>Fetal characteristics</i>	
Multiple gestation	IUGR, twin-twin transfusion syndrome, prematurity, birth trauma, asphyxia Monozygotic twins are 2–3 times more likely to have structural defects than singletons and dizygotic twins
IUGR	Fetal demise, congenital anomalies, perinatal depression, meconium aspiration, pulmonary hemorrhage, persistent pulmonary hypertension, hypotension, hypoglycemia, hypocalcemia, hypothermia, dyslipidemia, polycythemia, neutropenia, thrombocytopenia, acute tubular necrosis/renal insufficiency
Preterm delivery	RDS, patent ductus arteriosus, hyperbilirubinemia, intraventricular hemorrhage, retinopathy of prematurity, hypothermia, hypoglycemia, chronic lung disease, necrotizing enterocolitis, apnea of prematurity, other issues of preterm birth
Macrosomia/large for gestation	Congenital anomalies, birth trauma (cervical and brachial plexus injuries, phrenic nerve damage with paralysis of the diaphragm, fractured clavicles, cephalohematomas, subdural hematomas, and ecchymoses of the head and face), hypoglycemia, polycythemia
Post-term delivery/postmaturity syndrome	Stillbirth, asphyxia, perinatal depression, oligohydramnios, nonreassuring fetal heart rate tracing in labor, fetal macrosomia, birth injury, meconium aspiration, persistent pulmonary hypertension, hypoglycemia, hypocalcemia, and polycythemia
Abnormal fetal position/presentation	Congenital anomalies, birth trauma, hemorrhage, asphyxia

Abbreviation: IUGR, intrauterine growth restriction.

**Table 2** Intrapartum risk factors

<i>Maternal risk factors</i>	<i>Risk to fetus/newborn</i>
Maternal fever	Infection/sepsis
Maternal hypotension	Stillbirth, asphyxia
Rapid labor	Birth trauma, intracranial hemorrhage (ICH), retained fetal lung fluid/transient tachypnea
Prolonged labor >24 hours	Stillbirth, asphyxia, birth trauma
Prolonged second stage labor >2 hours	Perinatal depression
Cord prolapse	Stillbirth, asphyxia
Uterine tetany/rupture	Asphyxia
Meconium-stained amniotic fluid	Stillbirth, asphyxia, meconium aspiration syndrome, persistent pulmonary hypertension
Foul smelling of amniotic fluid/membranes	Infection
Obstetric analgesia and anesthesia	Respiratory depression, hypotension, hypothermia
Cesarean delivery	RDS, retained fetal lung fluid/transient tachypnea, blood loss
Elective LSCS < 39 weeks gestation	Increased rates of adverse respiratory outcomes, mechanical ventilation, newborn sepsis, hypoglycemia
<i>Fetal characteristics</i>	
Abnormality of fetal heart rate or rhythm	Congestive heart failure, heart block, hydrops, asphyxia
Persistent fetal tachycardia	Infection, maternal fever and medications
Fetal bradycardia	Congenital heart block associated with congenital heart malformation or maternal systemic lupus erythematosus
Loss of beat-to-beat variability in FHR	Depressed fetal central nervous system due to fetal immaturity, hypoxia, fetal sleep, or maternal medications
Decreased fetal movements	Fetal demise, asphyxia
<i>Placental anomalies</i>	
Small placenta	IUGR
Large placenta	Hydrops, maternal diabetes, large infant
Torn placenta and/or umbilical vessels	Blood loss
Short umbilical cord (< 40 cm)	Fetal akinesia sequence, respiratory insufficiency, pulmonary hypoplasia (Pena-Shokeir syndrome)
Abnormal attachment of vessels to placenta	Blood loss

Abbreviations: RDS, respiratory distress syndrome; IUGR, intrauterine growth restriction; FHR, fetal heart rate; LSCS, lower segment cesarean section.

**Table 3** Postnatal risk factors

<i>Risk factors: failed intrauterine to extrauterine transition</i>	
<i>Presenting features</i>	<i>Risk to newborn</i>
Respiratory distress	Respiratory morbidity like hyaline membrane disease, meconium aspiration syndrome, persistent pulmonary hypertension, air leak syndrome, early neonatal sepsis (pneumonia), transient tachypnea of newborn, chylothorax, pleural effusion, pulmonary hypoplasia, mechanical airway obstruction, perinatal asphyxia, congenital diaphragmatic hernia and other congenital lung malformations
Apnea soon after birth/crying	Extreme prematurity, congenital diaphragmatic hernia, pneumothorax, vagal stimulation (deep suction), perinatal asphyxia, neonatal seizure, inborn error metabolism
Cyanosis	Respiratory morbidities, critical congenital heart disease, methemoglobinemia, CNS malformations, perinatal asphyxia
Pallor/shock	Perinatal asphyxia, occult blood loss, myocardial dysfunction
Hypotonia	Perinatal asphyxia, neuromuscular disease, CNS malformation, inborn error metabolism
Low 5-min Apgar score	Prolonged transition (especially respiratory)
Low 10–15-min Apgar score	Perinatal depression and asphyxia, neuromuscular disorder
<i>Risk factors: congenital anomalies/birth injury</i>	
<i>Presenting features</i>	<i>Risk to newborn</i>
Caput succedaneum, cephalohematoma, subgaleal bleed	Birth injury

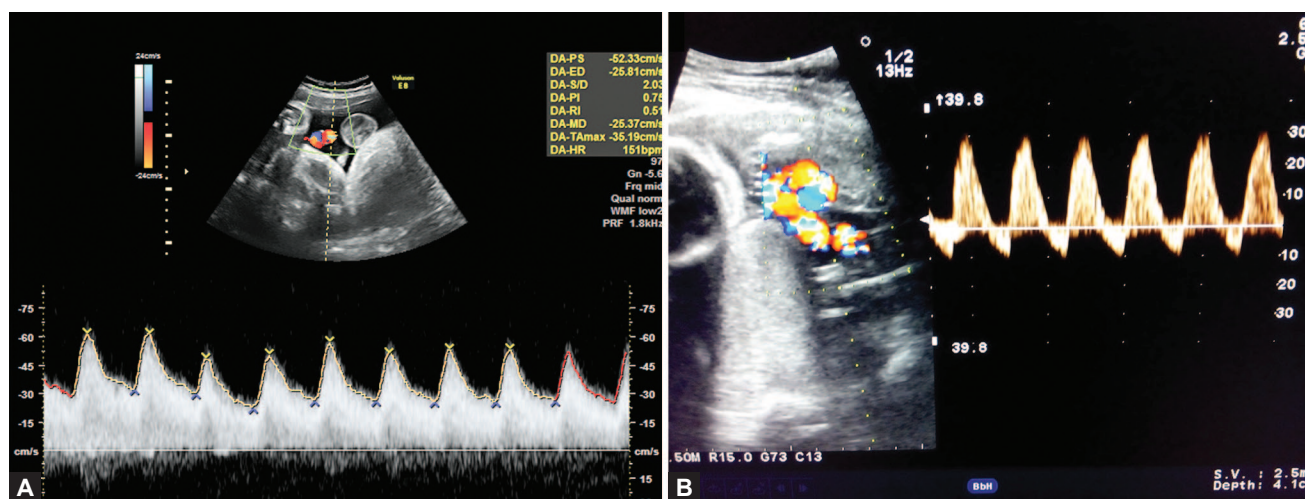
Contd...



Contd...

Dysmorphic features	Syndromes
Asymmetric crying facies	Congenital absence of the depressor anguli oris muscle (DAOM), facial palsy
Cyanosis improving with cry	Bilateral choanal atresia
Frothing	Tracheoesophageal fistula
Asymmetric Moro reflex	Erb's palsy, fracture clavicle, fracture humerus
"Frog" posture or generalized hypotonia	Congenital myopathy, severe HIE, inborn error of metabolism
Scaphoid abdomen	Congenital diaphragmatic hernia, meconium aspiration syndrome
Ambiguous genitalia	Congenital adrenal hyperplasia, disorders of sex development
Imperforate anus	Anorectal malformation
Single umbilical artery	IUGR, renal abnormalities
<b>Risk factors: neonatal morbidities</b>	
<i>Presenting features</i>	<i>Risk to newborn</i>
IUGR	Fetal demise, congenital anomalies, perinatal depression, meconium aspiration, pulmonary hemorrhage, persistent pulmonary hypertension, hypotension, hypoglycemia, hypocalcemia, hypothermia, dyslipidemia, polycythemia, neutropenia, thrombocytopenia, acute tubular necrosis/renal insufficiency
Preterm delivery	RDS, patent ductus arteriosus, hyperbilirubinemia, intraventricular hemorrhage, retinopathy of prematurity, hypothermia, hypoglycemia, chronic lung disease, necrotizing enterocolitis, apnea of prematurity and other issues of preterm birth
Hypothermia (temperature less than 95°F or < 35°C)	Sepsis, cold stress
Fever (temperature >100°F)	Sepsis, hypoxic ischemic encephalopathy, dehydration
Lethargy/poor suck/not feeding well	Sepsis, hypoglycemia, dyselectrolytemia, perinatal depression, hypoxic ischemic encephalopathy, inborn error of metabolism
Sharp weight loss	Dehydration, sepsis
Jaundiced within 24 hours of life	ABO, Rh, minor blood group incompatibility, polycythemia, G6PD deficiency, red cell membrane and enzyme defects, prematurity
Bulging anterior fontanel	Meningitis, hydrocephalus
Shrill cry/twitching	Sepsis, meningitis, intraventricular hemorrhage, neonatal seizures
Convulsions	Sepsis, meningitis, intraventricular hemorrhage, hypoglycemia, dyselectrolytemia, inborn error of metabolism
Pallor/shock	Concealed blood loss, shock, sepsis, hypoxic ischemic encephalopathy, anemia
Cyanosis	Circulatory failure, sepsis, critical congenital heart disease, hypoglycemia, methemoglobinemia
Apnea	Sepsis, neonatal seizures, hypoglycemia, dyselectrolytemia, extreme prematurity, hypothermia, hyperthermia, CNS malformation, hypoxic ischemic encephalopathy, anemia
Drizzling of saliva	Tracheoesophageal fistula, neonatal seizures, myopathies
Rapid or labored breathing or irregular respiration	Sepsis, pneumonia, aspiration, meconium aspiration syndrome, air leaks, transient tachypnea of newborn, circulatory compromise, congestive cardiac failure, hypoglycemia, hypoxic ischemic encephalopathy, inborn error metabolism
Grunting	Hyaline membrane disease, sepsis, pneumonia, aspiration, meconium aspiration syndrome, air leaks, circulatory compromise, congestive cardiac failure, hypoglycemia, hypoxic ischemic encephalopathy, inborn error metabolism
Abdominal distension, vomiting (bilious)	Sepsis, NEC, intestinal obstruction, volvulus/malrotation, meconium ileus, meconium plug, Hirschsprung disease, anorectal malformation
Sclerema	Sepsis
Bleeding from any sites	Hemorrhagic disease of newborn, sepsis, DIC, coagulopathy, thrombocytopenia
Edema	Renal failure, hydrops
Not passing urine within first 48 hours of life	Dehydration, obstructive uropathy, renal agenesis, renal failure
Not passing stools within first 24 hours of life	Passed in utero, meconium plug, anorectal malformation, hypothyroidism, Hirschsprung disease, intestinal obstruction/atresia

Abbreviations: CNS, central nervous system; IUGR, intrauterine growth restriction; RDS; respiratory distress syndrome; G6PD, glucose-6-phosphate dehydrogenase; NEC, necrotizing enterocolitis.



**Figures 1A and B** Umbilical artery Dopplers: showing (A) Normal flow and (B) Reverse end diastolic flow (REDF)

**Table 4** Maternal markers and risk to fetus

Maternal markers	Increased fetal risk
↑Amniotic fluid AFP and acetylcholinesterase (AChE)	Open neural tube defect
↑Serum AFP levels [ $>2.5$ MoM and $>3.5$ MoM for twins (15–20 weeks gestation)]	Neural tube defects (spina bifida, anencephaly, etc.) Abdominal wall defects (gastroschisis, omphalocele) Intestinal atresias (esophageal or intestinal obstruction) Renal anomalies, polycystic kidneys and renal agenesis Congenital nephrosis Osteogenesis imperfecta Congenital skin defects Cystic hygroma Cloacal exstrophy Pilonidal sinus Multifetal gestation Fetal demise Underestimated gestational age
↓Serum AFP levels (15–20 weeks of gestation)	Chromosomal trisomies Maternal diabetes Obesity Gestational trophoblastic disease Fetal demise Overestimated gestational age
↑β-hCG (10–20 weeks)	Trisomy 21
↓β-hCG (11–14 weeks)	Trisomy 13 and 18
↓PAPP-A (10–14 weeks)	Trisomy 21, 13, 18 or sex chromosomal abnormalities

Abbreviations: MoM, multiples of median; AFP, alpha fetoprotein; β-hCG, beta-human chorionic gonadotropin; PAPP-A, pregnancy-associated plasma protein-A.

### Monitoring of Fetal Well-being

**Fetal movements** Normal fetal movements are maternal perception of at least 10 fetal movements during 12 hours of normal maternal activity or at least ten fetal movements over 2 hours when the mother is at rest or at least four fetal movements in 1 hour when the mother is at rest and focused on counting. Periods of inactivity

more than 1 hour are unusual in a healthy fetus and should alert the physician to the possibility of fetal compromise.

**Nonstress test (after 32 weeks of gestation)** The nonstress test (NST) is performed by monitoring fetal heart rate (FHR) either through skin-surface electrodes strapped on to the maternal abdomen or using a Doppler ultrasonographic device. Uterine activity is simultaneously recorded using tocodynamometer, or palpation by trained personal, or the patient's report. It is based on the principle of reflex acceleration of FHR in response to fetal activity. A reactive NST is usually reassuring, with the risk of fetal demise being 3 per 1,000 in the next 7 days following the test. A nonreactive test is generally repeated later the same day or is followed by another test of fetal well-being like contraction stress test (CST) or an acoustic stimulation test (AST).

The criteria for a reactive test are as follows: (a) heart rate between 110 and 160; (b) normal beat-to-beat variability [5 beats per minute (bpm)]; and (c) two FHR accelerations of at least 15 bpm, lasting a total of 15 sec. Most NSTs are reactive within the first 20 min period, but an additional 20 min may be considered to account for fetal sleep cycle. A nonreactive test fails to meet these three criteria and there will be no acceptable acceleration (as defined by reactive NST) in 40 min period.

**Contraction stress test** The CST is based on the principle, that even brief reduction or elimination of intervillous perfusion during uterine contraction may result in brief hypoxia to the already compromised fetus resulting in FHR decelerations. A healthy fetoplacental unit has sufficient oxygen reserve to tolerate this brief hypoxic episode. If this fails, FHR begins to decelerate 15–30 sec after onset of the contraction, reaches its nadir after the peak of contraction, and does not return to baseline until after the contraction ends. This heart-rate pattern is known as a late deceleration or type II deceleration resulting from uteroplacental insufficiency.

Like NST, CST also monitors FHR and uterine contractions. A CST is considered completed if uterine contractions have spontaneously occurred within 30 min period with frequency of three within 10 min interval, lasting 40–60 sec each. Uterine contraction can be induced with intravenous oxytocin in absence of spontaneous contraction, when it is known as *oxytocin challenge test*.

A *CST is positive* if uterine contractions are associated with consistent late deceleration pattern. A CST is negative when at least three uterine contractions of at least 40 sec each, occur within a 10-min interval without associated late decelerations. The study is

considered hyperstimulated, if more than five uterine contractions occur in 10-min interval or each contraction last for more than 90 sec.

A *negative CST* is even more reassuring as compared to reactive NST, with the chance of fetal demise of approximately 0.4 per 1,000 within a week of negative CST. If a positive CST follows a nonreactive NST, the risk of stillbirth is about 88 per 1,000.

**Acoustic stimulation test** For a fetus showing a nonreactive NST, AST can be done by providing a brief exposure of vibroacoustic signal (devices emitting sound levels of approximately 80 dB at 80 Hz frequency for 1–3 sec) to the fetus. The sound emitting device called as artificial larynx is strapped over maternal abdomen to evoke FHR acceleration in response to fetal movements.

- **Reactive acoustic stimulation test:** Two FHR accelerations of at least 15 bpm, lasting a total of 15 sec, within 5 min after application of acoustic stimulus or an acceleration of at least 15 bpm above baseline lasting 120 sec.
- **Nonreactive acoustic stimulation test:** If after three applications of acoustic stimulation at 5-min intervals, no acceptable accelerations (as defined by reactive AST) occur for 5 min after the third stimulus.

Although the false-negative and false-positive rates (50–60%) are higher for an NST than a CST, it is easier to perform and therefore the method for first-line antenatal testing. The modified NST has become the initial testing procedure of choice, which comprises use of vibroacoustic stimulation during standard NST if no acceleration is noted in the preceding 5-min interval. The acoustic signal is repeated if 9 min have elapsed since the first acceleration (as reactive test is defined by the presence of at least two accelerations within 10 min interval). Vibroacoustic stimulation, thus reduces the rate of falsely worrisome NSTs and therefore adds to the specificity of the NST.

**Fetal biophysical profile** It consists of five components—the NST, fetal movements of flexion and extension, fetal breathing movements, fetal tone, and amniotic fluid volume (AFV). It is performed at 32–34 weeks of gestation for at risk pregnancies over a 30-min period and the presence of each component is assigned a score of two points for a maximum of 10 of 10. A modified biophysical profile refers to an NST and an amniotic fluid index.

A normal score is considered to be 8 of 10 with a nonreactive NST or 8 of 8 without the NST. Equivocal is 6 of 10 and abnormal is less than and equal to 4 of 10. This test assesses the presence of acute hypoxia (changes in the NST, fetal breathing, and body movements) and chronic hypoxia (decreased AFV). A normal fetal biophysical profile appears to indicate intact central nervous system (CNS) mechanisms, whereas factors depressing the fetal CNS reduce or abolish fetal activities. Thus, hypoxemia decreases fetal breathing and, with acidemia, reduces body movements. The biophysical profile offers a broader approach to fetal well-being than does the NST still allowing for a noninvasive, easily learned and performed method for predicting fetal compromise.

## Intrapartum Risk Factors

### Fetal Heart Rate Patterns

Fetal heart rate patterns reflect states of hypoxemia and subsequent acidosis in the fetus. The two common ways of FHR monitoring are cardiotocography and intermittent auscultation. **Cardiotocography** involves continuous monitoring via an electronic machine generating a print out of FHR and uterine contraction over a period of time. **Intermittent auscultation** of fetal heart sounds is usually done by a trained personal using stethoscope, handheld Doppler ultrasound device or by using a Pinard (special trumpet shaped device) over the mother's

abdomen. Reviews comparing the two methods do not find any significant difference of one over the other except that there was higher risk (20% more risk) of operative interventions in the electronic monitoring group as compared to intermittent auscultation in low-risk pregnancies. To be considered reassuring, a cardiotocograph tracing must have the following components:

- A baseline FHR of 110–160 bpm
- Absence of late or variable FHR decelerations
- Moderate FHR variability
- Age-appropriate FHR accelerations (two accelerations in 20 min of 15 beats above the baseline for 15 sec for  $\geq 32$  weeks' gestation, and 2 of 10 beats above the baseline for 10 sec for  $< 32$  weeks' gestation).

The FHR is interpreted with a three-tiered system as follows (**Figures 2A to D**):

- **Category I** (predictive of normal acid base status at that point of time): All of the following criteria must be present and if present, are predictive of normal acid-base status at that point of time:
  - Baseline heart rate: 110–160 bpm
  - Moderate variability
  - Absent late or variable decelerations
  - Present or absent early decelerations
  - Present or absent accelerations
- **Category II** (indeterminate): Includes all FHR's that are neither Category I nor Category III.
- **Category III** (predictive of abnormal acid-base status at the point of observation): These tracings are predictive of abnormal fetal acid-base status at the time of observation and need to be promptly evaluated. These include either of the following:
  - Absent baseline FHR variability and any of the following: recurrent late decelerations, recurrent variable decelerations, or bradycardia.
  - Sinusoidal pattern.

### Fetal Scalp pH

An intrapartum scalp pH above 7.20 with a base deficit less than 6 mmol/L is reassuring of fetal well-being.

**Digital stimulation of fetal scalp** Acceleration of FHR (15 bpm for 15 sec) from the baseline heart rate pattern in response to digital stimulation of fetal scalp in absence of uterine stimulation is a fairly reliable evidence of absence of fetal acidosis ( $\text{pH} > 7.2$ ) and is an alternative to fetal scalp pH determination.

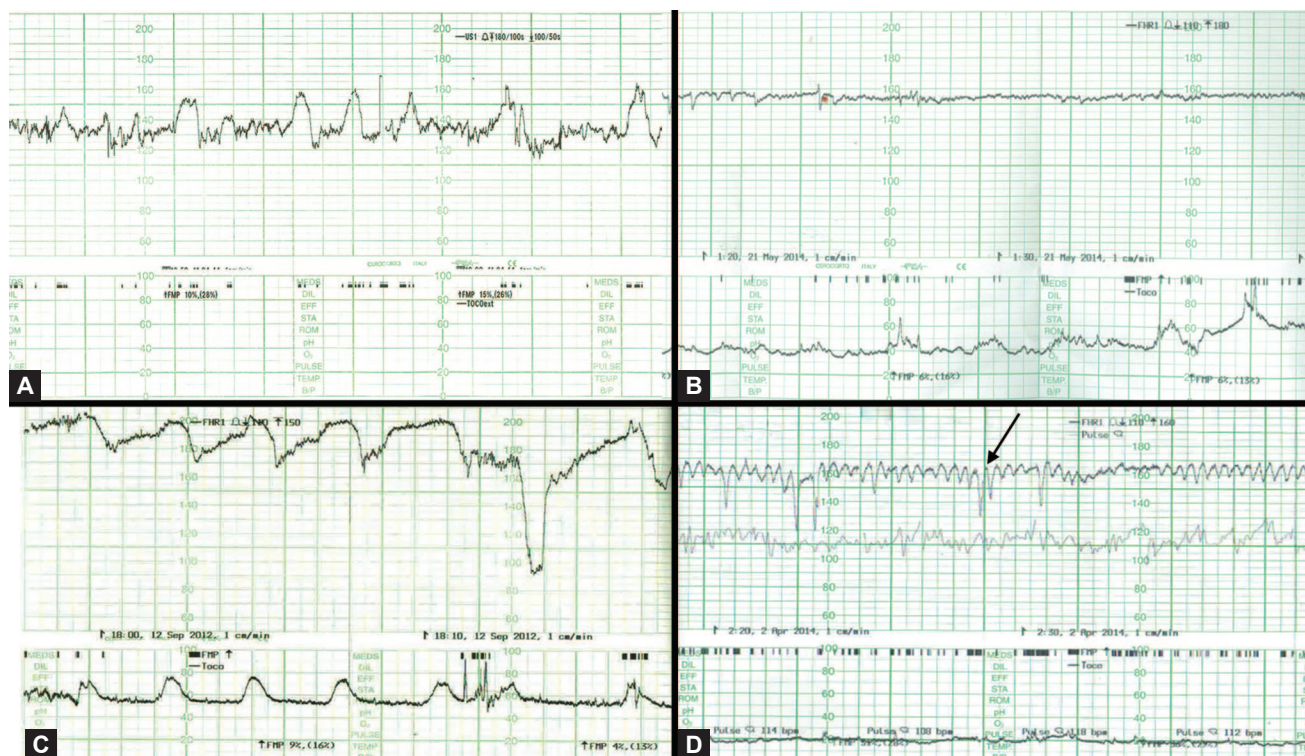
## Postnatal Risk Groups

Disorders of weight and gestation can be identified by the birth weight and gestational assessment soon after birth. Gestational age assessment can be done postnatally using the gestational assessment scales (New Ballards Score and Dubowitz scale) or based on the vascularity of lens using direct ophthalmoscopy. Postnatally, high-risk newborns can be identified at three important stages of examination (**Table 3**):

**Features suggestive of failed transition from intrauterine to extrauterine life** can be diagnosed soon after birth. A failed transition from fetal to newborn status may be due to inability to clear fetal lung fluid, decreased surfactant synthesis, inadequate functional residual capacity, elevated pulmonary vascular resistance, failure to increase systemic blood pressure after removal of the low-resistance placenta from the systemic circuit, persistence of fetal circulation and failure of shunt closure (ductus arteriosus and foramen ovale), or decreased pulmonary blood flow.

**Common congenital anomalies or signs and symptoms suggestive of birth injuries** could be identified after birth, after stabilization of cardiorespiratory status. Presence of *choanal*





**Figures 2A to D** (A) Category I CTG showing baseline FHR 130 bpm with moderate variability and frequent accelerations; (B) Category II CTG showing base FHR around 150–160 bpm with reduced variability with absence of accelerations and decelerations; (C) Category III CTG showing baseline FHR of 160–170 bpm with absent variability and recurrent late decelerations; (D) Category III CTG showing baseline FHR of 160–170 bpm for one of the twins (upper trace: arrow) and sinusoidal pattern

*atresia*, *trachea esophageal fistula* and upper gastrointestinal obstruction can be diagnosed by passing a nasogastric tube in presence of high-risk antenatal risk factors like polyhydramnios and sonographic abnormalities of gastric air (absent stomach bubble or double bubble sign). Inability to pass the nasogastric tube down the esophagus and presence of frothing may provide a clue to presence of tracheoesophageal fistula. The cyanosis with bilateral choanal atresia improves with crying. Baby presenting with apnea or respiratory distress soon after birth with scaphoid abdomen and right-sided heart sounds points toward the left sided congenital diaphragmatic hernia. Aspiration of more than 15–20 mL of gastric aspirate may be suggestive of *duodenal or upper gastrointestinal obstruction*. Palpable bladder with enlarged bilateral kidneys in a male baby points toward *posterior urethral valve*. *Developmental dysplasia of hip* in high-risk babies can be evaluated using Ortolani and Barlow test.

Neonatal morbidities like neonatal jaundice, infection, and manifestation of systemic diseases can be identified by detailed examination done within 24 hours of life and routine (daily) examination until discharge. Routine screening of well babies in the postnatal ward should include anthropometry, hearing screen, examination of red reflex, pulse oximetry screening and newborn screen for metabolic disorders (e.g., hypothyroidism, congenital adrenal hyperplasia, glucose-6-phosphate dehydrogenase deficiency, inborn errors of metabolism). Routine pulse oximetry screening after 24 hours of life (lower limb saturation < 95%) was noted to diagnose critical congenital heart disease with estimated sensitivity of 69.6%, and positive predictive value of 47.0% in a pooled study analysis.

### IN A NUTSHELL

1. Early recognition of high-risk antenatal, natal and postnatal factors will help identify these high-risk newborns which will then allow for early intervention.
2. Antenatal assessment includes gestational age assessment, ultrasonography, serum markers and assessment of fetal well-being using NST, CST, AST and biophysical profile.
3. During labor, the fetus must be closely monitored using the FHR patterns, scalp pH and FHR response to digital scalp stimulation.
4. Soon after birth, the baby is assessed to see if cardiorespiratory transition has been achieved. Subsequently, examination will help identify various congenital malformations/birth injuries and other neonatal morbidities.
5. Routine metabolic screen, universal hearing screen, and pulse oximetry screen are recent tools that are increasingly being used to identify high-risk babies before the onset of disease.

### MORE ON THIS TOPIC

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 101: Ultrasonography in pregnancy. *Obstet Gynecol.* 2009;113:451–61.  
 American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *Obstet Gynecol.* 2009;114:192–202.



- Cunniff C, American Academy of Pediatrics Committee on Genetics. Prenatal screening and diagnosis for pediatricians. *Pediatrics*. 2004;114:889-94.
- Driscoll DA, Gross S. Clinical practice. Prenatal screening for aneuploidy. *N Engl J Med*. 2009;360:2556-62.
- Hansen M, Kurinczuk JJ, Bower C, Webb S. The risk of major birth defects after intracytoplasmic sperm injection and in vitro fertilization. *N Engl J Med*. 2002;346:725-30.
- Marden D, McDuffie RS Jr, Allen R, Abitz D. A randomized controlled trial of a new fetal acoustic stimulation test for fetal well-being. *Am J Obstet Gynecol*. 1997;176:1386-8.
- Schenone MH, Mari G. The MCA Doppler and its role in the evaluation of fetal anemia and fetal growth restriction. *Clin Perinatol*. 2011;38:83-102.
- Tita ATN, Landon MB, Spong CY, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *N Engl J Med*. 2009;360:111-20.
- Vintzileos AM, Ananth CV, Smulian JC, et al. The impact of prenatal care on neonatal deaths in the presence and absence of antenatal high-risk conditions. *Am J Obstet Gynecol*. 2002;186:1011-6.
- Wiberg-Itzel E, Lipponer C, Norman M, et al. Determination of pH or lactate in fetal scalp blood in management of intrapartum fetal distress: randomised controlled multicenter trial. *BMJ*. 2008;336:1284-7.

## Chapter 14.2

# Birth Injuries

Neeraj Gupta

Injuries that are sustained during the process of birth (labor and delivery) are known as birth injuries. It also includes injuries related to intrapartum fetal monitoring. However, injuries sustained during amniocentesis, intrauterine transfusion or post-resuscitation is not included. Though there has been a reduction in the incidence of birth injuries with improved obstetric care, they still remain a significant cause of neonatal morbidity. Although many injuries are mild and self-limited, others are serious and potentially lethal. The knowledge about these injuries will help in their timely detection and early management, thus preventing physical and neurodevelopmental handicap. Moreover, the information about various predisposing risk factors may lead to their prevention.

Birth injuries are primarily of two types: those related to physical trauma during the process of birth (traumatic birth injuries) and those due to lack of oxygen (hypoxic-ischemic injury). Both these types of injuries can occur in isolation or in combination. This chapter focuses on the traumatic birth injuries. **Box 1** shows a comprehensive list of traumatic birth injuries highlighting the wide spectrum ranging from minor problems to severe injuries.

### EPIDEMIOLOGY

Birth injuries complicate around 2% of singleton vaginal deliveries and 1.1% of cesarean deliveries in developed world. According to National Neonatal-Perinatal Database 2002–2003, the reported incidence of birth injuries in India was 0.8% and 2.3% in intramural and extramural newborns respectively.

### ETIOLOGY

Various risk factors have been implicated in the causation of birth injuries. Discrepancy between fetal size (macrosomia, cephalopelvic disproportion and shoulder dystocia) or presentation (breech, face, brow and transverse) in relation to birth canal, presence of rigid pelvis (primiparous and old multiparous) or pelvic anomalies and the use of instruments (forceps and vacuum) are the usual factors resulting in majority of these injuries. Prematurity, prolonged labor and precipitous delivery are other risk factors. Cesarean section does not completely eliminate the risk; however, it is less as compared to vaginal delivery. In some cases the risk factors are not identifiable, making these injuries completely unpredictable and unavoidable.

### EVALUATION

Most of these injuries are detected immediately after birth or within first day of life. However, few of them [e.g., congenital muscular torticollis, subcutaneous fat necrosis (SFN)] are picked up late. A complete head to toe examination supplemented with detailed neurological examination primarily focusing on sensorium, symmetry of structure and function and complete range of motion rules out most of them.

### TYPES OF BIRTH TRAUMA

#### Soft Tissue Injuries

##### *Erythema, Abrasions and Lacerations*

These occur in the setting of forceps delivery or dystocia and are present at the site of instrument application or on presenting part

### BOX 1 Traumatic birth injuries

#### *Soft tissue injuries*

- Erythema, abrasions, lacerations
- Petechiae and ecchymosis
- Subcutaneous fat necrosis

#### *Head and neck injuries*

- Extracranial injuries
  - Scalp bruises and laceration
  - Chignon
  - Caput succedaneum
  - Cephalhematoma
  - Subgaleal hemorrhage
  - Skull fractures
- Intracranial injuries
  - Epidural hemorrhage
  - Subdural hemorrhage
  - Subarachnoid hemorrhage
  - Intraparenchymal hemorrhage
  - Intraventricular hemorrhage
  - Cortical contusion, diffuse axonal injury
- Sternocleidomastoid muscle injury

#### *Injuries to face*

- Facial fractures
  - Fractures and dislocations of facial bones
- Nasal injuries
  - Nasal septal dislocation
  - Nasal bone fracture
- Ocular injuries
  - Subconjunctival hemorrhage
  - External ocular muscles
  - Optic nerve
  - Retinal hemorrhage
- Ear injuries
  - Abrasion, lacerations and ecchymoses
  - Hematoma

#### *Nerve injuries*

- Facial nerve palsy
- Recurrent laryngeal nerve injury
- Spinal cord injury
- Phrenic nerve injury
- Brachial plexus injuries
  - Erb's palsy
  - Klumpke's paralysis
  - Total brachial plexus injury

#### *Bone injuries*

- Fracture of clavicle, ribs, humerus, femur
- Epiphyseal separation

#### *Intra-abdominal injuries*

- Rupture of liver
- Rupture of spleen
- Injury to adrenal gland

#### *Injuries related to intrapartum fetal monitoring*

- Injuries related to direct fetal heart rate monitoring
- Injuries related to fetal scalp blood sampling

respectively. These lesions resolve spontaneously and nothing needs to be done except maintaining local hygiene to prevent secondary infection. Lacerations may result following cesarean section. Superficial lacerations just require apposition of the margins with adhesive strips whereas the deeper ones require suturing.

#### *Petechiae and Ecchymosis*

They are commonly associated with breech delivery and tight nuchal cord. Early appearance, localized distribution, absence of bleeding from any other sites and no appearance of new lesions help in differentiating them from thrombocytopenia or

any other bleeding disorder. No treatment is required and they usually disappear within first week of life. Extensive ecchymosis may rarely result in significant hyperbilirubinemia necessitating phototherapy. Very rarely, the blood loss may be severe enough to cause anemia and shock.

### Subcutaneous Fat Necrosis

Subcutaneous fat necrosis of the newborn is an uncommon, transient, self-healing disorder of the adipose tissue that occurs primarily in term or post-term newborns. The exact cause is uncertain however, it is assumed to be due to ischemic injury under various circumstances such as meconium aspiration, birth asphyxia and trauma. SFN is characterized by indurated, erythematous to violaceous nodules and plaques on the back, arms, buttocks, thighs and cheeks (**Fig. 1**). Lesions generally vary in size from 1 cm to 10 cm. This condition is not recognized at birth unlike other birth injuries and usually presents during the first two weeks of life. This condition must be differentiated from sclerema neonatorum and cellulitis because prognosis is largely excellent and no active therapy is required. The lesions resolve spontaneously. The potential complications include hypercalcemia, hypertriglyceridemia, hypoglycemia and thrombocytopenia.



**Figure 1** Erythematous plaques over back and upper arms

Reproduced with permission: From Tzvi-Behr S, Megged O, Schlesinger Y, et al. Subcutaneous fat necrosis. *J Pediatr*. 2013;163:300. Copyright © 2013 Mosby, Inc.

## Head and Neck Injuries

### Extracranial Injuries

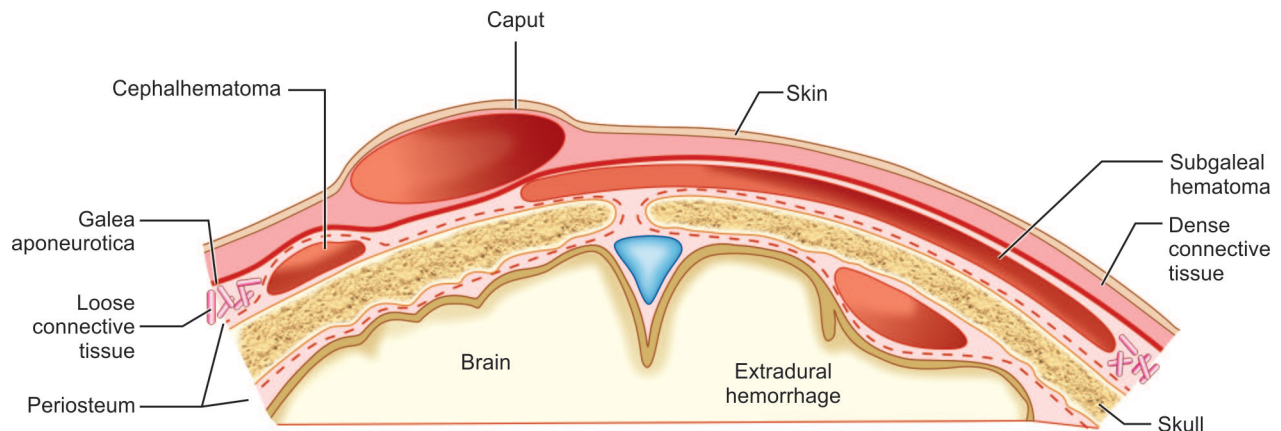
**Chignon** It is a temporary swelling over scalp after vacuum extraction. It occurs due to the vacuum force which draws the fetal scalp into the body of the cup resulting in characteristic mound of scalp tissue and edema. It is most prominent immediately after the removal of cup and typically resolves spontaneously within next 12–18 hours. No treatment is required.

**Caput succedaneum** It is a vaguely demarcated edematous swelling of the scalp above periosteum (**Fig. 2**) and is occasionally hemorrhagic. It is located over the presenting part during a vertex delivery and occurs after prolonged engagement of the fetal head or after vacuum extraction. It is present since birth and subsides in first 24–48 hours in contrast to cephalhematoma which appears later during the first 24 hours, does not cross midline and is limited by periosteal attachments. Occasionally it may be complicated by secondary infection and necrosis resulting in long-term scarring and alopecia.

**Cephalhematoma** It is a subperiosteal collection of blood (**Fig. 2**) that presents as well demarcated localized swelling over scalp with normal overlying skin. It commonly occurs over parietal bones (**Fig. 3**) and less often involves the occipital or frontal bones. It occurs due to the rupture blood vessels that traverse from skull to periosteum and does not cross suture lines due to the sharp limitation by periosteal attachments. It complicates 1–2% of deliveries and is more common with forceps use or vacuum extraction. The swelling is usually not apparent at birth due to slow subperiosteal bleeding and gradually develops over next 24 hours of life. It may be fluctuant and often the boundary is felt as slightly elevated ridge giving false sensation of central bony depression. Majority of the cephalhematomas resolves spontaneously over next few weeks. However, calcification of the hematoma can result in subsequent bony swelling which may persist for months together. Associated skull fracture may be present in 5–20% cases.

No treatment is required for uncomplicated cephalhematoma. Aspiration or incision is contraindicated due to the risk of secondary infection. Massive cephalhematoma may result in severe blood loss and significant hyperbilirubinemia necessitating appropriate treatment. Other complications include focal infection which may need surgical drainage and parenteral antibiotics as treatment.

**Subgaleal hemorrhage** It is a collection of blood between the periosteum of the skull and the galea aponeurotica (**Fig. 2**). This subgaleal space is a potential space which extends from the orbital



**Figure 2** Diagram depicting various layers of the scalp and their relationship to various hemorrhages

Reproduced with permission: From Colditz MJ, Lai MM, Cartwright DW, Colditz PB. Subgaleal hemorrhage in the newborn: A call for early diagnosis and aggressive management. *J Paediatr Child Health*. 2014. © John Wiley and Sons.



**Figure 3** Bilateral cephalhematoma in a 5 days old term male infant born by spontaneous vaginal delivery

ridges anteriorly to the nape of the neck posteriorly and to the level of the ears laterally resulting in accumulation of blood across the entire calvarium. Subgaleal hemorrhage occurs because of the traction on the scalp during deliveries which result in injury to the bridging veins between the scalp and dural venous sinuses. Risk factors include vacuum and forceps deliveries. It presents as a diffuse fluctuant swelling over the scalp. Progressive accumulation of blood may result in anterior displacement of ears and periorbital swelling along with pallor, hypotonia and shock. Early recognition and intense monitoring including serial hematocrit monitoring is crucial as the massive blood loss may result in high mortality (up to 25%). Treatment includes volume replacement with saline and packed red blood cells along with supportive care. Coagulopathy, if present, needs to be corrected. Phototherapy may be required for hyperbilirubinemia. Surgical drainage is occasionally required in case of unremitting clinical deterioration.

**Skull fractures** These may be linear or depressed and occur due to forceps application or forceful contact of the fetal skull against the maternal bony pelvis or uterine myoma during prolonged and difficult labor.

**Linear fractures** usually affect parietal bones and are often asymptomatic unless associated with intracranial hemorrhage (ICH). They are often associated with cephalhematoma. Uncomplicated linear fractures do not require any therapy and heal without any sequelae. Occasionally a linear fracture may be associated with dural tear leading to herniation of leptomeninges and brain parenchyma resulting in formation of leptomeningeal cyst. Rapid growth of the head may point towards the development of leptomeningeal cyst. Repeat skull radiographs within 8–12 weeks to detect early widening of the fracture line may help in picking up this complication at an early stage resulting in timely excision.

**Depressed fractures** usually involve parietal or frontal bones and appear as visible and palpable indentations in the skull. They are due to inward buckling of the resilient calvarial bones resulting in *ping pong* deformity without any discontinuity. They are also often asymptomatic unless associated with ICH. Skull radiograph shows inward buckling of bone. Cranial CT scan may be needed in symptomatic infants to detect associated intracranial injury. Asymptomatic fractures need no treatment, while symptomatic ones may need surgical intervention.

**Fracture at the base of skull** causes separation of the basal and squamous portions of the occipital bone resulting in severe hemorrhage and cerebral contusion. It occurs during breech

delivery and infant presents with shock, neurological abnormalities and leakage of cerebrospinal fluid from nose or ears. Supportive measures, blood replacement, antibiotics to prevent secondary infection of meninges and immediate neurosurgical intervention are required for successful outcome.

### *Intracranial Injuries*

The prevalence of symptomatic ICH in term infants is around 5.1–5.9 per 10,000 live births. Risk factors include macrosomia, nonvertex presentation, difficult instrumental delivery and bleeding diathesis. Most infants are symptomatic within first 24–48 hours after birth and present with neurological symptoms including seizure and apnea.

**Epidural/extradural hemorrhage** Epidural hemorrhage is very rare and occurs due to the injury to middle meningeal artery. The blood collects between the dura and inner table of the skull (**Fig. 2**). Infant can deteriorate quickly because of the arterial source of bleeding. Approximately half of the cases are associated with large cephalhematoma or linear skull fracture. Cranial CT establishes the diagnosis. Most patients require surgical drainage and prognosis is good except when associated with other ICH or brain injury.

**Subdural hemorrhage** Subdural hemorrhage (SDH) is the most common traumatic ICH in newborns with a prevalence of 2.9–10 per 1,000 live births. It is caused due to the rupture of draining veins and sinuses present in the subdural space. Forces during delivery may cause laceration of the tentorium cerebelli resulting in rupture of various sinuses including straight sinus, vein of Galen transverse sinus or occipital sinus resulting in infratentorial SDH. Supratentorial SDH is caused either due to the laceration of the falx cerebri resulting in rupture of inferior sagittal sinus or superficial veins present over the cerebral convexity. Clinical presentation depends upon the site and amount of blood accumulated. Infants with infratentorial SDH are more likely to present with features of raised intracranial pressure and can deteriorate very rapidly. Cranial CT confirms the diagnosis. Management is supportive and includes volume replacement, and treatment of seizures. Most infants do not require surgical intervention however, large SDH with features suggestive of brainstem compression or rapid neurological deterioration require prompt surgical drainage. Bleeding diathesis should be ruled out in large SDH. Prognosis is generally good however, depends upon the size of SDH along with any associated brain parenchymal injury. The potential complications include obstructive hydrocephalus and chronic subdural effusion.

**Subarachnoid hemorrhage** Subarachnoid hemorrhage (SAH) is caused due to the rupture of the bridging veins of the subarachnoid space or small leptomeningeal vessels. The most common symptom is seizures that often occur on the second day of life. Cranial CT confirms the diagnosis; however, MRI brain is more useful to determine coexisting ICH and other parenchymal pathology. Management is supportive and prognosis is good unless complicated by cortical or hypoxic injury. Occasionally, posthemorrhagic hydrocephalus may develop in large SAH warranting serial monitoring of head circumference and cranial ultrasonography to look for increasing ventricular size.

**Intraparenchymal hemorrhage** Primary traumatic intraparenchymal hemorrhage is uncommon in newborns and is more often due to the rupture of an aneurysm or coagulation disturbance. Cranial CT or MRI confirms IPH along with other associated cranial injuries. Management is largely supportive. Prognosis depends upon the location and size of the IPH along with gestational age of the infant.



### *Sternocleidomastoid Muscle Injury*

Injury to sternocleidomastoid muscle (SCM) results from abnormal pressure or trauma to the SCM during intrauterine or perinatal period resulting in hematoma and subsequent fibrosis and shortening. Most infants present during second and third week of life with a well circumscribed hard palpable mass of about 1–2 cm diameter in the middle part of SCM. Treatment includes active and passive stretching of the muscle several times a day to prevent torticollis. Most patients improve within 3–4 months.

## INJURIES TO FACE

### Facial Fractures

Facial fractures may occur due to delivery by forceps or during breech deliveries. The usual bones which are involved are maxilla, mandible and the lacrimal bones. Infants present with facial asymmetry along with edema, ecchymoses and crepitus. There may be associated respiratory distress with poor feeding. Appropriate radiograph confirms the diagnosis and cranial CT or MRI may be required to evaluate retro-orbital or cribriform plate disruption. Airway should be maintained and treatment should begin immediately in consultation with plastic surgeon, dental surgeon and otorhinolaryngologist. Prompt treatment is required because lacrimal and maxillary fractures begin to heal within 7–10 days and mandibular fractures within 10–14 days. Untreated fractures can lead to facial deformities, malocclusion and subsequent mastication problems.

### Nasal Injuries

The most common nasal injury is dislocation of the cartilaginous part of the nasal septum from the vomerine groove with a reported prevalence of 0.6–0.9% of all deliveries. The other injuries include fracture of the nasal bone, edema of the nasal passage and misshapen nose. All these injuries are caused due to the compressive forces during delivery. Infants may develop respiratory distress and cyanosis and examination may reveal deviation of the nose to one side. Septal dislocation can be differentiated from the more commonly occurring misshapen nose by a simple compression test. Application of pressure on the tip of the nose causes collapse of the nostril and the deviated nasal septum to become more prominent whereas no nasal deviation occurs in a misshapen nose. Nasal septal dislocation must be reduced within 3 days by an otorhinolaryngologist as untreated dislocations may result in increased risk of long-term septal and cosmetic deformity. Nasal fractures must also be treated promptly like facial bone fractures as they begin to heal within 7–10 days after injury.

### Ocular Injuries

Subconjunctival and retinal hemorrhages are common after vaginal deliveries and results from increased venous congestion during the process of birth. However, these lesions usually resolve spontaneously within 1–2 weeks and do not require any specific treatment. Other significant ocular injuries include lid lacerations, orbital fracture, lacrimal gland and duct injury, rupture of Descemet's membrane of the cornea (resulting in clouding of cornea and must be differentiated from congenital glaucoma), corneal abrasion, hyphema (blood in the anterior chamber), vitreous hemorrhage, optic nerve injury and injury to external ocular muscles. These injuries are caused due to inappropriate forceps placement, abnormal presentation or rarely due to displacement of fetal monitoring electrodes. Prompt evaluation and management by an ophthalmologist is required to prevent permanent damage.

### Ear Injuries

Ears get injured either during forceps delivery or due to fetal malposition. Superficial lacerations of the pinna may be sutured by a pediatrician. However, if cartilage is involved then otorhinolaryngologist should be consulted because of the risk of perichondritis and subsequent ear deformities. Hematoma of the pinna should be drained promptly because of its tendency to organize early leading to the formation of cauliflower ear. Temporal bone injury can cause middle and inner ear complications including hemotympanum and ossicular disarticulation.

## NERVE INJURIES

### Facial Nerve Injury

It is the most common peripheral nerve injury in neonates and occurs in 0.1–0.7% of live births. Prolonged pressure from the sacral promontory during intrauterine period or application of forceps during delivery causes compression of the peripheral portion of the nerve as it exits through the stylomastoid foramen or runs over the ramus of mandible resulting in facial nerve palsy. Though the paralysis is present since birth, it is usually detected on the first or second day of life. In peripheral injury, the entire side of the face is involved with affected side of the face being expressionless, absence of wrinkles over the forehead and flat nasolabial fold. Infant is unable to close the ipsilateral eyelid completely and the angle of the mouth deviates towards the unaffected side while crying. If only one of the peripheral branches of the facial nerve is involved then the paralysis is limited to the focal group of facial muscle namely forehead, eyelid or mouth. In central facial nerve palsy, paralysis is limited to lower two-thirds of the contralateral side of the face. Movement of the forehead and eyelid is preserved. Traumatic facial nerve injury needs to be differentiated from developmental or syndromic etiologies and congenital hypoplasia of depressor anguli oris muscle.

Treatment involves protection of the involved eye by patching and using artificial tears to prevent corneal injury. Most patients recover spontaneously within first 2 weeks of life. Surgical intervention is considered only after lack of resolution during 1 year of observation. In patients with no evidence of recovery, electrodiagnostic studies may be useful to predict prognosis.

### Recurrent Laryngeal Nerve Injury

It is caused due to excessive traction on the fetal head during breech delivery or after forceps application. The left nerve is more commonly involved than right one due to its longer course. Bilateral involvement is more common due to hypoxia or brainstem hemorrhage rather than trauma. Infants with unilateral involvement are often asymptomatic at rest but may develop inspiratory stridor, respiratory distress and hoarseness while crying. Bilateral involvement invariably presents with severe respiratory distress and cyanosis. Differential diagnosis of unilateral involvement includes laryngeal malformations. Unilateral involvement usually recovers spontaneously within 6 weeks. Frequent and small feeds may be required to decrease the risk of aspiration. Intubation may be required in cases of persistent respiratory distress. Bilateral involvement is usually severe and often requires intubation to support airway.

### Spinal Cord Injury

Spinal cord injuries are rare but catastrophic. These occur due to excessive longitudinal traction or rotation of the spinal cord during mid-forceps application or difficult breech extraction. The various spinal injuries include epidural hematoma, vertebral artery injuries, hematomyelia, spinal artery occlusion, and transection of the spinal cord. High cervical or brainstem injury often results

in stillbirth. Surviving infants may be in poor condition with respiratory failure and shock. Infants with upper or mid-cervical cord injury present with respiratory depression and apnea. The extremities are flaccid with absent deep tendon reflexes. There may be associated urinary retention and patulous anus. Injury to lower cervical and thoracic cord may be partly reversible but with long-term neurological sequelae. Differential diagnosis includes intracranial injury, congenital hypotonia, myelodysplasia associated with spina bifida occulta and neuromuscular diseases.

Ultrasonography is the diagnostic method of choice however; the initial suspicion of spinal injury may get delayed because of associated hypoxic-ischemic encephalopathy which clouds the clinical picture. Magnetic resonance imaging provides better visualization of the spinal cord and is the preferred modality. Treatment is supportive and involves neurosurgeons. If cord injury is suspected at the time of birth, the head, neck and spine should be immobilized. In general, the prognosis is poor and depends on the severity and the location of the spinal injury.

### Phrenic Nerve Injury

Phrenic nerve (nerve root- C3, C4 and C5) usually gets injured due to the hyperextension of the neck during breech or difficult forceps delivery. Most of the cases have unilateral involvement and three-fourth of the cases have associated brachial plexus injury. The infant may present with respiratory distress and cyanosis. Examination reveals decreased movement of the ipsilateral hemithorax and paradoxical breathing. Chest radiograph shows the elevation of diaphragm on the affected side. Initial treatment is supportive and includes airway care to prevent atelectasis and pneumonia. Ventilation may be required to support respiratory distress. Most patients recover in 1–3 months without any sequelae. Refractory cases require surgical plication of diaphragm.

### Brachial Plexus Injury

Brachial plexus injury is not uncommon with a prevalence of around 0.1–0.2% of all the births. It is caused due to the excessive traction on the cervical nerve roots during delivery. The potential risk factors include macrosomia, shoulder dystocia, difficult delivery, breech extraction and instrumental deliveries. Injury to the brachial plexus results in paralysis of the upper extremity. It manifests in three different forms depending on the nerve roots involved:

- **Erb-Duchenne (Erb's) palsy:** It is the most common form of brachial plexus injury and accounts for 90% of the cases. It results from injury to the C5 and C6 nerve roots of the upper trunk and occasionally involves C7. The upper limb is typically adducted and internally rotated at the shoulder joint, extended and pronated at the elbow joint with flexion of the wrist and fingers resulting in characteristic *waiter's tip* posture (**Fig. 4**). Moro's and biceps reflexes are absent, but grasp reflex is preserved. Phrenic nerve may also be injured in around 5% cases.
- **Klumpke's paralysis:** It results from injury to the C8 and T1 nerve roots and accounts for less than 1% of all the brachial plexus injuries. It involves intrinsic muscles of the hand and long flexors of the wrist and fingers. Grasp reflex is typically absent however biceps and radial reflexes are intact. There may be associated features of ipsilateral Horner syndrome (ptosis, miosis and enophthalmos) due to the involvement of sympathetic fibers which are embedded in T1 nerve root.
- **Total brachial plexus injury:** It involves all the nerve roots from C5 to T1 and accounts for 10% of the cases. The entire upper limb is flaccid with loss of all the reflexes (including grasp reflex) and absence of sensation.



**Figure 4** Waiter's tip posture of the right arm in Erb's palsy. Note the characteristic posture involving adduction and internal rotation at shoulder, extension at elbow, pronation of forearm and flexion of wrist and fingers

Reproduced with permission: From Chauhan SP, Yang LJ. Neonatal brachial plexus palsy—management and prognostic factors. *Semin Perinatol.* 2014;38:222–34. Copyright © 2014 Elsevier Inc.

Initial management is conservative and involves physical therapy involving passive range of motion exercises at all the joints to prevent contractures. This should be started after first week of life once the postinjury neuritis gets resolved. Prognosis depends upon the severity of nerve injury which ranges from neurapraxia (with rapid recovery) to nerve root avulsions (with no spontaneous recovery). Most (50–80%) infants recover spontaneously by 3 months of age. Infants with no recovery by 3–6 months of age are candidates for surgical intervention.

## BONE INJURIES

### Clavicular Fracture

It has been reported in up to 3% of the neonates. Most clavicular fractures occur during normal spontaneous vaginal delivery, however, the incidence increases in the presence of shoulder dystocia, macrosomia and breech delivery. Clavicular fracture may be complete or incomplete (greenstick). Incomplete fractures are usually asymptomatic at birth and are first detected after the appearance of an obvious swelling (callus) in the supraclavicular fossa during second week of life. Up to 40% of the clavicular fractures are not identified until after discharge from the hospital. The most common symptom at birth includes decreased movement of the ipsilateral arm. Examination may reveal crepitus, a palpable bony abnormality, obliteration of the supraclavicular depression due to the spasm of SCM and an asymmetric Moro's reflex. Diagnosis is confirmed by a radiograph (**Fig. 5**) which also helps in ruling out the humeral fracture. Treatment involves analgesics and immobilization of the arm. Recovery is complete without any sequelae.

### Fracture of the Humerus

It is the most common long bone which gets fractured at the time of birth. It typically occurs during difficult delivery of the extended arms in breech presentation and shoulders in the vertex presentation. Other risk factors include shoulder dystocia, macrosomia, cesarean delivery and low birth weight. Most fractures occur at the proximal third of the humerus. The first symptom is



**Figure 5** A full-term newborn via spontaneous vaginal delivery. Note the right clavicle fracture in the distal one-third in this newborn with meconium aspiration

*Reproduced with permission:* From Huisman TAGM, Hillenbrand CM, Tekes A, Pinto PS, Huisman TA. Birth-related injury to the head and cervical spine in neonates. *Magn Reson Imaging Clin N Am.* 2011;19:777-90. Copyright © 2011 Elsevier Inc.

decreased or absent movement of the involved limb. There may be associated localized swelling, deformity, crepitation, and increased pain with the movement of the involved limb. Moro's reflex may be sluggish or absent on the involved side. Greenstick fracture may be overlooked until a callus is noted. Diagnosis is confirmed by a radiograph. Treatment involves reduction of the displaced fracture followed by splinting for 2–4 weeks in an adducted position. Radial nerve injury may be associated with humeral fracture.

### Fracture of the Femur

It is the most common fracture of the lower extremity and involves the proximal half of femur. Risk factor includes breech delivery or cesarean section. Newborns with congenital hypotonia are also prone. Examination reveals an obvious deformity of the thigh along with decreased movements. Diagnosis is confirmed on radiograph. Treatment involves traction and suspension of both legs in a spica cast or Pavlik harness even if the fracture is unilateral. Prognosis is excellent.

### Epiphyseal Separation

These are rare injuries and occur due to the vigorous pulling of an extremity at the time of birth. The upper femoral and humeral epiphyses are most often involved and get separated from the underlying metaphysis. It is important to differentiate epiphyseal separation from the dislocations as the management differs. Dislocations especially of the hip and knee joints are due to intrauterine positions rather than trauma at the time of birth. Decreased movement of the involved extremity along with swelling and tenderness of the overlying soft tissue is the usual presentation in epiphyseal plate separation unlike dislocations. Diagnosis is confirmed on ultrasonography because epiphysis is not ossified at birth. Treatment involves immobilization for 10–14 days. Severe displacements may result in significant growth disturbance and permanent deformity of the involved extremity later on in the life.

### Fracture of the Ribs

These are extremely rare and occur when the anterior shoulder is impacted behind the symphysis pubis and the other shoulder tries to descend resulting in compression of the fetal thorax. These are usually asymptomatic and are detected when a chest radiograph is done for other reasons including suspected clavicular fracture or respiratory distress. No specific treatment is required and recovery is excellent.

### INTRA-ABDOMINAL INJURIES

Intra-abdominal injuries are rare and may involve liver, spleen, kidneys and adrenal gland. These injuries occur as a result of direct trauma, compression of the chest against solid organs or tearing of ligamentous insertion of liver and spleen during delivery. Ultrasonography is the best bedside modality to diagnose these injuries; however CT may be required in selective cases. Management includes restoration of blood volume and correction of underlying coagulopathy. Laparotomy is required in refractory cases who do not improve on conservative management.

### Hepatic Injury

Liver is the most frequently injured intra-abdominal organ. Injury varies from asymptomatic subcapsular hematoma and laceration to complete rupture resulting in rapid death. Subcapsular hematoma may present with nonspecific signs of blood loss including pallor, tachycardia, tachypnea, pathological jaundice and poor feeding. A mass may be palpable in the right upper quadrant of the abdomen. Serial hematocrits may suggest blood loss. Rupture of the enlarging subcapsular hematoma causes circulatory collapse and hemoperitoneum resulting in abdominal distension and discoloration of the overlying abdominal skin.

### Splenic Injury

The presentation is similar to hepatic injury. Occasionally, there may be a palpable mass in left upper quadrant with abdominal radiograph revealing medial displacement of the gastric air bubble.

### Adrenal Injury

The relatively large size along with increased vascularity of the adrenal glands in newborns may contribute to this injury. 90% of adrenal hemorrhages are unilateral and involves the right sided gland. There may be associated features of adrenal insufficiency in form of vomiting, diarrhea, dehydration, hypoglycemia and refractory shock apart from features of blood loss and hemoperitoneum. A flank mass may be palpable and one needs to consider neuroblastoma and Wilms tumor as possible differential diagnosis in such cases. Treatment includes steroid replacement apart from conventional management as in hepatic and splenic injury.

### INJURIES RELATED TO INTRAPARTUM FETAL MONITORING

#### Injuries Related to Direct Fetal Heart Rate Monitoring

Electrodes placed on the fetal scalp or presenting part for fetal heart rate monitoring can cause superficial abrasions or lacerations at the site of placement of an electrode. Occasionally, facial or ocular trauma may result from malpositioned electrode. These injuries require no specific therapy beyond local treatment.

### IN A NUTSHELL

1. Birth injuries constitute an important preventable cause of physical and neurological handicaps.
2. Important risk factors that increase the risk of birth injuries include macrosomia, breech presentation, instrumental vaginal delivery, shoulder dystocia and maternal pelvic anomalies.
3. The most frequent traumatic birth injuries are soft tissue injuries with laceration being the most common injury associated with cesarean section.
4. Most extracranial injuries resolve spontaneously except subgaleal hemorrhage which may result in massive blood loss leading to shock and death. Skull fractures are usually benign except large depressed fractures and fracture involving the base of the skull, both of which may prove fatal.
5. Intracranial injuries include epidural, subdural, subarachnoid, intraparenchymal and intraventricular hemorrhage. The decision for neurosurgical intervention is based upon the clinical condition of the patient including evidence of increased intracranial pressure, and the nature and size of the injury.
6. The most common peripheral nerve injury is facial nerve injury and most patients recover spontaneously within first two weeks of life. Although spinal cord injuries are rare, they generally have a poor prognosis due to high mortality rate and increased chances of permanent neurologic impairment among the survivors.
7. Fractures due to birth trauma may involve ribs, clavicle, humerus and femur. These require immobilization and generally resolve within two to four weeks with excellent long-term prognosis.
8. Intra-abdominal injuries are rare and may involve liver, spleen, kidneys and adrenal gland. Their presentation and management varies depending upon the degree of internal bleeding.

### Injuries Related to Fetal Scalp Blood Sampling

Hemorrhage and breakage of the blade inside the scalp are the known complications associated with fetal scalp blood sampling. Local pressure and occasionally suturing is required to treat hemorrhage. The broken blade inside the fetal scalp needs to be removed soon after delivery to prevent secondary infection.

### MORE ON THIS TOPIC

- Doumouchtsis SK, Arulkumaran S. Head trauma after instrumental births. *Clin Perinatol*. 2008;35:69-83.
- Moczygemba CK, Paramsothy P, Meikle S, et al. Route of delivery and neonatal birth trauma. *Am J Obstet Gynecol*. 2010;202:361.
- Rosenberg AA. Traumatic birth injury. *Neoreviews*. 2003;4:e270-6.
- Uhing MR. Management of birth injuries. *Clin Perinatol*. 2005;32:19-38.
- Yang LJ. Neonatal brachial plexus palsy—management and prognostic factors. *Semin Perinatol*. 2014;38:222-34.



## Chapter 14.3

# Jaundice in the Newborn

Sheila S Mathai, Kannan Venkatnarayan

Jaundice is the visible manifestation of yellowness of the skin and sclera due to elevated serum bilirubin levels. It is seen in neonates when the serum bilirubin levels exceed 5–7 mg/dL (86–119  $\mu$ mol/L). Jaundice is seen first on the skin rather than the sclera in neonates as the eyes are difficult to examine in a baby. Hyperbilirubinemia typically refers to serum bilirubin levels beyond the normal range. Approximately, 70–80% of babies develop some jaundice during the early neonatal period, due to physiological hyperbilirubinemia. Though this is self-limiting in most cases without treatment, severe hyperbilirubinemia can occur due to various reasons in babies. Bilirubin is neurotoxic in neonates and healthy babies can sometimes sustain irreversible brain damage if hyperbilirubinemia is not managed promptly. Adverse consequences include the classic manifestations of kernicterus, isolated auditory impairment or subtle, processing disturbances.

## EPIDEMIOLOGY

An increased incidence of hyperbilirubinemia is associated with risk factors like racial, genetic, familial, maternal and neonatal factors. In India, a higher incidence is seen in Western, Northwestern and Eastern regions. Reasons for such racial variations are not clear and could include genetic and environmental traits affecting red blood cell (RBC) membrane stability and the prevalence of conditions such as glucose-6-phosphate dehydrogenase (G6PD) deficiency in the community. Recently, the gene for the enzyme responsible for bilirubin conjugation, uridine diphosphate glucuronosyltransferases 1A1 (*UGT1A1*), located on chromosome 2, along with genetic analysis of the *G6PD* genes, have thrown new light on the understanding of racial differences and familial causes of hyperbilirubinemia. Specific mutations affecting the promoter (noncoding) region of the amelogenesis imperfecta (AI) exon of the gene, such as increase in TATA repeats (TATA box mutation), is associated with hyperbilirubinemia in Gilbert syndrome. This mutation in isolation is benign but if associated with mutations in the *G6PD* gene has been found to markedly increase the risk for hyperbilirubinemia in Indian neonates. The Crigler-Najjar syndromes are usually caused by one or more mutations in any of the five exons of the *UGT1A1* gene that result in almost absence of the conjugating enzyme activity (Type 1) or severely reduced but phenobarbital-inducible enzyme activity (Type 2).

## BILIRUBIN METABOLISM

Bilirubin is the by-product of heme break down, 75% of which is generated from RBC and the rest from ineffective erythropoiesis, tissue heme and other heme proteins. The heme is oxidized to biliverdin in the reticuloendothelial system by heme oxygenase and subsequently reduced to bilirubin by biliverdin reductase. The former reaction results in release of carbon monoxide (CO) and iron (which is reutilized). Catabolism of one mole of hemoglobin results in the production of one mole each of CO and bilirubin. Bilirubin, in the unconjugated form, is nonpolar and insoluble in water but very lipophilic. In physiological quantities, it is a natural antioxidant and the so-called physiological hyperbilirubinemia of the newborn may actually have undocumented benefits. It is bound with albumin which prevents it from crossing the blood-brain barrier and entering the central nervous system. Approximately

7–8 mg of bilirubin can bind to 1 g of albumin. Bilirubin exists in the plasma in four forms: unconjugated bilirubin bound to albumin, which forms the major, conjugated bilirubin, which exists in the mono and diglucuronide forms, free, unbound, unconjugated bilirubin and  $\delta$ -fraction which is only found in prolonged states of conjugated hyperbilirubinemia, wherein conjugated bilirubin is covalently bound to albumin. Albumin-bound bilirubin is taken up by hepatocytes and bound to intracellular Y proteins (ligandins) for transportation to the smooth endoplasmic reticulum. Here the unconjugated bilirubin (indirect) is converted to water-soluble, polar, conjugated bilirubin, which is excreted into the biliary canaliculi by active transport. It enters the intestine and is excreted after conversion to stercobilin by gut bacteria. The intestine contains the enzyme  $\beta$ -glucuronidase which can unconjugate bilirubin resulting in it getting reabsorbed and delivered back to liver (enterohepatic circulation of bilirubin). The applied aspects of bilirubin metabolism are mentioned in **Table 1**.

## ETIOLOGY

### Physiological Jaundice

A relatively lower life span of RBCs, increased RBC mass, immature conjugation of bilirubin, with higher levels of monoglucuronide rather than diglucuronide forms, paucity of intestinal bacteria, enhanced  $\beta$ -glucuronidase activity in the gut and decreased motility of intestines, all contribute to the physiological jaundice of the newborn. Typically, this results in total serum bilirubin (TSB) levels of up to 10–14 mg/dL between 72 hours and 120 hours of life followed by a decline to normal by 7–10 days of life. This physiological hyperbilirubinemia is exaggerated in pretermers. Babies with physiological jaundice are essentially well and do not require treatment. Any other pattern of hyperbilirubinemia should be considered pathological unless proved otherwise. Common causes of pathological, unconjugated hyperbilirubinemia are given in **Box 1**. The term exaggerated physiological jaundice is sometimes used to describe a condition wherein the serum bilirubin briefly reaches phototherapy (PT) levels but no definite cause is found and the baby remains well. This may be seen in babies with marginal polycythemia, hidden subcutaneous blood collections or due to unknown reasons.

### Breastmilk and Jaundice

Breastfeeding, compared to formula feeding, is associated with an increased incidence of jaundice. Almost 13% of breastfed babies versus 4% of formula fed babies have TSB levels of 12 mg/dL or higher with 2% having levels exceeding 15 mg/dL. Two separate patterns of jaundice in breastfed infants are described: breastfeeding jaundice and breastmilk jaundice and it is important to distinguish between them (**Table 2**). Current consensus is not to interrupt breastfeeding irrespective of jaundice.

### Hemolytic Disease of Newborn

The most common cause of hemolysis is due to isoimmune hemolytic disease caused by blood group incompatibility between mother and fetus. Rh and ABO isoimmunization are the most common.

### Rh Incompatibility

While Rh hemolytic disease of newborn (Rh-HDN) has almost been eliminated in the developed world due to use of anti-D IgG combined with aggressive fetal surveillance, this disease is still a major burden in developing countries including India. The estimated annual number of Rh-HDN cases occurring in India is approximately 56,700. The Rh-negative mother is sensitized to the Rh antigen present on the fetal RBCs, due to fetomaternal

**Table 1** Applied aspects of bilirubin metabolism

<i>Steps in bilirubin metabolism</i>	<i>Relevance</i>	<i>Application in clinical practice</i>
Heme breakdown results in bilirubin production	Neonates have a high RBC mass and lower life span of RBC than adults (90 versus 120 days) Conditions associated with hemolysis results in high bilirubin load (1 g hemoglobin yields approximately 35 mg of bilirubin)	Partly explains physiological hyperbilirubinemia  Conditions such as G6PD deficiency, Rh isoimmunization, ABO incompatibility, polycythemia and extravascular blood accumulation are considered risk factors for severe hyperbilirubinemia In acute hemolysis, both rate of fall of packed cell volume (PCV) and rate of rise of serum bilirubin considered for need of exchange transfusion
Heme breakdown to biliverdin is mediated by heme oxygenase (HO) and CO is released as by-product	Rate of production of carbon monoxide directly correlates with bilirubin production Blockage of CO activity can lead to reduced production of bilirubin	End tidal carbon dioxide (EtCO <sub>2</sub> ) estimation by breath analyzer has been studied as a novel tool to assess at-risk babies for hyperbilirubinemia Use of metalloporphyrins (tin mesoporphyrin) has been tried as a modality of treatment for neonatal hyperbilirubinemia
Bilirubin is transported by binding to albumin	Bilirubin bound to albumin is safe and does not enter CNS as it cannot cross the blood-brain barrier Preterm have low albumin levels	High rates of bilirubin production saturate the albumin sites, thus decreasing the risk of entry of unbound, unconjugated bilirubin into the brain Unconjugated bilirubin is highly lipophilic and deposits in the brain resulting in tissue injury which may be permanent Risk of neurotoxicity is directly proportional to molar ratio of bilirubin to albumin
Bilirubin is taken-up by hepatocytes	Cytoplasmic protein ligandin (Y protein) transports bilirubin to smooth endoplasmic reticulum (SER)	Phenobarbital induces ligandin protein formation as well as proliferation of SER and hence has a therapeutic role
Unconjugated bilirubin (UCB) is conjugated by UDPGT1A in SER to conjugated bilirubin (CB)	Conjugation is an important step to convert bilirubin into a water-soluble, nontoxic compound	The UDPGT enzyme activity is less in preterm babies and varies with population, depending on its genetic expression
Conjugated bilirubin is excreted in bile by stools. CB can be converted to UCB by intestinal enzyme $\beta$ -glucuronidase, which is then resorbed	Reabsorption of UCB from GI tract and delivery back to liver for reconjugation is called enterohepatic circulation	Conditions causing slow clearance of meconium from intestine (such as pyloric stenosis, hypothyroidism, and intestinal atresias) account for enhanced enterohepatic circulation Breastmilk has significant $\beta$ -glucuronidase activity

*Abbreviations:* GI, gastrointestinal; CO, carbon monoxide; UDPGT, uridine diphosphate glucuronosyltransferase; G6PD, glucose-6-phosphate dehydrogenase; RBC, red blood cell.

hemorrhage which may be as little as 0.1 mL. Major sensitization occurs during delivery. The initial maternal antibody response is IgM which does not cross the placenta, but the later produced IgG antibodies cross the placenta and attach to the fetal Rh antigen-positive cells, making them susceptible to destruction in the reticuloendothelial system. Depending on the degree of destruction, manifestations may range from hydrops fetalis, due to severe anemia and congestive cardiac failure (25%) or rapid rise in bilirubin soon after delivery to no symptoms at all (15–20%). The degree of sensitization in the mother depends on the antigenicity of fetal RBCs, the specific antigen involved (D is more antigenic than C or E Rh-antigens) and the amount of fetomaternal hemorrhage. It is also likely to be more in later pregnancies. Concomitant presence of ABO incompatibility reduces the chances of Rh isoimmunization due to premature destruction of fetal RBCs by maternal ABO system. With the development of fetal anemia, middle cerebral artery peak systolic velocity (MCA-PSV) increases. Measurement of this by antenatal fetal Doppler can determine the severity of the disease, with values more than 1.5 multiples of median (MoM) for gestational age being an indication for in utero blood transfusion. The other means of in utero assessment remains the optical density measures of amniotic fluid for bilirubin with plotting on Liley and Queenan charts.

### **ABO Incompatibility**

This occurs due to maternal anti-A or anti-B antibodies reacting with fetal RBC antigen and typically occurs with maternal O blood group,

as antibodies produced in them are of IgG type whereas other blood group individuals produce IgM antibodies which do not cross the placenta. Though the mechanism of disease is similar to Rh-HDN, the disease due to ABO incompatibility is generally milder and presents later. This is probably due to the ubiquitous nature of AB antigens resulting in a relatively weaker antibody response.

### **Minor Blood Group Incompatibility**

Isoimmunization against Kell, Kidd, Lutheran and other red cell antigens also rarely cause neonatal jaundice. They should be suspected in babies presenting with hyperbilirubinemia and anemia suggestive of hemolysis within the first 24 hours of life with no setting for Rh or ABO incompatibility but with positive direct Coombs test.

### **Red Blood Cell Enzyme Abnormalities**

Glucose-6-phosphate dehydrogenase deficiency is the most common cause in this category and can result in severe hyperbilirubinemia. The disease is widely prevalent in many parts of the world such as Greece, Africa and East Asia. In India, the incidence is high, with 13 different biochemical variants, and ranges from 0% to 27%. It is seen in higher frequency in certain tribals and minority communities. In the absence of G6PD, the pentose phosphate pathway cannot generate nicotinamide adenine dinucleotide phosphate (NADPH), which is an important source of protons that are required for the generation of reduced glutathione, an antioxidant. In G6PD deficiency, RBCs are unable

**BOX 1 Causes of unconjugated hyperbilirubinemia**

- A. *Excessive production of bilirubin*
  1. *Blood group incompatibility*
    - a. Rh isoimmunization
    - b. ABO incompatibility
    - c. Minor blood group incompatibility
  2. *Red blood cell enzyme abnormalities*
    - a. Glucose-6-phosphate dehydrogenase deficiency
    - b. Pyruvate kinase deficiency
  3. *Red blood cell membrane defects*
    - a. Hereditary spherocytosis
    - b. Elliptocytosis
    - c. Poikilocytosis
  4. *Extravascular blood breakdown*
    - a. Cephalhematoma, subgaleal bleed
    - b. Tissue bruising
    - c. Fractures
  5. *Polycythemia*
  6. *Sepsis*
- B. *Impaired conjugation*
  1. *Hormonal deficiency*
    - a. Hypothyroidism
    - b. Hypopituitarism
  2. *Disorders of enzyme/inhibitors of enzyme*
    - a. Crigler-Najjar syndrome type I
    - b. Crigler-Najjar syndrome type II (Arias disease)
    - c. Gilbert disease
    - d. Lucey-Driscoll syndrome
    - e. Breastmilk jaundice
- C. *Enhanced enterohepatic circulation*
  1. Intestinal obstruction, pyloric stenosis
  2. Ileus, meconium plugging, cystic fibrosis
  3. Breastfeeding jaundice

to tackle oxidant stresses such as those induced by sepsis, drugs and chemicals. G6PD enzyme activity is heterogeneous in deficient neonates with five levels of activity: Class I, severe deficiency; II, severe deficiency with 1–10% residual enzyme activity; III, moderate deficiency with 10–60% residual enzyme activity; IV, normal enzyme activity at 60–150%; and V, increased enzyme activity at more than 150%. Hyperbilirubinemia in these neonates is a manifestation of close interaction of various genotypic and phenotypic factors, such as late preterm, sepsis, dehydration, exposure to drugs and TATA box mutations of the *UGT1A1* gene.

**NEUROTOXICITY OF BILIRUBIN**

Unconjugated bilirubin can cross the blood-brain barrier due to many factors. These include alterations in the bilirubin-binding capacity of albumin and other proteins and disruption of the blood-brain barrier due to underlying conditions like asphyxia, meningitis or acidosis. Increased bilirubin production can overwhelm the normal buffering capacity of the blood and result in the production of bilirubin acid, which is highly neurotoxic. Unconjugated bilirubin is toxic to a plethora of neural cells like astrocytes, microglia and oligodendrocytes. It induces apoptosis, necrotic cell death and neurite outgrowth. In addition, its immunostimulant effects lead to the release of proinflammatory cytokines and secondary neuronal damage. The clinical manifestation of bilirubin toxicity is assumed to be due to integrated nerve disturbance. The exact level of TSB at which neuronal damage occurs is still elusive and multiple guidelines have been developed incorporating various risk factors for neurotoxicity. Recent evidence from the follow-up of large, randomized-control studies it has been shown that, in micropreemies, a mean difference of 2.2 mg% of TSB between the intervention and treatment group resulted in significant neurodevelopmental benefit including a reduction in athetosis and severe hearing loss. That this benefit occurred at the cost of increase in mortality in a subgroup of babies (birth weight 501–750 g) underlines the complex nature of bilirubin both as a natural protective antioxidant and an agent of neurotoxicity.

**Clinical Manifestations**

The initial features of bilirubin neurotoxicity are reversible. Brain-stem auditory evoked response (BAER) can show early signs of acute bilirubin encephalopathy with characteristic changes in the wave latency and magnitude. BAER shows significant prolongation of latencies of waves III and IV-V, and interpeak I-III and I-V, suggesting interference in brainstem conduction in neonates with TSB of 10–20 mg/dL (171–342  $\mu$ mol/L). These are reversed rapidly with either an exchange transfusion (ET) or a spontaneous decline in TSB concentrations. Acute bilirubin encephalopathy typically progresses through three stages:

**Stage 1**

It occurs during the first few days, with the infant showing decreased activity, poor suck, hypotonia and a slightly high-pitched cry. If the TSB level is rapidly decreased (by ET) the abnormalities are often reversed.

**Table 2** Distinguishing features between *breastfeeding jaundice* and *breastmilk jaundice*

	<i>Breastfeeding jaundice</i>	<i>Breastmilk jaundice</i>
Clinical presentation	Hyperbilirubinemia with significant weight loss in the first week of life	Persistence or prolongation of apparent physiological jaundice in an otherwise healthy term beyond day 14
History	Multiple issues related to breastfeeding resulting in inadequate feeding with poor stool output	Exclusively breastfed, good lactation, gaining weight well, passing adequate stools History of jaundice in previous siblings
Cause	Increased enterohepatic circulation due to decreased gut motility secondary to infrequent feeding Poor calorie intake interfering with conjugation of bilirubin	Largely unknown. Plausible mechanisms include presence of unknown inhibitory substance in breastmilk that interferes with conjugation of bilirubin (3 $\alpha$ 20 $\beta$ pregnanediol, lipases, and free fatty acids), increased enterohepatic circulation due to excess $\beta$ -glucuronidase in breastmilk and slow colonization of intestine by bacteria
Course	May need phototherapy for a few days. Responds rapidly to measures to ensure adequate breastmilk feeding	Total serum bilirubin (TSB) levels increase till 4–6 weeks and subsequently normalize by 8–12 weeks of age. Maximum TSB may rarely reach 20 mg/dL If breastfeeding is interrupted, the TSB levels rapidly decline and do not rise again to previous high values
Management	Ensure adequate breastfeeding and management of hyperbilirubinemia as per guidelines	Except in rare instance, it is not advisable to stop or interrupt breastfeeding as the potential disadvantages of this outweigh any gains

## Stage 2

It develops a few days later with the infant demonstrating rigid extension of the extremities, tight-fisted posturing of arms, crossed extension of legs and a high-pitched cry. These signs may be accompanied by seizures, backward arching of the neck (retrocollis) and trunk (opisthotonos), along with increased body temperature.

## Stage 3

It typically begins after the first week, with hypertonia, marked retrocollis, opisthotonos, stupor or coma. A scoring system can be used to assess the severity of the condition (**Table 3**).

After several months, in patients who survive, chronic bilirubin encephalopathy (kernicterus) develops. Classical kernicterus is a well-described clinical tetrad of abnormal movements and muscle tone, auditory processing disturbance with or without hearing loss, oculomotor impairments, especially that of upward vertical gaze, and dysplasia of the enamel of deciduous teeth.

Subtle kernicterus or bilirubin-induced neurologic dysfunction (BIND) refers to individuals with subtle neurodevelopmental disabilities without classical findings of kernicterus (**Table 4**).

## Prevention of Bilirubin Neurotoxicity

Factors that increase susceptibility to neurotoxicity in the jaundiced neonate are mentioned in **Box 2**. Numerous recent epidemiological studies have shown increasing trends in the prevalence of kernicterus. A plausible reason for this is the failure to practice accepted guidelines for the management of neonatal jaundice amongst pediatricians. Under-estimating severity of jaundice visually and lack of concern regarding the neurotoxic potential of bilirubin are also contributory factors. Compared with Western data, kernicterus has been reported at lower levels of peak TSB in India. Proposed mechanisms included late referrals, concomitant morbidities, higher incidence of G6PD deficiency and genetic increase in blood-brain barrier permeability. In a study at a tertiary care center in northern India, 21.8% neonates with non-hemolytic jaundice and TSB greater than and equal to 18 mg% had features of kernicterus when brought to the hospital. In another study, about 10% of neonates with TSB of 20–25 mg/dL presented with established neurological deficits. In a study on term infants with hyperbilirubinemia of mixed etiology, 10 out of 15 neonates with TSB of 21–25 mg/dL developed transient abnormalities in BAER and 11% had developmental delay at 1 year of age. These studies suggest that more importance needs to be given to babies with jaundice. Protocols regarding early discharge, appropriate follow-up, evaluation of TSB level based on the infant's age in hours and recognition of risk factors for severe hyperbilirubinemia are available and need to be followed meticulously to prevent unacceptable neurological sequelae.

## ASSESSMENT OF THE JAUNDICED NEONATE

Modified Maisels criterion is a useful initial clinical tool to decide if jaundice is pathological and includes any of the following:

- Clinical jaundice within the first 24 hours of life
- TSB levels increasing by more than 0.2 mg/dL (3.4  $\mu$ mol/L) per hour or 5 mg/dL (85  $\mu$ mol/L) per day
- Total serum bilirubin concentration exceeding the 95th percentile for age (in hours)
- Direct bilirubin concentration exceeding 1.5–2 mg/dL (26–34  $\mu$ mol/L)
- Clinical jaundice persisting for more than 2 weeks in a full-term infant.

The maternal and birth history, condition of neonate and physical findings all give clues as to the likely etiology of the

**Table 3** Bilirubin-induced neurologic dysfunction (BIND) score rating for awake or sleep states in infants (> 34 weeks' gestational age) with hyperbilirubinemia

Signs	Sleep state	Mild	Moderate	Advanced
Score rate		1	2	3
Mental	Awake	Agitated	Irritable	Seizures
	Sleep	Poor arousal	Lethargic	Semicoma
Tone	Awake	Hypertonia	Arching	Opisthotonos
	Sleep	Hypotonia	Limp	Flaccid
Cry	Awake	Shrill	Piercing	Inconsolable
	Sleep	Weak	Whimper	Almost absent
BIND score (1–9)		1–3	4–6	7–9
Automated auditory brainstem response (AABR) that is referred as an additional score. Thus, infant with a score of 3 plus a referred AABR = total BIND score of 4.				

Abbreviation: BIND, bilirubin-induced neurologic dysfunction.

Source: Johnson L, Bhutani VK. The clinical syndrome of bilirubin-induced neurologic dysfunction. *Semin Perinatol.* 2011;35:101-13.

**Table 4** Classification of bilirubin neurotoxicity (kernicterus)

Subtype	Description
Classic kernicterus	Classic triad or tetrad of: <ol style="list-style-type: none"> <li>1. Auditory neuropathy/auditory dyssynchrony <math>\pm</math> hearing loss or deafness</li> <li>2. Neuromotor symptoms, e.g., dystonia, hypertonia <math>\pm</math> athetosis</li> <li>3. Oculomotor paresis of upward gaze</li> <li>4. Enamel dysplasia of the deciduous teeth</li> </ol> Note that the oculomotor and dental criteria may be variably present or absent
Auditory kernicterus	Predominantly auditory symptoms, i.e., auditory neuropathy/auditory dyssynchrony with minimal motor symptoms
Motor kernicterus	Predominantly motor symptoms, e.g., dystonia $\pm$ athetosis with minimal auditory symptoms
Subtle kernicterus or bilirubin-induced neurological dysfunction (BIND)	Subtle neurodevelopmental disabilities without classical findings of kernicterus that, after careful evaluation and consideration, appear to be due to bilirubin neurotoxicity. These may include disturbances of sensory and sensorimotor integration, central auditory processing, coordination and muscle tone

Source: Shapiro SM. Definition of the clinical spectrum of kernicterus and bilirubin-induced neurologic dysfunction (BIND). *J Perinatol.* 2005;25:54-9.

## BOX 2 Factors that increase susceptibility to bilirubin neurotoxicity

- Birth asphyxia
- Caloric deprivation
- Temperature instability
- Prolonged hyperbilirubinemia
- Sepsis
- Lower gestational age
- Hypoalbuminemia
- Low birth weight
- Acidosis
- Hypercarbia
- Excessive hemolysis



jaundice (**Table 5**). Holistic clinical assessment of a jaundiced neonate includes assessment of etiology, risk factors for significant hyperbilirubinemia and clinical features of BIND. Clinical assessment based on cephalocaudal progression of jaundice as described by Kramer is still used though it is not accurate in dark-skinned babies and when the jaundice is decreasing (**Table 6**). Knudsen postulated that the cephalocaudal progression of jaundice can be explained by the conformational changes of the bilirubin-albumin complex. Although the initial binding of bilirubin to albumin is extremely rapid, final conformational

changes may not occur for about 8 min. Thus, blood leaving the reticuloendothelial system and going to the proximal parts of the body contains bilirubin that is less tightly bound to albumin than that which subsequently reaches the distal parts of the body. Bilirubin that is less tightly bound to albumin is more likely to precipitate as bilirubin acid in the phospholipid membranes in the skin and subcutaneous tissues, which is why the face appears jaundiced before the abdomen or the legs.

The World Health Organization (WHO), in its guidelines on neonatal jaundice, relies on clinical assessment for deciding

**Table 5** History and clinical examination in neonatal jaundice

Information	Significance
<i>Family history</i>	
Parent or family history of anemia	Hereditary hemolytic anemia like hereditary spherocytosis, G6PD deficiency
Previous sibling with neonatal jaundice	As above with possible genetic factors like TATA box mutations, isoimmune hemolysis or breastmilk jaundice
History of liver disease in family	Disorders such as cystic fibrosis, galactosemia, tyrosinemia, Crigler-Najjar syndrome
<i>Maternal history</i>	
Unexplained illness during pregnancy	Consider intrauterine infections particularly of TORCH group
Diabetes mellitus	Increased incidence of jaundice in IDMs
Drug ingestion during pregnancy	Ingestion of sulfonamides, nitrofurantoin, antimalarials may initiate hemolysis in G6PD deficient neonate
<i>History of labor and delivery</i>	
Vacuum extraction	Increased incidence of cephalhematoma or subgaleal hemorrhage
Use of oxytocin, epidural analgesia, excessive IV fluids	Increased incidence of hyperbilirubinemia due change in blood osmolarity
Delayed cord clamping	Increased incidence of polycythemia
Low Apgar score/resuscitation	Increased incidence of jaundice in asphyxiated infants
<i>History</i>	
Delayed passage of meconium	Increased enterohepatic circulation
Dark-colored urine, staining diapers with or without pale colored stools	Consider cholestasis after ruling out dehydration. Needs urgent evaluation
Breastfeeding failure	Results in delay in bilirubin conjugation and increased enterohepatic circulation
Vomiting	Suspect sepsis, galactosemia, or pyloric stenosis
<i>Physical examination</i>	
Preterm/late preterm infant	At-risk for significant hyperbilirubinemia due to immaturity of bilirubin metabolism
Sick newborn: on inotropes, ventilation, etc.	Lower threshold of TSB for specific treatment due to increased risk of bilirubin toxicity
Temperature instability	Lower threshold of TSB for specific treatment due to increased risk of bilirubin toxicity, consider sepsis
Excessive weight loss	Breastfeeding failure jaundice needs to be considered
Excessive lethargy, tone abnormalities	Early features of BIND, sepsis
Small for gestational age	Infants frequently polycythemic
Head size	Microcephaly: seen with intrauterine infections
Cephalhematoma	Significant breakdown of bilirubin with prolonged jaundice
Plethora	Polycythemia
Pallor	Suspect hemolysis
Petechiae	Suspect congenital infection, overwhelming sepsis
Appearance of umbilical stump	Omphalitis and sepsis may produce jaundice
Hepatosplenomegaly	Suspect hemolytic anemia or congenital infection
Optic fundus abnormalities	Chorioretinitis suggests congenital infection
Umbilical hernia	Consider hypothyroidism

*Abbreviations:* G6PD, glucose-6-phosphate dehydrogenase; TSB, total serum bilirubin; IDM, insulin-dependent diabetic mothers; TORCH, toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex; BIND, bilirubin-induced neurologic dysfunction.

**Table 6** Dermal staining and level of serum bilirubin

Area of body	Range of TSB (mg/100 mL)
Face	4–8
Upper trunk	5–12
Lower trunk and thighs	8–16
Arms and lower legs	17–20
Palms and soles	> 20

need for PT or referral. Jaundice is labeled severe if it appears on day 1 or involves arms and legs on day 2. Jaundice on palms and soles are considered a danger sign, requiring admission. These criteria are useful in settings where in-house facilities for TSB are not available, during home visits by peripheral health workers or in a district hospital/first referral unit during off-working hours. However, reliability of clinical assessment of bilirubin by different cadres of health workers is debatable and needs to be studied.

In the clinical assessment of a case of hyperbilirubinemia one should ask the following questions:

- *Is it physiological or pathological?* Appearance of jaundice within 24 hours, increase in serum bilirubin beyond 5 mg/dL/day, peak levels above the expected normal range, presence of clinical jaundice beyond 2 weeks and conjugated bilirubin (dark urine staining the clothes) would be categorized under pathological jaundice.
- *Is it hemolytic?* Onset of jaundice within 24 hours, presence of pallor or hepatosplenomegaly or suggestive family history of significant early-onset jaundice should raise a suspicion of hemolysis.
- *Is there a serious underlying condition?* Lethargy, poor feeding, failure to thrive, hepatosplenomegaly, temperature instability or apnea may be a marker of an underlying serious disease which could be either sepsis, urinary tract infection, a serious metabolic problem or bilirubin encephalopathy.
- *Is there cholestasis?* Presence of jaundice beyond 2 weeks, dark urine (staining the diaper) or pale colored stools would suggest cholestatic jaundice.

### Laboratory Assessment

Measurement of TSB can be done by simple colorimetric method, the prototype of which is the van den Bergh test which is a modification of the Ehrlich diazo reaction. Conjugated bilirubin gives a direct test while unconjugated bilirubin is indirectly calculated. Amongst the automated methods, newer versions such as Ektachem system are more accurate than others as it gives accurate estimates of  $\delta$ -bilirubin as well. High performance liquid chromatography, which gives the most accurate value of different fractions of bilirubin, is costly and not easily available. Spectrophotometry measures absorbance of bilirubin near 460 nm light spectrum. Inference by hemoglobin is resolved by analysis of a two-component system.

*Transcutaneous bilirubinometry* is a noninvasive technique of assessment of bilirubin, which is a useful screening tool. Second generation, hand-held bilirubinometers display TSB in mg/dL and  $\mu\text{mol/L}$  on a liquid-crystal display (LCD) screen. The calibration-tip fitted equipment is placed on the forehead of the baby and switched on. The equipment usually averages five readings. Use of a small PT patch, which can be removed and replaced, is in vogue for keeping a measurement area unexposed to light in babies under PT. This helps in giving more accurate readings. The recurrent expenditure is in the requirement of a new calibration tip for each reading. The advantage is that it a noninvasive point-of-care estimation. However, accuracy depends on the quality of

the equipment. Other investigations that need to be carried out in a jaundiced baby depend on the clinical presentation and clinical course and are given in **Table 7**.

### MANAGEMENT

A number of guidelines are available from different countries which lay down approaches to stratify, detect, treat and follow-up at-risk babies for significant hyperbilirubinemia so as to prevent the development of its neurotoxic sequelae. The most commonly used nomogram is that of American Academy of Pediatrics (AAP). The National Neonatology Forum (NNF) has adapted many of these in its own guidelines (**Box 3**).

### Predischarge Risk Stratification

Predischarge risk stratification needs to be done so as to devise an effective protocol for the follow-up of babies with neonatal jaundice. The AAP guidelines have identified certain risk factors which, when combined with hour-specific TSB based on nomograms, can be used to identify high-risk babies who can be followed up more closely. This predischarge risk stratification may need to be

**Table 7** Laboratory evaluation of the jaundiced neonate

Problem	Assessments
Jaundice in first 24 hours	TSB, Hb, PCV, peripheral smear for hemolysis, reticulocyte count, direct Coombs, G6PD screen
Jaundice in a sick neonate	TSB, sepsis screen, blood cultures, LFT, TORCH titers
Jaundice present at or beyond age 2 weeks, or sick infant	Total and direct (conjugated) bilirubin level If direct bilirubin elevated, evaluate for causes of cholestasis Thyroid and galactosemia screen

*Abbreviations:* TSB, total serum bilirubin; Hb, hemoglobin; PCV, packed cell volume; G6PD, glucose-6-phosphate dehydrogenase; LFT, liver function test; TORCH, toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex.

modified in the Indian setting due to a higher prevalence of G6PD deficiency, lower albumin at birth and seasonal variations. Besides, it is not always possible in our setting to estimate a predischarge TSB/transcutaneous bilirubin. However, it is still prudent to stratify babies based on known risk factors especially in cases of early hospital discharges. The NNF of India has brought out guidelines for follow-up of babies with jaundice after discharge (**Table 8**).

### Phototherapy

The primary aim of PT is to convert unconjugated, lipid-soluble bilirubin into a nondangerous form so as to prevent it from entering the brain and causing neuronal damage. Bilirubin is a pigment that absorbs light best at a wavelength of 450 nm. When light in this spectrum is delivered to the skin, the bilirubin rapidly forms configurational isomers from its native form, 4Z, 15Z. The most abundant of these isomers is 4Z, 15E and accounts for 20% of TSB in babies receiving PT. However, these isomers are reversible as soon as the lights are switched off and are not the main means of sustained reductions of TSB. The formation of structural isomers, of which the most prominent is lumirubin, is an irreversible process and is the main basis of reduction of TSB. The formation of lumirubin is directly proportional to the intensity of the PT. Photo-oxidation products are also formed but do not play an important role in the elimination of bilirubin. Rebound increase in serum bilirubin can occur after stopping PT after an apparent initial reduction of TSB.

**BOX 3 Available guidelines for management of neonatal hyperbilirubinemia****USA**

American Academy of Pediatrics (AAP) guidelines  
American Academy of Pediatrics Subcommittee on hyperbilirubinemia.  
Management of hyperbilirubinemia in the newborn infant 35 or more  
weeks of gestation. *Pediatr.* 2004;114:297-316

**India**

National Neonatology Forum India. Management of neonatal hyper-  
bilirubinemia. Evidence Based Clinical Practice Guidelines, 2010. pp.  
139-53

**UK**

NICE guidelines (by National Collaborating Center for Women's and  
Children's Health, commissioned by National Institute for Health and  
Clinical Excellence (NICE), RCOG)  
<http://www.nice.org.uk/guidance/index.jsp?action=byId&o=11660>

**Germany**

<http://www.awmf.org/leitlinien/detail/II/024-007.html>

**Israel**

Kaplan M, Merlob P, Regev R. Israeli guidelines for management of  
neonatal hyperbilirubinemia and prevention of kernicterus. *J Perinatol.*  
2008;75:157-63

**Norway**

Bratlid D, Nakstad B, Hansen TWR. National guidelines for treatment of  
jaundice in the newborn. *Acta Paediatr.* 2011;100:499-505

**Sweden**

<http://blf.net/neonatal/new-varprogr.html>

**Switzerland**

<http://www.neonet.ch>

**The Netherlands**

[http://www.nvk.nl/Kwaliteit/Richtlijnenenindicatoren/Richtlijnen/  
Hyperbilirubinemie/tabid/329/language/nl-NL/Default.aspx](http://www.nvk.nl/Kwaliteit/Richtlijnenenindicatoren/Richtlijnen/Hyperbilirubinemie/tabid/329/language/nl-NL/Default.aspx)

**Table 8** NNF India guidelines for follow-up of babies for hyperbilirubinemia after discharge from hospital

Scenario	Age at discharge	Follow-up
No risk factors present*	24–72 hours	48 hours after discharge
	> 72 hours	Follow-up optional
Risk factors present**	24–48 hours	24 hours after discharge**
	49–72 hours	48 hours after discharge**
	73–120 hours	48 hours after discharge

\*The risk factors for consideration would include history of jaundice needing treatment in previous sibling, setting of blood group incompatibility, visible jaundice at discharge, gestation less than 38 completed weeks, high prevalence of G6PD deficiency, primipara mother, weight loss at discharge > 3% per day or > 7% cumulative weight loss.

\*\*May need a repeat visit depending on physician's assessment.

### Phototherapy Devices

The efficacy of PT is influenced by the following factors: (1) the spectrum of light delivered, blue-green region being the most effective; (2) the energy output or irradiance of the PT light, measured in  $\mu\text{W}/\text{cm}^2/\text{nm}$ ; and (3) the surface area of the infant exposed to PT (the spectral power is the product of the irradiance and the surface area exposed); (4) initial bilirubin values. Brief details of different devices available and technique of administration, impact, monitoring and side effects are given in **Box 4**. Clinical trials have shown that none of the devices are superior to one another. However, the LED lights have a longer life (> 20,000 hours), lower heat output, and lower infrared emission besides being of reasonable cost and hence are preferred. Intensive

PT needs to be administered in babies nearing bilirubin thresholds for ET and double surface PT is the preferred modality whenever feasible. To be labeled as intensive, PT should be continuous, with as much spectral power as possible.

### Initiation of Phototherapy

For babies born more than 35 weeks gestation, AAP guidelines recommended for initiation of PT are based on risk factors (prematurity, sickness) along with TSB levels. Babies more than 38 weeks who are well may be started on PT at TSB levels of 12 mg% at 24 hours and 16 mg% at 48 hours and 18 mg% at 72 hours. For high-risk babies (< 35 weeks or sick) the threshold for starting PT should be 2/3rds of these values. These recommendations may need to be modified for Indian setting. Since AAP guidelines specify therapy only till 7 days postnatal age and evidence is lacking for starting thresholds beyond this age, bilirubin thresholds for babies presenting beyond this duration should be considered as at day 7.

For babies less than and equal to 35 weeks period of gestation, it is generally recommended to treat hyperbilirubinemia at lower levels in comparison to term infants. The general guide is to start PT when TSB is 0.5% and 0.75% of the body weight in healthy and sick infants respectively and do ET when TSB is more than 1% of

**BOX 4 Facets of phototherapy****Classification of light source**

1. Fluorescent-tube devices
2. Metal halide bulbs
3. Light-emitting diodes (LEDs)
4. Fiber-optic cables

**Standards for phototherapy devices**

**Light wavelength:** 460–490 nm most effective. Special blue (BB) compact fluorescent lamps (CFL) and high-intensity Gallium nitrite LEDs also effective and long-lasting.

**Measuring light irradiance:** Different types of fluxmeters/dosimeters exist. It is best to use that given by the manufacturer. AAP recommendation: At least  $30 \mu\text{W}/\text{cm}^2/\text{nm}$ . Doses  $>65 \mu\text{W}/\text{cm}^2/\text{nm}$  may have unknown side effect. Useful life of bulbs not to exceeded. Footprints for measures to be taken from several sites of body.

**Optimal body surface area (BSA):** Should be > 90%, change of position every 2–3 hours to maximize BSA exposed. Exposed BSA more important than number of phototherapy devices used. Minimize diapers, eye patch areas. Circumferential phototherapy important. If in incubator, phototherapy should be perpendicular to avoid reflectance.

**Impact of phototherapy:** Should be evident after 4–6 hours with fall in TSB of at least 2 mg/dL. Intensive phototherapy for very high TSB to avoid exchange transfusion.

**Monitoring**

Ensure adequate hydration, nutrition, and temperature control. Clinical improvement or progression of jaundice should also be assessed, including signs suggestive of early bilirubin encephalopathy such as changes in sleeping pattern, deteriorating feeding, pattern, or inability to be consoled while crying.

**Other issues**

**Use of eye patches:** No evidence to support. May increase conjunctivitis.

**Use of diapers:** To be used for hygiene, not necessarily for gonadal protection.

**Contraindication:** Congenital porphyria or those treated with photosensitizing drugs.

**Side effects**

Increased oxidant stress, lipid peroxidation, riboflavin deficiency. Recent clinical reports of other adverse outcomes (e.g., malignant melanoma, DNA damage, and skin changes) have yet to be validated. Phototherapy does not exacerbate hemolysis. Bronze baby syndrome occurs if phototherapy is administered in conjugated hyperbilirubinemia.

the bodyweight in grams. For babies born with birth weight less than 2,500 g, various thresholds that have been mentioned for PT and ET are given in **Box 4**.

### Stopping Phototherapy

Phototherapy may be discontinued when serum bilirubin level have fallen at least 2 mg/dL below the PT threshold for that postnatal age. If the underlying disease is hemolytic in nature or if PT has been initiated early and discontinued before the infant is 3–4 days old, a follow-up bilirubin measurement within 24 hours after discharge is recommended. For infants who are readmitted with hyperbilirubinemia and then discharged, significant rebound is rare, but a repeat TSB measurement or follow-up 24 hours after discharge is an option. However, clinically significant rebound increase in TSB after stopping PT have been found in cases of prematurity, direct Coombs test positivity and in those treated for less than 72 hours. These risk factors should be taken into account when planning post-PT follow-up.

### Exchange Transfusion

Removal of the neonate's blood in aliquots with replacement with safe blood has always been an option to remove bilirubin from the body rapidly. However, with better PT this modality is now being used rarely. Knowledge of this practice is important as it can be life and brainsaving.

### Indications

As per the NNF India guidelines, the decision to perform an ET is based on the TSB value for that postnatal age, level of sickness of the baby, the likely etiology and presence or absence of bilirubin encephalopathy. Important risk factors to consider exchange at lower TSB levels include presence of acidosis, low albumin level, blood-brain barrier disruption (e.g., intracranial hemorrhage, asphyxia, sepsis, meningitis), Coombs positive jaundice, G6PD deficiency, displacers of bilirubin (e.g., free fatty acids from intralipid, ibuprofen, ceftriaxone) and encephalopathy. One should consider an early ET in case of hydrops, history of previous sibling requiring exchange because of Rh isoimmunization, cord Hb < 11 g/dL, cord TSB > 5 mg/dL, rate of rise of TSB > 1 mg/dL/hour despite PT, any TSB > 12 mg/dL in first 24 hours and TSB > 20 mg/dL in the early neonatal period particularly if due to hemolysis (**Table 9**).

### Procedure

For Rh isoimmunization, the best choice would be O-negative packed cells suspended in AB-positive plasma. O-negative whole blood crossmatched with baby's blood group may also be used. For ABO isoimmunization, O group (Rh compatible) packed cells suspended in AB plasma or O group whole blood (Rh compatible with baby) should be used. In other situations, baby's blood group should be used. All blood must be crossmatched against maternal plasma as well (**Table 10**).

The blood volume required for ET is  $2 \times (80\text{--}100 \text{ mL/kg}) \times \text{birth weight in kg}$ . Though evidence suggests that the use of peripheral arterial route for exchange is associated with fewer complications than using the umbilical route, the procedure requires more expertise. The most common route used is the single umbilical catheter via the umbilical vein, which is inserted approximately 3 cm and 5 cm (in preterm and term babies respectively) with the use of appropriately matched blood, done in aliquots of 5–8% of bodyweight (**Fig. 1**). The procedure needs to be done under strict asepsis and hemodynamic monitoring. Though some studies have shown benefits of transfusing 20% albumin prior to ET, its routine use is not recommended.

**Table 9** Indications for phototherapy and blood exchange transfusion in low birth weight babies

Birth weight (grams)	Guidelines for phototherapy (mg/dL)		Consider exchange transfusion (mg/dL)
	Healthy infant	Sick infant	
< 1000	5–7	4–6	10–12
1,000–1,500	7–10	6–8	12–15
1,501–2,000	10–12	8–10	15–18
2,001–2,500	12–15	10–12	18–20

**Table 10** Choice of blood group for exchange transfusion

Maternal blood group	Infant blood group	Donor blood group
O	O or A or B or AB	O
A or B or AB	O or A or B or AB	Baby blood group or O group
Rh-negative	Rh-positive or negative	Rh-negative



**Figure 1** Exchange transfusion using umbilical venous route

### Emergency Approach to Neonatal Hyperbilirubinemia

A neonate presenting with severe hyperbilirubinemia should be urgently evaluated for features of acute bilirubin encephalopathy and must be initiated on intensive PT as an emergency measure even before all investigations are available. Since studies have shown that many such babies come from community with significant dehydration, IV fluids need to be administered. Besides, arrangements for ET must be made and undertaken if the dangerous bilirubin thresholds are reached.

### Additional Therapies

#### Intravenous Immunoglobulin

Intravenous immunoglobulin therapy inhibits hemolytic breakdown of RBCs by causing nonspecific blockade of Fc receptors in the reticuloendothelial system and has been used effectively in immune hemolytic anemia. In a meta-analysis which included seven studies that investigated the role of IVIG in hemolytic anemia, significant reduction in maximum TSB and the need



for ET has been reported. However, there was a trend toward increased need for packed cell transfusion due to anemia after first week of life. No significant difference was observed in a small randomized controlled trial comparing 0.5 and 1 g/kg dose of IVIG.

### Phenobarbitone

Phenobarbitone is a potent inducer of uridine diphosphate glucuronosyltransferase (UDPGT) and has, in addition, multiple actions at other levels of bilirubin metabolism in the liver. PB has been used in the prevention of neonatal jaundice for very low birth weight (VLBW) babies and in the treatment of hyperbilirubinemia of Crigler-Najjar syndrome, Dubin-Johnson syndrome and neonatal cholestasis. A meta-analysis of three studies has concluded that PB reduces peak serum bilirubin, duration and need of PT and need of ET in preterm VLBW neonates. In a recent study, on the role of prophylactic oral phenobarbitone in Rh-

HDN no significant reduction of total duration of PT or significant rebounds of TSB was found in the PB group.

### Fluid Supplementation

Studies have shown that provision of extra fluid to babies undergoing PT reduces the total duration of PT and also the need for ET significantly. Standard care consisted of conventional PT combined with 20 mL/kg per day of extra oral feeds (expressed breastmilk or formula) until PT is discontinued. However, routine IV fluid prescription to babies under PT is not recommended in view of the potential risk of sepsis and needs to be considered on case to case basis.

### Other Available Modalities

A list of various other pharmacological agents that have been tried in neonatal jaundice with its evidence and current recommendations is described in **Table 11**.

**Table 11** Pharmacotherapy for neonatal unconjugated hyperbilirubinemia

Drug	Mechanism of action	Evidence	Remark
Metalloporphyrin	Reducing bilirubin production by inhibiting heme oxygenase	Cochrane Three studies (N = 170); poor quality nonblinded trials Short-term benefits: lower maximum plasma bilirubin level, decreased need for phototherapy, fewer plasma bilirubin measurements and a shorter duration of hospitalization Photosensitivity rash—adverse effect	Routine use cannot be recommended Newer more safe molecules than Tin(Sn) metalloporphyrins evolving
Clofibrate	Increased elimination Reducing enterohepatic circulation	Cochrane Fifteen studies, 13 done in Iran, 2 in preterm, 13 in term. For preterm neonates, there was a significantly lower bilirubin level in the 100 mg/kg clofibrate after 48 hours  For the term neonates, there were significantly lower bilirubin levels in the clofibrate group after both 24 and 48 hours of treatment Significantly lower duration of phototherapy for both preterm and term neonates None of the studies reported on bilirubin encephalopathy rates, neonatal mortality rates, or the levels of parental or staff satisfactions with the interventions Loose stools, bloating may be side effect	Thirteen of the 15 studies done in Iran. Short-term benefits in term babies, Nonhemolytic setting  Long-term benefits not yet proven Single dose of clofibrate seems promising Larger studies required from different countries
Activated charcoal	Increased elimination  Reducing enterohepatic circulation	No recent evidence, seems to have nearly gone off practice with effective PT Quasi controlled study have shown activated charcoal beneficial as adjunct to PT. The combination drops TSB more than PT	Based on small studies  Activated charcoal and agar might be useful adjuncts to PT
Agar		Oral agar versus combination of agar + PT—Max drop in TSB with combination. Oral agar equally effective as PT	No recent large studies
Yinzhihuang	Chinese herb	Oral solution is a herbal extract with the main components of <i>Herba Artemisiae Scopariae</i> , <i>Scutellaria</i> , <i>Lonicera Japonica</i> and <i>Gardenia jasminoides</i>	For interest sake Apparently useful Not sure whether we have an Indian counterpart
Prebiotics		Prebiotics added to formula feeding results in more stools and lower TcB levels in healthy infants with moderate hyperbilirubinemia	An emerging option, in its early stages Not recommended at this point
D-Penicillamine	Probably influences Bil- Alb binding	Few studies early mid 70 seemed to reduce TSB levels; toxicity high	Historical with other safer treatments in line

Abbreviations: TSB, total serum bilirubin; PT, phototherapy; TcB, transcutaneous bilirubin.

## NEONATAL CHOLESTASIS

(Also See Section 37)

Neonatal cholestasis is defined as conjugated hyperbilirubinemia occurring in the newborn as a consequence of diminished bile flow. Conjugated hyperbilirubinemia in a neonate is defined as a serum direct/conjugated bilirubin concentration (*a*) greater than 1 mg/dL if the TSB is < 5 mg/dL; or (*b*) > 20% of TSB if the TSB is > 5 mg/dL. Conjugated hyperbilirubinemia is always pathological at any age and needs urgent evaluation. The issue here is not neurotoxicity (as the conjugated bilirubin cannot cross the blood-brain barrier) but hepatotoxicity as the pent-up bilirubin or the underlying etiology damages liver cells leading to chronic liver failure. The urgency in evaluation is mainly to rule in extrahepatic biliary atresia, a condition which requires time-bound surgical management. The outcomes of surgical interventions are better if performed before 2 months of age. A list of common causes of cholestasis is mentioned in **Box 5**. Special investigations include imaging like ultrasound of liver and gallbladder, radioisotope scan with hepatobiliary iminodiacetic acid scan and magnetic resonance cholangiography. It is usually not easy to make a definite diagnosis of the etiology in the early stages of the disease and when in doubt, a peroperative cholangiography is performed before surgery. In many cases of neonatal cholestasis, liver transplant is the only treatment option available.

### Follow-up

All neonates with significant hyperbilirubinemia must be followed up for hearing assessment and developmental delay.

### IN A NUTSHELL

1. Neonatal hyperbilirubinemia is a common condition in newborns.
2. Some known and many unknown risk factors predispose neonates to the risk of bilirubin neurotoxicity. This can vary from subtle manifestations such as BIND to the most severe form, namely kernicterus.
3. By following standard protocols, taking a detailed history, doing a thorough clinical examination, using available investigations judiciously and management modalities effectively and ensuring an adequate follow-up, prevention of these complications is possible.
4. Phototherapy still forms the backbone of effective management of unconjugated hyperbilirubinemia.
5. Neonatal cholestasis should be suspected clinically and investigated rapidly to rule out surgically treatable conditions.

### MORE ON THIS TOPIC

- American Academy of Pediatrics, Subcommittee on Neonatal Hyperbilirubinemia. Clinical practice guideline: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatr*. 2004;114:1138.
- Bhatia V, Bavdekar A, Matthai J, et al. Management of neonatal cholestasis: consensus statement of the Pediatric Gastroenterology Chapter of Indian Academy of Pediatrics. *Indian Pediatr*. 2014;51:203-10.

### BOX 5 Causes of neonatal cholestasis

#### A. Biliary ductal obstruction/malformation

1. Extrahepatic biliary atresia
2. Choledochal cyst
3. Intrahepatic biliary atresia/bile duct paucity
4. Spontaneous rupture of bile duct
5. Alagille syndrome
6. Congenital hepatic fibrosis
7. Intrahepatic biliary paucity with lymphedema (Aagaenae's syndrome)
8. Polysplenia syndrome with heterotaxy
9. Progressive familial intrahepatic cholestasis syndrome

#### B. Idiopathic neonatal hepatitis

#### C. Inspissated bile syndrome

#### D. Infections

1. Bacterial sepsis
2. Urinary tract infections
3. Toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex (TORCH) group of infections
4. Syphilis
5. Reovirus
6. Echovirus
7. Tuberculosis
8. Coxsackie B virus

#### E. Metabolic disorders

1. Galactosemia
2. Hereditary fructose intolerance
3.  $\alpha$ -1 antitrypsin deficiency
4. Tyrosinemia
5. Glycogenosis IV
6. Cystic fibrosis
7. Wolman disease
8. Niemann-Pick disease
9. Gaucher disease
10. Hypothyroidism

#### F. Total parenteral nutrition

#### G. Chromosomal disorders

1. Trisomy E
2. Down syndrome

Bhutani VK, Committee on Fetus and Newborn, American Academy of Pediatrics. Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2011;128:e1046-52.

Johnson L, Bhutani VK. The clinical syndrome of bilirubin-induced neurologic dysfunction. *Semin Perinatol*. 2011;35:101-13.

Maisels MJ. Jaundice. In: MacDonald MG, Mullett MD, Seshia MMK (Eds). *Avery's Neonatology: Pathophysiology and Management of the Newborn*. 6<sup>th</sup> ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.pp.768-846.

National Neonatology Forum India. Management of neonatal hyperbilirubinemia. Evidence Based Clinical Practice Guidelines. 2010.pp.139-53.

Shapiro SM. Definition of the clinical spectrum of kernicterus and bilirubin induced neurologic dysfunction (BIND). *J Perinatol*; 2005;25:54-9.

Wong RJ, DeSandre GH, Sibley E, Stevenson DK. Neonatal jaundice and liver disease. In: Fanaroff AA, Martin RJ, Walsh MC (Eds). *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. Philadelphia, PA: Mosby; 2006.pp.1419-52.

## Chapter 14.4

# Infant of Diabetic Mother

*Srinivas Murki, Tejo Oleti Pratap*

Adult onset diabetes mellitus is an increasing problem due to the changing lifestyle and altered genetic factors. Recent evidence from India and other regions of the world report the incidence of diabetes complicating pregnancy ranging from 5% to 10%. Diabetes in a pregnant mother increases the risk of complications to the mother-fetal/infant dyad. When the onset of diabetes occurs prior to pregnancy, it is considered pregestational (type 1 or 2 diabetes mellitus diagnosed prior to pregnancy) and that which occurs during pregnancy is labeled as gestational diabetes. Although the incidence of gestational diabetes is more than the pregestational diabetes, there is an increasing trend in the incidence of the latter. A newborn born to a mother with pregestational diabetes has more complications than that born to a mother with gestational diabetes. Also the perinatal morbidity and mortality is higher in infants of poorly controlled diabetic mothers than those born to well-controlled diabetic mothers.

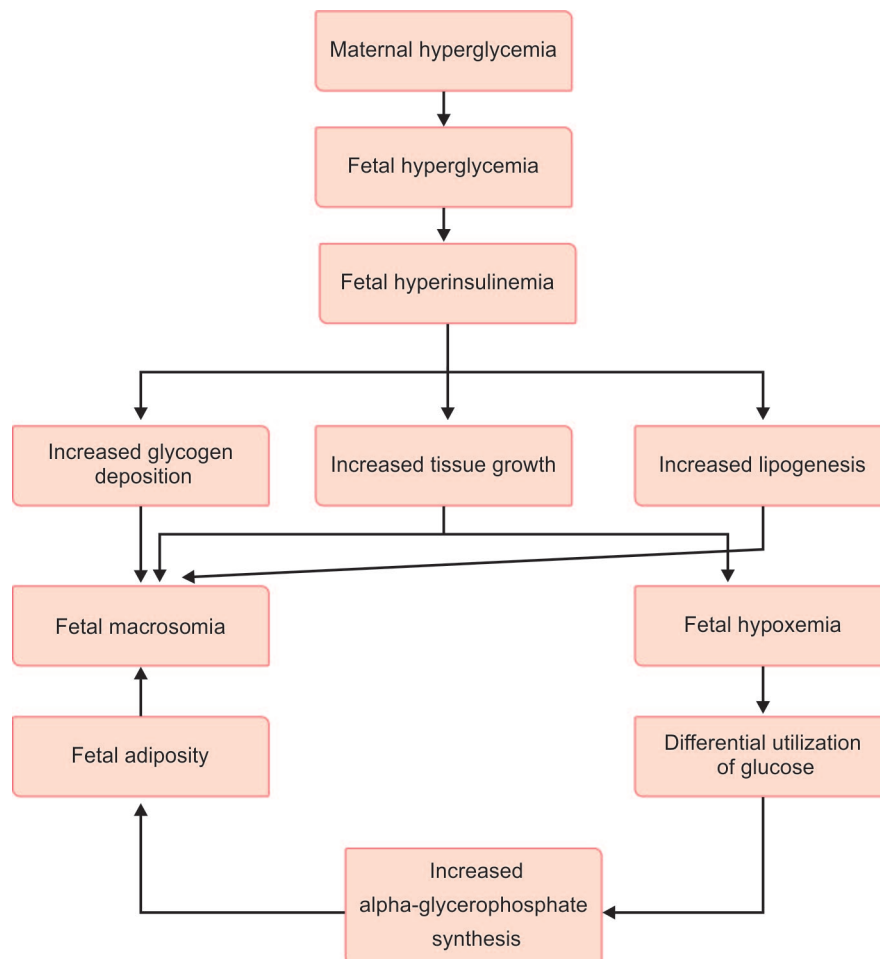
### PATHOGENESIS

Pederson in 1954 had postulated that uncontrolled maternal hyperglycemia has multiple effects on the developing fetus. Later in

Macfarlane CM et al. (1988) proposed a modified hypothesis to that of Pederson to explain pathways to fetal macrosomia in mothers with hyperglycemia (**Flow chart 1**). But, not all fetal complications are a direct consequence of maternal glycemic control. Prior to 20 weeks of gestation, fetal pancreatic islet cells usually do not secrete insulin in response to maternal hyperglycemia, and the effects at this period of gestation are the direct consequence of hyperglycemia. The fetal complications in later gestation are the result of fetal hyperglycemia, hyperinsulinemia or combined effect of both.

Poor control during the first trimester results in abortions or major malformations. When glycemic control is poor in the second trimester it is associated with higher risk of pregnancy-induced hypertension and preterm labor. Inadequate glycemic control in the third trimester is associated with fetal macrosomia and its attendant complications during delivery such as cesarean birth and birth trauma. It is also associated with higher neonatal complications associated with macrosomia such as respiratory distress syndrome, hypoglycemia and polycythemia. Fetal hyperglycemia with resultant fetal hyperinsulinemia contributes to increased fetal substrate uptake resulting in increased oxygen consumption making the developing fetus suffer from chronic hypoxemia. Fetal hypoxemia leads to altered utilization of glucose leading to metabolic acidosis in tissues and also increases the hypoxia in utero. Fetal hypoxia also results in increased amniotic fluid erythropoietin (EPO) levels. Increased red cell mass (polycythemia) due to high levels of erythropoietin leads to relative iron deficiency of major organs including brain and heart.

**Flow chart 1** Modified Pedersen hypothesis



## CLINICAL FEATURES AND NEONATAL COMPLICATIONS

Uncontrolled maternal glucose control during pregnancy is associated with a number of neonatal complications.

### Fetal Growth

Macrosomia or large for gestational age (LGA) is one of the cardinal features of infant of diabetic mother (IDM) especially when mothers have had poor glycemic control beyond 20 weeks of gestation. Large face with prominent cheeks, plethora, hairy pinna and excess body hair are the other common features seen in these neonates (**Fig. 1**). In the past the incidence of macrosomia amongst IDMs was reported to be about 60%, but with early diagnosis and more aggressive glycemic control, the reported incidence has dropped to less than 30%. Not all LGA infants born to diabetic mothers are macrosomic. In contrast to a constitutionally large infant where all anthropometric centiles (weight, length and head circumference) are proportionally higher, in IDMs, the weight centiles are disproportionately higher (usually above the 95th percentile) than the length and head circumference centiles. The expected difference between head circumference and chest circumference is often reduced (due to adiposity in the chest). A higher ponderal index, and *mid-arm circumference to head circumference ratio*, may guide in helping to differentiate an IDM LGA infant from other large for gestational age infants. Macrosomia in IDMs is a good predictor of the risk of metabolic problems such as hypoglycemia, hypocalcemia, and polycythemia. Large infants are more predisposed to shoulder dystocia and obstructed labor which increase the incidence of birth traumas (clavicular/humerus fracture, brs/phrenic nerve palsy, cephalhematoma/sub-galeal bleeds).

In contrast mothers with poorly controlled pregestational diabetes are at increased risk of having growth retarded or small for gestational age infants (probably due to associated diabetic vasculopathy).

### Malformations

Incidence of malformations is 3–8 times more common in IDMs than controls. Some of the common malformations associated with maternal diabetes include:

- **Central nervous system:** Neural tube defects, anencephaly and holoprosencephaly.
- **Cardiac:** Ventricular septal defect (VSD), patent ductus arteriosus, transposition of great vessels and truncus arteriosus.
- **Gastrointestinal tract:** Lazy left colon syndrome (also called small left colon syndrome), intestinal duplications and atresia.
- **Genitourinary:** Ureteral duplication, renal agenesis, hydronephrosis.
- **Caudal regression syndrome,** flexion contractures, vertebral defects and cleft palate.

Although cardiac malformations are more common, caudal regression syndrome is very specific to uncontrolled maternal diabetes.

### Hypoglycemia

Hypoglycemia is commonly seen in macrosomic or growth retarded infants born to diabetic mother compared to infants born appropriate for gestational age. In the large infants, hypoglycemia is usually a reactive phenomenon secondary to persistence of fetal hyperinsulinism into the neonatal period. Hypoglycemia may be compounded additionally by the perinatal anoxia, which increases catecholamine and glucocorticoid levels and contribute to glycogen depletion. The high neonatal insulin levels tend to persist for up to 72 hours and may rarely last up to one week. On the other hand, in the growth retarded infants, hypoglycemia is due to depletion of



**Figure 1** Infant of diabetic mother: Macrosomia, relative small head compared to body, chubby cheeks, plethoric face and hairy pinna

glycogen reserves. Symptoms of hypoglycemia include jitteriness, seizures, tachypnea, apnea and sweating. IDMs would need the close monitoring of blood glucose, and sufficient exogenous glucose to maintain glucose levels above 40 mg/dL.

### Hypocalcemia and Hypomagnesemia

Both hypocalcemia and hypomagnesemia (serum magnesium < 1.5 mg/dL) are probably due to delayed transition from fetal to neonatal parathyroid function. Both could be seen in up to 50% of IDMs. Hypomagnesemia may also be due to maternal magnesium deficiency resulting from increased magnesium loss in the urine among mothers with glycosuria. Symptoms of hypocalcemia and hypomagnesemia are similar, and include jitteriness, convulsions, sweating, and tachypnea. The symptoms usually appear in the first 24–72 hours.

### Respiratory Distress

Infants of diabetic mothers are more likely to develop respiratory distress after birth which may be due to respiratory distress syndrome (due to surfactant deficiency), transient tachypnea of newborn (due to cesarean delivery and/or birth asphyxia). IDMs are more likely to develop RDS compared to gestation matched infants born to nondiabetic mothers, as insulin antagonizes cortisol induced maturation of type II alveolar cells (and therefore decreased surfactant synthesis); this risk being seen up to 38 weeks of gestation age. Persistent pulmonary hypertension may complicate the course of RDS, particularly with co-existing polycythemia.

### Others

**Cardiac failure** Asymmetric septal hypertrophy or cardiomyopathy may be seen in up to 30% of IDMs, but only a third of them go on to develop frank congestive heart failure. Septal hypertrophy is the direct consequence of fetal hyperglycemia inducing hyperinsulinism and deposition of glycogen in the cardiac septum. Symptoms of cardiac failure can be exacerbated in the presence of polycythemia.

**Hyperbilirubinemia** IDMs are increased risk of hyperbilirubinemia because of higher red cell mass, ineffective erythropoiesis and delayed maturation of enzymatic pathways in liver.

**Polycythemia** Polycythemia defined as hemoglobin more than 20 g/dL or a hematocrit more than 65% is reported in up to 20–30%



**Table 1** Fetal and neonatal complications in neonates born to mother with diabetes mellitus and their management

<i>Problem</i>	<i>Pathophysiology</i>	<i>Prevention/management</i>
Malformations	Maternal hyperglycemia during the initial 14 weeks of gestation alters the maturation of different growth factor pathways and causes dys-organogenesis	Better periconceptional glycemic control Folic acid prophylaxis
Recurrent abortions	Uncontrolled maternal hyperglycemia and other associated morbidities lead to first trimester abortions	Better periconceptional glycemic control
Prematurity	Uncontrolled maternal hyperglycemia, fetal macrosomia, IUGR and iatrogenic termination	Good antenatal care and fetal monitoring Good glycemic control during pregnancy Antenatal steroids if expected delivery between 24 weeks and 34 weeks of gestation
Intrauterine death	Maternal microvasculopathy leads to increased placental resistance. Disproportionate fetal growth which is not met by the normal placenta predisposes them to adverse outcomes	Good antenatal care and fetal monitoring Good glycemic control during pregnancy
Macrosomia	Fetal hyperinsulinemia leads to increased adiposity and organomegaly. However, it will not affect the head size as brain glucose utilization is not dependent on fetal insulin levels	Better periconceptional glycemic control Good antenatal care and fetal monitoring Better antenatal glycemic control Care during delivery to avoid birth trauma
Growth retardation	Maternal microvascular changes leads to increased placental resistance and impairs the nutritional needs of the growing fetus	Better periconceptional glycemic control Good antenatal care and fetal monitoring Maternal nutrition and supplements
Respiratory distress syndrome	Fetal hyperinsulinemia impairs the maturation of surfactant. It will inhibit the incorporation of choline component in DPPC. It also impairs the release of various growth factors for production of mature surfactant and maturation of ion channels required for clearance of lung fluid	Better antenatal glycemic control Antenatal steroids as appropriate Provide adequate respiratory support—oxygen/CPAP/ventilation
Hypoglycemia (glucose < 40 mg/dL)	Fetal hyperinsulinemia, macrosomia, perinatal asphyxia and feeding difficulties predisposes these neonates to hypoglycemia	Screening blood sugars at 1, 6, 12, 24, 48 and 72 hours of life Supervised and schedule feeding, lactation support Early and aggressive therapy to prevent recurrence and seizures
Hypocalcemia (Total serum calcium level < 7 mg/dL)	Delayed transition from fetal to neonatal parathyroid control, Vitamin D antagonism due to elevated cortisol levels at intestinal level, asphyxia and relative prematurity at birth complicate the calcium metabolism	Monitor for jitteriness and other symptoms Screening for serum calcium at 2 and 12 hours Calcium supplementation for symptomatic newborns
Hypomagnesemia (< 1.5 mg/dL)	All the factors that operate in calcium metabolism will also operate for magnesium metabolism. Other factors include low maternal magnesium levels due to excess urinary losses secondary diabetic nephropathy	Monitor for symptoms of hypocalcemia Screen for low magnesium levels in nonresponsive hypocalcemia Treat symptomatic neonates with magnesium supplement
Hyperbilirubinemia	Excess red blood cell mass and relative immaturity of hepatic conjugating enzymatic pathways will increase the bilirubin levels	Monitor the neonates for hyperbilirubinemia Provide follow-up for early discharges
Feed intolerance	Prematurity, perinatal asphyxia and altered bowel motility in these neonates causes feed intolerance	Monitor for early symptoms Rule out other causes such as lactation counseling
Polycythemia	Intrauterine hypoxia leads to excess production of erythropoietin and other growth factors. This results in increased erythroid mass (around 30%)	Screening hematocrit at 2, 6, 12 and 24 hours of life Adequate fluids and liberal feeding Partial exchange transfusion (PET) in symptomatic cases
Hypertrophic cardiomyopathy	Fetal hyperglycemia with secondary hyperinsulinemia contributes to hypertrophy of ventricular wall and septum. Septal hypertrophy causes diastolic dysfunction	Screening by fetal/neonatal ECHO Management of heart failure B-blockers for improving the diastolic function Avoid digoxin and prolonged inotropic support

Abbreviations: IUGR, intrauterine growth restriction; CPAP, continuous positive airway pressure.

of IDMs at birth. Polycythemia can result in increased blood viscosity and if persistent can result in seizures, stroke, necrotizing enterocolitis and renal vein thrombosis. Polycythemia infants are usually plethoric, lethargic and may have jitteriness.

**Iron deficiency** Several studies have shown that two-thirds of IDMs and most of IDMs who are macrosomic are iron deficient at birth. Most of these infants have low serum ferritin levels; the more severely affected infants would also have increased total iron

binding capacity, decreased transferring saturations and increased free erythrocyte protoporphyrin levels. Perinatal iron deficiency may place IDMs at increased risk of neurologic injury when associated with perinatal anoxia.

**Central nervous system** IDMs are likely to have neurologic symptoms such as depression, irritability, jitteriness and convulsions. These could be due to multiple factors—perinatal anoxia, birth trauma, hypoglycemia, hypocalcemia, polycythemia, and hypoxia.

## MANAGEMENT

Common perinatal problems and their management are summarized in **Table 1**. Periconceptional glycemic control is required to avoid embryopathy and fetal wastage. Early screening, good glycemic control during pregnancy with diet, exercise and insulin would improve the perinatal outcomes.

**Delivery room management** There must be a team of well trained nurses and pediatricians along with the obstetrician to manage the birth of an IDM because of the risks of shoulder dystocia and perinatal asphyxia and depression. The team must be capable to effectively resuscitating these babies at birth. The team must also be able to perform a complete physical examination of the infant to identify malformations and stabilize the infant in case of respiratory distress.

**Monitoring in the NICU** The infant must be closely monitored for respiratory distress, hypoxia, hypoglycemia and polycythemia at frequent intervals (**Table 1**).

**Feeding and hypoglycemia** IDMs who are asymptomatic should be allowed to breastfeed which should be initiated within the first hour of birth. Infants with poor sucking may be fed by orogastric feeding. Monitoring for blood sugar should continue as per frequency outlined in **Table 1**. Those who develop hypoglycemia should be treated using standard guidelines (Chapter 14.4).

**Respiratory distress** All IDMs with respiratory distress must be provided oxygen supplementation and ventilation as required. All these infants should have a chest skiagram to differentiate RDS, transient tachypnea of the newborn (TTN), pneumonia or pneumothorax. If chest X-ray suggests RDS, these infants may need surfactant treatment in addition to respiratory support. TTN would only require oxygen or rarely ventilator support for about 24–72 hours. However, all infants must undergo an echocardiography to identify presence or absence of a cardiac malformation and asymmetrical septal hypertrophy.

**Asymmetrical septal hypertrophy** Symptomatic infants should be treated with beta-blockers as it improves outflow obstruction. Oral propranolol is started at 0.25 mg/kg/dose q6h, increase as needed to a maximum of 3.5 mg q6h. If using intravenous route starting dose is 0.01 mg/kg over 10 min q6h, increase as needed to maximum to 0.15 mg/kg q6h. Propranolol administration must be under careful blood pressure monitoring.

**Polycythemia** All symptomatic infants and those with a hematocrit more than 70% must undergo partial exchange transfusion to reduce viscosity.

**Hypocalcemia and hypomagnesemia** Only symptomatic infants should be treated. Hypocalcemia should be treated by infusing 2 mL/kg of 10% calcium gluconate (adequate equal dilution) through a large vessel (to prevent extravasations and subcutaneous necrosis) slowly under cardiac monitoring. This should be followed by 75 mg/kg/day of calcium as infusion. Refractory or recurrent

hypocalcemia associated with hypomagnesemia can be treated by 0.12 mL/kg of 50% magnesium sulphate intramuscularly (this would increase the serum magnesium by 1 mg/dL over 6 hours and correct the hypocalcemia).

## OUTCOMES

The prenatal exposure of the fetus to hyperglycemia and its postnatal consequence may result in adverse neurological and neurodevelopmental outcomes. Neurodevelopment outcome of IDM with good euglycemia during antenatal period is similar to that of normal controls. However, poorly controlled blood sugars in the antenatal period may result in adverse long-term outcomes. IDMs have a higher risk than their peers for diabetes mellitus, impaired glucose intolerance and obesity. The lifetime risk of infants of diabetic mother for type 1 diabetes mellitus is 2% compared to 0.3–0.4% in infants not having any family history.

### IN A NUTSHELL

1. Poor glycemic control in pregnancy is associated with increased risk of adverse fetal and neonatal outcomes.
2. Fetal macrosomia is associated with increased risk of perinatal asphyxia, birth trauma, neonatal hypoglycemia, polycythemia and asymmetrical septal hypertrophy.
3. All IDMs must be carefully examined for malformations and monitored for respiratory distress, hypoglycemia, hypocalcemia and polycythemia.
4. All IDMs with respiratory distress must undergo a chest skiagram and echocardiography (to exclude cardiac malformation and asymmetric septal hypertrophy).
5. Only symptomatic IDMs need to manage in NICU, the others can be managed in a well baby area with adequate monitoring.

## MORE ON THIS TOPIC

- Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. *Pediatrics*. 1990;85:1-9.
- Dabelea D, Knowler WC, Pettitt DJ. Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. *J Matern Fetal Med*. 2000;9:83-8.
- Macfarlane CM, Tsakalakos N. The extended Pedersen hypothesis. *Clin Physiol Biochem*. 1988;6:68-73.
- Nold JL, Georgieff MK. Infant of the diabetic mothers. *Pediatr Clin N Am*. 2004;51:619-37.
- Rizzo TA, Dooley SL, Metzger BE, et al. Prenatal and perinatal influences on long-term psychomotor development in offspring of diabetic mothers. *Am J Obstet Gynecol*. 1995;173:1753-8.
- Sells CJ, Robinson NM, Brown Z, Knopp RH. Long-term developmental follow-up of infants of diabetic mothers. *J Pediatr*. 1994;125:S9-17.

## Chapter 14.5

# Neonatal Hypoglycemia

Shiv Sajjan Saini, Praveen Kumar

Diagnosis and management of neonatal hypoglycemia is both challenging and controversial. There is no clear definition and *safer limits* of blood sugar levels in neonates. These limits might conceptually be different among neonates of variable gestational ages with different maturity levels, influence of intrauterine growth retardation, and levels of illness severity. What makes it even more complex is the perinatal adaptation after birth. The fine balance between glucose utilization and production is responsible for maintenance of stable blood sugar levels. This balance is secondary to coordinated changes in the concentrations of insulin and the counter-regulatory hormones, principally growth hormone, cortisol, glucagon, and catecholamines. However, immaturity of these pathways leads to disturbances in glucose homeostasis mainly hypoglycemia. The neonatal hypoglycemia is usually transient but less frequently persistent. Hypoglycemia in neonatal period may be asymptomatic or can present with ominous signs like seizures. Any type of hypoglycemia, however, can lead to significant neurological morbidity and long-term complications. Hence, neonatal hypoglycemia should always be given urgent attention. In this chapter, the authors have reviewed the definition, pathophysiology, methods of measurement of blood sugar, prevention, and treatment of neonatal hypoglycemia.

## PHYSIOLOGICAL CONSIDERATIONS

The fetus is mainly dependent on transplacental transfer of nutrients including glucose. Although fetus is equipped with gluconeogenic enzymes at 2 months, endogenous glucose production is not physiological in fetal life. Glucose crosses the placenta by facilitated diffusion and hence fetal blood glucose concentrations are slightly lower than mother. A part of maternal glucose is converted by the placenta to lactate, which is released into the fetal and maternal circulation in 1:3 ratio. Although glucose is the principal energy substrate for the human fetus, lactate acts a major substrate for both oxidative and non-oxidative metabolism. At birth, glucose level in the umbilical venous blood is 80–90% of maternal levels. There is a sharp decline in neonatal blood glucose concentration after cord clamping due to sudden cessation of maternal glucose supply. The neonatal blood glucose concentration reaches its nadir by 1 hour of age before recovering and stabilizing by 3 hours of life.

This postnatal adaptation is achieved with the help of metabolic changes including hepatic glycogenolysis, gluconeogenesis; lipolysis, fatty acid  $\beta$ -oxidation with generation of ketone bodies, and proteolysis that generates lactate and other substrates for gluconeogenesis. There is substantial variability in blood glucose levels during postnatal adaptation, both within individual neonates and among neonates of different gestational ages and growth patterns. There are major endocrine changes including fall in plasma insulin levels, marked rise in plasma glucagon, catecholamine surge after stress of birth, and rise in growth hormone concentration. Ketone bodies and lactate serve as important alternative fuels for maintaining cerebral energy supply. Newborn brain has 5–40 fold greater capacity to utilize ketone bodies compared to that of infant or adult brain. Lactate appears to be important for neonates in the immediate postnatal life.

There is a greater fall in blood glucose levels among preterm neonates after birth as compared to term infants. There are conflicting reports of glucose production rates in preterm neonates

as compared to term neonates in postnatal life. Some reports suggest higher circulating levels of gluconeogenic substrates and low activity of microsomal glucose-6-phosphatase (the final enzyme of glycogenolysis and gluconeogenesis) leading to lower levels in preterm neonates; while some showed similar glucose production rates as compared to term neonates. However, preterm infants, in the first week of postnatal life, lack a mature counter-regulatory ketogenic response to low blood glucose levels which can persist during first 8 postnatal weeks and even beyond. Preterm neonates display higher plasma immunoreactive insulin concentrations at low blood glucose levels as compared to term counterparts. The basal insulin concentrations decrease with increasing maturity.

## DEFINITION

The *low level* of blood glucose is difficult to define in neonates because of several reasons. Neonates of various gestation ages have variable maturity of nervous system and variable capacity to manifest the signs and symptoms of hypoglycemia. The *critical limit* of blood glucose levels required for integrity of neonatal brain function is currently unknown. Additionally, hypoglycemia often occurs in association with other morbidities, which in turn could potentiate brain injury. Along with comorbidities, the *safe glucose limits* are likely to be higher as compared to isolated hypoglycemia. Various definitions of hypoglycemia have been proposed by different authors.

Conventionally, hypoglycemia is defined by a value lying outside the normal distribution obtained in healthy neonates, i.e., less than 2 standard deviations (SD). The statistical abnormality is not sine qua non with biological abnormality. Additionally, minus 2 SD cut-off values might vary with the gestational age, postnatal age, type of feeding and physiological state. Finally this cut-off does not consider the complexities of the metabolic milieu, the availability of alternative substrates and the clinical condition of the baby. The clinical manifestations of hypoglycemia (i.e., lethargy, tremor, sweating, cyanosis, jitteriness, hypotonia, coma, and seizures) are well recognized and may be useful to define hypoglycemia. However, majority of these signs are nonspecific and certain signs like jitteriness may be seen even in normal healthy neonates. More importantly, the clinical definition may not cover neonates with asymptomatic hypoglycemia, which can cause hypoglycemic brain injury. Furthermore, the levels of blood glucose at which clinical manifestations appear may be different from the levels at which biochemical injury occurs leading to long-term neurological sequelae. Hence, clinical definition alone cannot be used for clinical purposes, nevertheless presence of clinical signs of encephalopathy such as decreased level of consciousness or seizures should put physician on red alert. Stimulation of counter-regulatory hormonal response at *threshold* blood glucose concentrations can also be used to define hypoglycemia. However, there is little information available on this complex issue. Additionally, preterm neonates have limitations in mounting a mature counter-regulatory response to low blood glucose levels, making this judgment unsuitable for them. Change in neurophysiological functions, e.g., evoked potentials in response of *low glucose* levels, could be another way to define hypoglycemia. The cut-off levels associated with adverse neurodevelopmental outcomes could also be used to define hypoglycemia. However, there is limited literature about these definitions and the association of such *thresholds* of blood sugar values to neurophysiological properties, hormonal mechanisms or neurodevelopmental outcomes are poorly reproducible.

Hence, it is difficult to identify any particular levels of plasma glucose values that define *pathologic hypoglycemia*. In the absence of unanimous definition of hypoglycemia, *operational thresholds* may be a useful guide for clinicians to take appropriate action rather than diagnostic of a disease. However, the operational thresholds are expert consensus, which are not evidence based and there is

no evidence to suggest improved outcomes following operational threshold. Nevertheless, American Academy of Pediatrics (AAP) recommends cut-off levels of plasma sugar of 47 mg/dL for all neonates.

## GLUCOSE METABOLISM AND BRAIN INJURY

Glucose and oxygen are the principle substances required for energy production in brain. Glucose supply to the brain is regulated by the plasma glucose concentration through facilitated diffusion via glucose transporter 1 (GLUT-1) and GLUT-3. It gets converted to glucose-6-phosphate (via hexokinase), which enters glycolytic pathway to produce energy [adenosine triphosphate (ATP)]; enters hexose monophosphate (HMP) shunt to produce reducing equivalents (for lipid synthesis and nucleic acid synthesis) and gets converted to glycogen. This glycogen is stored in astrocytes and used for energy production. In situations of low blood glucose levels, the cerebral blood flow increases initially so as to increase glucose supply to the brain. Initial metabolic changes include attempts to preserve cerebral energy status by utilizing alternative fuels and initiation of glycogenolysis. In addition to alternative fuels like lactate and ketone bodies, amino acids may also be alternative substrates, as the concentrations of most amino acids decrease sharply along with increase in brain ammonia levels. The concentration of ammonia increases in proportion to decrease in levels of amino acids. Hence, even early in course of hypoglycemia the consciousness levels may fall despite relative preserved ATP levels. This can explain the dissociation between cerebral energy metabolism and neuronal functions during hypoglycemia in some cases. Nevertheless the newborn brain shows relative resistance towards neuronal injury to hypoglycemia, which may be secondary to relatively lower cerebral energy requirements, increase in cerebral blood flow in early phases of hypoglycemia, increased capacity of neonatal brain to utilize alternative brain fuels and relatively less effect on cardiovascular system due to abundant endogenous carbohydrate stores compared to adults. Ketone bodies are taken up by carrier-mediated transport, metabolized after getting converted to acetyl coenzyme A. The therapeutic role of exogenous ketone bodies in hypoglycemia is not known. Lactate gets oxidized to pyruvate by lactate dehydrogenase which is utilized to produce energy.

With continuation of hypoglycemia, energy deficit occurs in cells. In such conditions, there is failure of energy dependent  $\text{Na}^+$ / $\text{K}^+$ -ATPase which renders neurons to lose their ability to maintain normal ionic gradients; i.e., changes in intracellular  $\text{Ca}^{++}$  and extracellular  $\text{K}^+$  concentration. There is intracellular accumulation of  $\text{Na}^+$  and extracellular accumulation of  $\text{K}^+$  leading to sustained membrane depolarization. Intracellular accumulation of  $\text{Na}^+$  would lead to activation of  $\text{Na}^+/\text{Ca}^{2+}$  exchange system and intracellular  $\text{Ca}^{2+}$  accumulation. This leads to phospholipase activation, release of excitatory amino acids (e.g., aspartate and glutamate) from synaptic nerve endings, increase in reactive oxygen and nitrogen species, cellular injury. With continuing hypoglycemia, changes secondary to hypoxia, ischemia and seizures may add to the insult. These combined effects are of major concern as it increases the chances of brain injury even if individual insults are not of sufficient magnitude to cause injury by themselves.

## Pathological Changes in Hypoglycemic Brain Injury

As hypoglycemia quite often coexists with other morbidities, it is difficult to define exact neuropathology in such newborns. However, the topography of the hypoglycemic brain injury is peculiarly shown to have predilection for parieto-occipital cortex. Less commonly it involves hippocampus, caudate nucleus, and putamen. Primarily neurons are involved in hypoglycemic brain

injury but glia are also affected. Hypoglycemia induces apoptotic cell death oligodendrocyte precursor cells and inhibits their differentiation and myelination. The sequelae of hypoglycemic brain injury include microcephaly, widened sulci and atrophic gyri, diminished cerebral white matter and dilated lateral ventricles.

## EPIDEMIOLOGY

Hypoglycemia is commonly associated with a variety of neonatal illnesses. The incidence of hypoglycemia varies with proportion of term and preterm neonates in the population, intrauterine growth status, type and pattern of feeding, screening timings and methods, sickness level and definition used for the diagnosis of hypoglycemia. Lucas et al. found that among 661 preterm neonates of birth weight less than 1850 g, 66% had at least one value of blood glucose less than 2.6 mmol/L ( $< 45$  mg/dL approximately) and 28% had at least one value less than 1.6 mmol/L ( $< 30$  mg/dL approximately). In a study from New Delhi, 107 (7%) neonates were found to have hypoglycemia (cut-off blood sugar  $< 30$  mg/dL) among 2,248 neonates of all gestational ages. The incidence among all preterm neonates was 12.8%. The maximum incidence was noted among small or large for gestation preterm neonates as 20.6 and 21.7%. Similarly among 92 neonates weighing less than or equal to 1,750 g at birth, incidence of hypoglycemia was found to be 26% in a study from Chandigarh.

## CLINICAL FEATURES

The clinical manifestations of hypoglycemia are predominantly nonspecific and related to central nervous system. Commonly hypoglycemia in neonates present with jitteriness, irritability, varying degree of depressed consciousness, seizures, apnea, tachypnea and hypotonia. Singhal et al. have found that among 43 symptomatic neonates out of a cohort of 2248, lethargy was most common symptom (81%), followed by jitteriness (67%), apnea or tachypnea (42%), hypotonia (40%), seizures (30%), and circumoral cyanosis (19%). It is important to realize that hypoglycemia can be asymptomatic. Singhal et al. have found proportion of asymptomatic neonates as 60% among 107 neonates with hypoglycemia.

Based on the clinical setting of hypoglycemia, time and severity of presentation, the neonates with *symptomatic hypoglycemia* can be classified into four categories:

1. *Early transitional adaptive hypoglycemia*: This form manifests in first 6–12 hours of life, after sudden cessation of maternal blood supply. Such neonates fail to mount appropriate metabolic adaptive responses in immediate postnatal life. It is seen that glycolytic and gluconeogenic responses of the neonate are blunted and insulin secretion increases in immediate postnatal life if the mother receives excess glucose in intravenous fluids during intrapartum period. Additional risk factors include neonates who experience hypothermia or asphyxia, large for gestational age infants born to diabetic [infant of diabetic mother (IDM)] or nondiabetic mothers. This form of hypoglycemia lasts briefly, and is mild in severity. The response to treatment is good but the ultimate prognosis depends mainly on the underlying cause.
2. *Secondary associated hypoglycemia*: This form is associated with illnesses other than hypoglycemia particularly involving central nervous system, e.g., birth asphyxia, intracranial hemorrhage; congenital anomalies and other systemic disorders. This variety of hypoglycemia also remains for short duration, is mild in severity and responds rapidly to treatment.
3. *Classic transient neonatal hypoglycemia*: This group predominantly consists of small for gestation term infants, who may concomitantly have polycythemia. The hypoglycemia



manifests in later part of first day. This variety of hypoglycemia is generally moderate to severe, of prolonged duration and often requires high glucose infusion rates.

4. **Severe recurrent hypoglycemia:** This variety is characterized by recurrent or persistent hypoglycemia which occurs in term appropriate for gestational age neonates with endocrinopathies or hereditary metabolic defects. The hypoglycemia is usually severe and is difficult to treat. Neonates are invariably symptomatic. The prognosis depends on the timely detection, appropriateness of therapy and underlying cause.

## MONITORING OF BLOOD GLUCOSE

All preterm and small for date neonates have decreased body stores of glycogen; are associated with other illnesses and hence require blood glucose screening to detect hypoglycemia. Neonates born to mothers with diabetes especially IDM neonates and many large for gestation age infants have excess insulin secretion in the immediate neonatal period, which makes them vulnerable for harmful effects of hypoglycemia. Apart from these neonates, all *unwell* neonates should be monitored for hypoglycemia. Common indications of monitoring blood glucose in newborns are shown in **Table 1**.

### When to Screen 'At-Risk' Neonates?

The neonates, who are predisposed for higher insulin levels, become symptomatic very early in postnatal life. Due to raised levels of insulin, the alternative fuels (ketone bodies and lactate) are less in such neonates, making them even more vulnerable to harmful effects of hypoglycemia. Hence, IDM and severely intrauterine growth retarded neonates deserve screening right from cord blood. This should be followed by the routine screening in the postnatal life for initial 48 hours. Preterm and neonates with intrauterine growth restriction, who are *at risk* should get initial screening within 1 hour of life. All neonates who are symptomatic should be immediately screened get blood glucose levels checked immediately. Screening the asymptomatic at-risk neonates should be performed within the first hours of birth. Standard textbooks and guidelines recommend blood glucose monitoring at 1 hour, 2 hours, 3 hours, 6 hours and then 6 hourly till 48–72 hours by when feeding is likely to be established. Blood glucose should be checked immediately prior to feed, as the screening should be able to identify lowest blood glucose levels.

### Methods of Blood/Plasma Sugar Estimation

An ideal method of blood glucose determination is by laboratory estimation. There are three enzymatic methods namely glucose oxidase, hexokinase, and dehydrogenase method. Plasma glucose measurements are 10–18% higher than blood glucose values. However, the results are not available quickly while using laboratory methods and hence these methods are not very useful for a bedside physician in a symptomatic neonate. At bedside, the

blood glucose measurements are performed with the help of point-of-care glucose meters. The results are available within few seconds and as small as 0.3  $\mu$ L blood sample is required. Hence, all over the world point of care glucometer devices are used for routine measurements, for taking treatment decisions. Glucose values given by point-of-care devices or glucometer might vary from the actual laboratory values by as much as 10–20 mg/dL. These glucometers devices have greatest variation at low glucose concentrations. Due to these limitations the low values by glucometer devices must be confirmed by laboratory methods. Care should be taken to draw the sample in a *glycolytic inhibitor* like fluoride, else the glucose values might be falsely low due to ongoing glycolysis in the sample. Treatment of suspected hypoglycemia should not be postponed awaiting laboratory confirmation as the delay in initiating management might result in hypoglycemic brain injury. However, the scientific evidence showing mitigation of neurologic sequelae by such rapid treatment is also lacking.

One should be aware that some biological parameters might also influence blood glucose values. These include metabolic acidosis, hypoxia, hypoperfusion, or edema. Glucose oxidase method might give abnormally low values at high blood oxygen levels. High hematocrit levels might display falsely low levels. Red blood corpuscles contain proportionally less water than plasma. This problem can be taken care by estimating plasma glucose rather than whole blood. High bilirubin levels may interfere with some analyzers. The glucose concentration in arterial blood is slightly higher than capillary which in turn is slightly higher than venous blood, although the differences are not clinically significant. However, these changes might be relevant if tissue glucose demands increases, e.g., under anaerobic conditions. Blood glucose values, in capillary blood in setting of peripheral circulatory failure, are unreliable as the blood flow is reduced. It is important to get a free-flowing sample, as *squeezing* the tissues to get blood causes hemolysis and alters blood glucose values. Use of alcohol antiseptic solutions for skin preparations might contaminate the sample to give erroneously high values. Delay in processing the sample might also give erroneous values due to ongoing glycolysis. Sodium fluoride added to blood inhibits glycolysis; however longer delays should still be avoided as fluoride is not able to completely prevent it. The sample should be deproteinized (e.g., using perchloric acid) and chilled to avoid glycolysis in such cases. Deproteinization also reduces the interference with hemolysates, uric acid, and bilirubin.

In addition to laboratory methods and glucometers, blood gas and electrolyte analyzers can directly measure blood glucose by electrochemical biosensors. Furthermore, now-a-days continuous glucose monitoring is also possible with the help of subcutaneous glucose oxidase-based platinum sensors or microdialysis. The glucose value measured by sensors is averaged for every 5 min and glucose trend is generated. The risks and benefits of such systems need to be fully evaluated before introducing them in routine clinical

**Table 1** Indications of monitoring blood glucose

Maternal indications	Neonatal indications
<ul style="list-style-type: none"> <li>Maternal drug ingestion, e.g., <math>\beta</math>-blockers, oral hypoglycemics, <math>\beta</math>-sympathomimetics</li> <li>Insulin dependent diabetic mothers</li> <li>Gestational diabetic mothers</li> <li>Massively obese mothers</li> <li>Mothers given large amounts of parenteral glucose during labor and delivery</li> <li>Mothers given parenteral glucose too rapidly prior to delivery</li> </ul>	<ul style="list-style-type: none"> <li>Prematurity</li> <li>Small or large for gestational age</li> <li>Hypothermia</li> <li><i>Sick looking or unwell neonate</i></li> <li>Sepsis</li> <li>Hypoxia ischemia</li> <li>Polycythemia</li> <li>Congenital heart diseases</li> <li>Total parenteral nutrition</li> <li>Blood exchange transfusion</li> <li>Suspected inborn errors of metabolism</li> </ul>

practice. These devices are invasive, expensive, need calibration, and are associated with a significant lag time in collection and measurement. Their role is currently restricted in research settings.

## PREVENTION

The most common reason for low blood glucose levels in immediate postnatal life is delay in normal metabolic adaptation after birth. Therefore, breast or enteral feeds should be initiated within half hour of life in appropriately grown term healthy neonates. In preterm infants of less than 32 weeks gestation or those with neonatal morbidities (e.g., asphyxia or respiratory distress) or any illness interfering with enteral nutrition, intravenous dextrose infusions should be started immediately after stabilization. Glucose delivery in intravenous infusions should correlate with endogenous glucose production. Hence, a glucose infusion rate of 6 mg/kg/min is appropriate for most preterm infants. Wherever there is no contraindication for feeds, an early enteral feeds should always be attempted and gradually increased along with. Late preterm infants of 33–36 weeks gestation require careful nursing to establish enteral feeds due to their physiological handicaps. Expressed breastmilk should always be the first option for enteral nutrition; however supplementary feeds might be needed if breast-feeding is not fully established. The amino acids in enteral feeds might be additional stimulation for gluconeogenesis and hence reduce the duration of intravenous fluids.

## TREATMENT

The management in cases of neonatal hypoglycemia should account for the overall metabolic and physiologic status of the neonate. One should avoid unnecessarily disruption of mother-infant relationship and breastfeeding. The intervention for *low* blood glucose levels should be tailored to the clinical scenario and individualized for infant in consideration. For example, a symptomatic neonate with a plasma glucose concentration of less than 40 mg/dL deserves immediate intravenous glucose treatment and further evaluation. On the other hand a breastfed, asymptomatic term neonate may only require frequent feeding and intravenous therapy may be required only for glucose values less than 25 mg/dL (birth to 4 hours of age) or less than 35 mg/dL (4–24 hours of age) (American Academy of Pediatrics recommendations 2011, **Figure 1**). In such cases glucose value should be rechecked 1 hour after feeding. If the repeat blood glucose levels are recorded lower than 25 mg/dL, or lower than 35 mg/dL, respectively, intravenous glucose infusion should be started. No such guidelines are available for preterm neonates less than 34 weeks and a cut-off of 40 mg/dL should be followed in these neonates. All cases of hypoglycemia whether symptomatic or asymptomatic deserves prompt attention and intervention due to risk of neuronal injury. A reasonable (although empirical) cut-off of blood glucose for treating symptomatic infants is 40 mg/dL. Rapid correction in neonatal hypoglycemia can be achieved with glucose *minibolus* (200 mg glucose/kg, 2 mL/kg of 10% dextrose), as this quickly raises the blood glucose concentration. A minibolus must always be followed by intravenous glucose infusion. If the minibolus is not followed by continuous infusion, a rebound hypoglycemia ensues. The glucose infusion should be initiated at an infusion rate of 6–8 mg/kg/min. After initiation of IV dextrose infusion, repeat blood glucose performed within 20–30 min. If the repeat blood sugar is in *hypoglycemic* range then the glucose infusion rate should be hiked in steps of 2 mg/kg/min. This hike should continue every 20 min until the blood glucose values are maintained between 40 mg/dL and 50 mg/dL. After stabilization of blood glucose levels, frequency of monitoring should be decreased to 4–8 hourly preprandial values. Usually the glucose levels are stabilized between 5 mg/kg/min and 8 mg/kg/min glucose infusion. If the glucose infusion is not maintained after 24 hours at this infusion rates, then consideration

should be given to possibility of hyperinsulinemia. A concentration of more than 12.5% glucose can cause injury to peripheral veins, hence a peripherally inserted central catheter line should be placed. While tapering off, the glucose infusion should be slowly tapered by 2 mg/kg/min every 6–12 hourly to avoid wide swings in blood glucose concentrations. In cases where intravenous line is not available, an intramuscular glucagon may act as a temporary measure to raise blood glucose. Side-effects of glucagon include vomiting, diarrhea, and hypokalemia; at high doses it may stimulate insulin release.

## Refractory or Persistent Neonatal Hypoglycemia

Refractory or persistent hypoglycemia is defined as the requirement of a glucose infusion rate more than 12 mg/kg/min to maintain normoglycemia or persisting or hypoglycemia beyond first 5–7 days of life. Although traditionally it is defined beyond 5–7 days of life, recent AAP recommendations suggest considering this diagnosis beyond 24 hours of life if the blood sugar requirements are above 8 mg/kg/min. The causes of refractory or persistent hypoglycemia are related to endocrine or metabolic disturbances (**Table 2**).

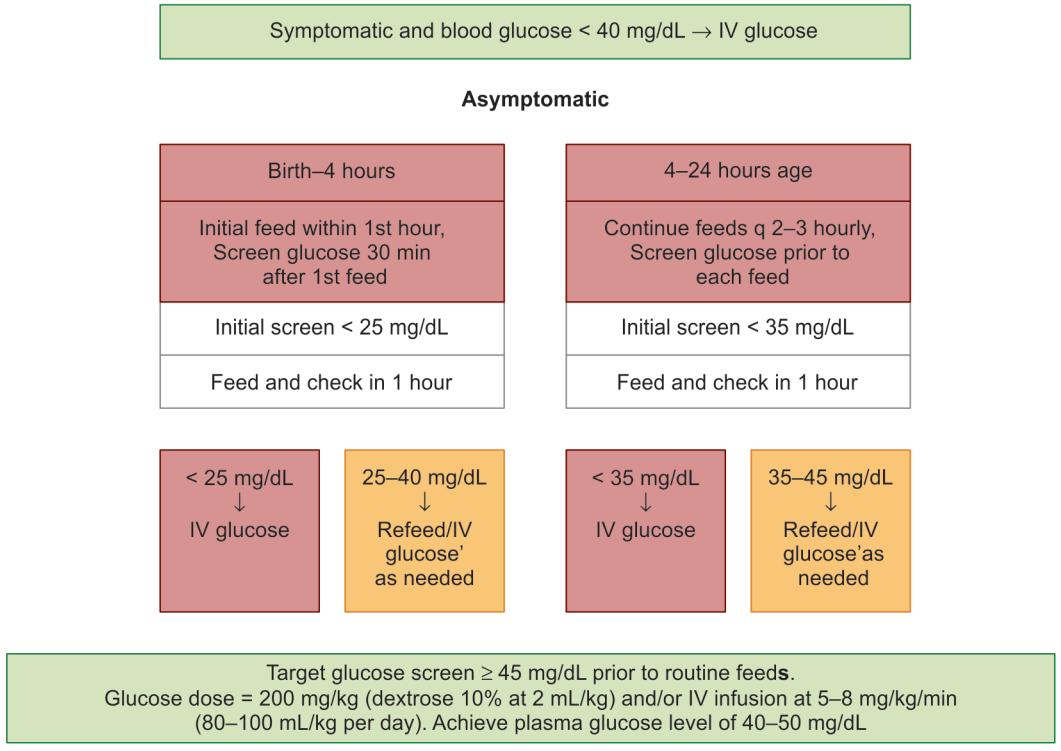
Congenital hyperinsulinism is the most common cause of persistent hypoglycemia, which is also known as persistent hyperinsulinemic hypoglycemia of infancy (PHHI). The diagnosis is confirmed by:

- Hyperinsulinemia (defined as plasma insulin > 2  $\mu$ U/mL), concomitantly with laboratory hypoglycemia (< 50 mg/dL); and/or
- Evidence of excessive insulin effect in form of:
  - Glucose infusion rate more than 8 mg/kg/min
  - Plasma free fatty acids less than 1.5 mmol/L
  - Hypoketonemia (plasma  $\beta$ -hydroxybutyrate < 2.0 mmol/L)
  - Glycemic response (glucose > 30 mg/dL) to 50  $\mu$ g/kg IV glucagon

Insulin levels are relevant only if sample is obtained during hypoglycemia. Insulin-glucose ratio can also be calculated (normal up to 0.2). An elevated insulin-glucose ratio (> 0.4) is found in hyperinsulinemic states. A *normal* or increased level of insulin is considered abnormal if it occurs along with hypoglycemia. PHHI results from elevated secretion of insulin. Due to anabolic effects of insulin, alternative fuels (ketones and lactate) levels decrease and hence newborn brain under such circumstances is particularly vulnerable to hypoglycemic injury. There is a risk of neonatal seizures and neuronal injury if it is left untreated. Hypoglycemia presents early within 72 hours after birth and half of the patients symptomatic hypoglycemia mainly in the form of seizures. The affected neonates may present with other signs of hypoglycemia. Occasionally, hyperinsulinism can be associated with syndromes such as Beckwith-Wiedemann syndrome (BWS), Sotos syndrome, Perlman syndrome, etc.

The treatment should be aggressive due to increased chances of neuronal injury. Invariably these neonates are already on intravenous glucose at the time of diagnosis of hyperinsulinemia. Medical management options include drugs such as diazoxide, nifedipine and octreotide. Diazoxide activates sulfonylurea 1 receptors and blocks insulin secretion. Diazoxide (5–20 mg/kg/day in three divided doses orally) is well tolerated by neonates except in premature neonates. It causes sodium and fluid retention, which may cause edema, heart failure or pulmonary hypertension. Hypertrichosis may occur after prolonged use. Two episodes of hypoglycemia [< 54 mg/dL] occurring in 24-hour period defines diazoxide unresponsiveness. Octreotide (5–25  $\mu$ g/kg/day 6–8 hourly SC injection or IV infusion) must be tried in these cases before considering surgery. Higher doses may suppress both glucagon and growth hormone and worsen hypoglycemia. Transiently some patients may develop vomiting and/or diarrhea and abdominal distension, which spontaneously resolves within 7–10 days. Calcium channels blockers (nifedipine, 0.25–2.5 mg/kg/day in two divided oral doses) can also be tried in such cases. Surgery is considered if medical management is not successful. Patients must be assessed for histological form of

Screening and management of postnatal glucose homeostasis in late preterm and term SGA, IDM/LGA (Late preterm) infants 34–36 weeks, and SGA (screen 0–24 hours); IDM and LGA ≥ 34 weeks (screen 0–24 hours)



**Figure 1** Treatment of neonatal hypoglycemia

Adapted and modified from: Committee on fetus and newborn. Postnatal glucose homeostasis in late preterm and term infants. Pediatrics 2011.

**Table 2** Causes of refractory or persistent hypoglycemia

<i>Hormone deficiencies</i>	Multiple endocrine deficiency	Congenital hypopituitarism Anterior pituitary “aplasia” Congenital optic nerve hypoplasia
	Primary endocrine deficiency	Isolated growth hormone deficiency Adrenogenital syndrome Adrenal hemorrhage
<i>Hormone excess with hyperinsulinism</i>	Beckwith-Wiedemann syndrome Hereditary defects of pancreatic islet cells	
<i>Hereditary defects in carbohydrate metabolism</i>	Glycogen storage disease Fructose intolerance Galactosemia Glycogen synthase deficiency Fructose-1, 6-diphosphatase deficiency Ketogenic and ketolytic defects	
<i>Hereditary defects in amino acid metabolism</i>	Maple syrup urine disease Propionic acidemia Methylmalonic acidemia Tyrosinosis	
<i>Hereditary defects in fatty acid metabolism</i>	3-OH-3-methylglutaryl-CoA lyase deficiency Acyl-CoA dehydrogenase--medium, long chain deficiency Mitochondrial/3-oxidation and degradation defects	

Reproduced with permission: From Kumar PS. An update on neonatal hypoglycemia. In: Rigobilo E. Hypoglycemia—Causes and Recurrences. Rijeka: InTech; 2011. pp. 55-84.

hyperinsulinemia beforehand as there are two histological forms (focal and diffuse) of hyperinsulinemia which differ in choice of surgery. Positron emission tomography (PET, 18F-fluoro-L-dopa isotope) can differentiate between the two histological forms. PET has replaced previously employed pancreatic catheterization with pancreatic venous sampling. The focal form, which occurs due to focal adenomatous hyperplasia of islets  $\beta$ -cells within the pancreatic tissue, requires partial and selective pancreatectomy. However, in diffuse form, all the  $\beta$ -cells of the pancreas are abnormal. Hence, subtotal pancreatectomy may improve the patient's condition.

### MORE ON THIS TOPIC

- Committee on Fetus and Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2011;127:575-9.
- Dhingra A, Agrawal SK, Kumar P, Narang A. A randomised controlled trial of two feeding schedules in neonates weighing  $\leq 1750$  g. *J Matern Fetal Neonatal Med*. 2009;22:198-203.
- Jaiswal A, Murki S, Gaddam P, Reddy A. Early neonatal morbidities in late preterm infants. *Indian Pediatr*. 2011;48:607-11.
- Kumar PS. An Update on neonatal hypoglycemia. In: Rigobilo E, editor. *Hypoglycemia-Causes and Recurrences*. Rijeka, Croatia: InTech; 2011. pp. 55-84.
- Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *BMJ*. 1988;297:1304-8.
- Narayan S, Wazir S, Mishra S. Management of neonatal hypoglycemia. In: Bhakoo ON, Kumar P, Jain N, et al. *Evidence Based Clinical Practice Guidelines*. India: National Neonatology Forum; 2010. pp.63-76.
- Singhal PK, Singh M, Paul VK, et al. Neonatal hypoglycemia—clinical profile and glucose requirements. *Indian Pediatr*. 1992;29:167-71.

### IN A NUTSHELL

1. Neonatal hypoglycemia is a common metabolic disorder. It can lead to neuronal injury and long-term neurodevelopmental problems.
2. Both asymptomatic and symptomatic forms can cause long-term problems.
3. The operational threshold values of blood glucose  $< 40$  mg/dL (plasma glucose  $< 45$  mg/dL) should be used to guide management. All at risk neonates and all sick neonates should be monitored for hypoglycemia.
4. Screening for hypoglycemia can be done by glucometer devices but confirmation should always be done by laboratory estimation.
5. Treatment should be prompt and should not be delayed while awaiting laboratory confirmation.
6. Asymptomatic hypoglycemia in neonates more than 34 weeks neonates can be managed with a trial of measured oral feeds if blood glucose is less than 25 mg/dL in first 4 hours, or less than 35 mg/dL in 4–24 hours of age and there is no contraindication to feeding. In other neonates or all symptomatic neonates with hypoglycemia, a mini-bolus of 2 mL/kg 10% dextrose should be given followed by continuous infusion of 6–8 mg/kg/min of 10% dextrose.
7. Refractory or persistent hypoglycemia should be suspected and investigated if the glucose infusion requirement is consistently more than 8 mg/kg/min beyond 24 hours or the hypoglycemia persists more than 5–7 days.
8. Babies with hypoglycemia should be followed up for neurodevelopmental sequelae.



## Chapter 14.6

# Anemia and Polycythemia

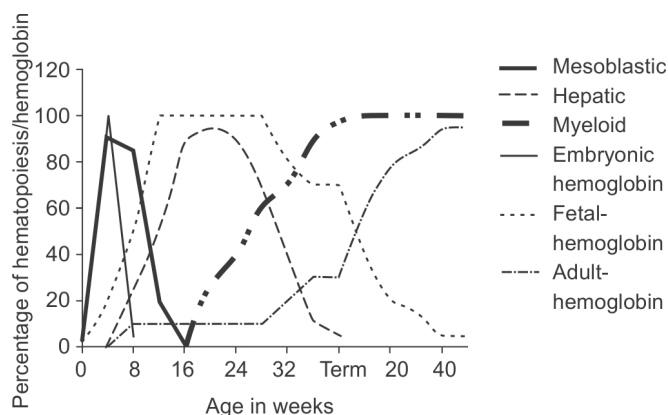
Venkateshan Sundaram, Bikramjit Das

## ANEMIA

Hematopoiesis is the process of formation of differentiated blood cells from multipotent stem cells, derived from the yolk sac. There are three phases of hematopoiesis and the site of hematopoiesis changes during each of these phases and in tandem with the maturation of gestational age—the yolk sac from 2nd week to 8th week (mesoblastic phase); liver till 30 weeks (hepatic phase) and bone marrow after that (myeloid phase) (**Fig. 1**). Several growth factors have been implicated in the process of erythropoiesis, the most important among them being the erythropoietin (EPO). At birth with exposure to higher concentrations of oxygen, the newborn undergoes critical changes in erythropoiesis. The hemoglobin concentration can undergo rapid changes making the evaluation of anemia difficult. Various obstetric complications and placental malformations, auto- and allo-immune disorders, failure of bone marrow and defects in the red cell membrane, hemoglobin, and enzymes may all precipitate the onset of anemia early.

## PATHOPHYSIOLOGY

The fetus accretes iron primarily from two sources—maternal iron and destroyed fetal RBCs. Fetal accretion of iron mainly occurs during the last trimester at an average rate of 1.6–2 mg/kg/day, where a term neonate at birth has an iron store of about 75 mg/kg of body weight. This is also reflected in the cord ferritin levels that increases with gestation and is more than 60 µg/L in term neonates. Around 75–85% of the body iron is in the form of hemoglobin within RBC, around 10% as nonhemoglobin proteins (myoglobin, cytochromes), and the remaining 10–15% is stored in the marrow and liver as ferritin and hemosiderin. The factors, which influence the perinatal iron status of the fetus and neonate, are shown in **Box 1**. Babies born to anemic mothers have decreased iron stores and are predisposed to early onset anemia during infancy. Multiple pregnancies increase the iron requirements for the fetus, which the normal iron supplementation may not be sufficient to maintain. As majority of iron accretion occurs in last trimester, preterm babies have decreased stores. Intrauterine growth restriction, although may have higher hematocrit at birth, are prone to early onset anemia after birth due to their higher basal metabolic demands.



**Figure 1** Developmental hematopoiesis and various hemoglobin compositions. Bold lines represent various phases of hematopoiesis, unbold lines represent various types of hemoglobin

## BOX 1 Factors influencing perinatal iron balance in fetus and neonate

### Factors which cause negative iron balance

- **Maternal conditions:** Iron deficiency, smoking, malnutrition
- **Fetal conditions:** Multiple pregnancy, prematurity, IUGR, prematurity, fetomaternal bleeding
- **Neonatal conditions:** Early cord clamping, increased phlebotomy losses, inadequate iron supplements, restrictive transfusion practice, exchange transfusions, infections, exclusive breastfeeding, cow milk feeding

### Factors which cause positive iron balance

- **Maternal conditions:** Iron supplement
- **Fetal conditions:** Multiple pregnancy, prematurity, IUGR, prematurity, fetomaternal bleeding
- **Neonatal conditions:** Delayed cord clamping, decreased phlebotomy losses, adequate postnatal iron supplements, liberal transfusion practice, iron fortified formulas

Abbreviation: IUGR, intrauterine growth retardation.

Delayed cord clamping at birth is one intervention which has been shown to increase ferritin and result in decreased need for blood transfusion in both term and preterm neonates. The distribution of blood in the fetoplacental unit at term is around 40:60 at term between placenta and baby. The placenta contains an even greater blood volume in preterm neonates with the ratio being almost 60:40. The amount of placental transfusion depends on the timing of cord clamping. Around 20–30 mL/kg of baby weight equivalent blood volume can be transfused from the placenta to the neonate by delaying the cord clamping by 45–60s in preterm neonates at birth.

Despite the iron stores bestowed at birth, there are several neonatal factors that predispose a neonate to develop anemia in the postnatal life:

- The rapid phase of postnatal growth and associated increase in extracellular volume and intracellular volume requires expansion of erythropoiesis.
- Decreased survival of RBCs (around 70–90 days as compared to 120 days in adults).
- Decreased EPO levels (erythropoietin becomes negligible after the first week), probably due to increased tissue oxygen delivery.
- Decreased deformability of neonatal RBC, which results in sequestration in splenic sinusoids and destruction.
- Decreased protein intake in postnatal life; neonates with protein intake of 3.5 g/kg/day have hemoglobin 1–1.5 g/dL higher than those with protein intake of 2 g/kg/day.
- Phlebotomy losses. Some have suggested that sampling losses are major cause of anemia in a preterm neonate. Studies have shown that sick preterm neonates may have sampling losses to the extent of 11–22 mL/kg during the first 2 weeks of life.
- Infections are common among the very preterm neonates. As many as 50% of extreme preterm neonates suffer at least one episode of sepsis, and this is higher in developing countries. Sepsis increases erythropoiesis and consumption of iron stores, may result in disseminated intravascular coagulation and blood loss, and suppresses the marrow via cytokine-mediated mechanisms.
- Some neonatal care facilities use recombinant erythropoietin routinely to improve erythropoiesis in very preterm neonates. This increases the iron requirements, which if not provided adequately, can quickly result in deprivation of ferritin stores and result in anemia.

A complex interplay of these factors leads to progressive utilization of the iron stores. In the absence of EPO, erythropoiesis is not stimulated [evident by the reduced reticulocytes (1–3%)]. This state continues till a nadir is reached at about 6–8 weeks in term neonates and about 1–4 weeks earlier in preterm neonates.

This nadir and associated hypoxia triggers the release of EPO and resultant erythropoiesis. In some extreme preterms, this point may be reached as early as 1–2 months, hence the justification for early iron supplements in this population. Although breastmilk contains less amount of iron, but its bioavailability is better. Thus, term babies on exclusive breastfeeding need additional iron supplements after usually 4–5 months.

## ETIOLOGY

Anemia in neonates is primarily due to three basic mechanisms: blood loss, hemolysis and failure of production (**Box 2**). The common causes encountered in the neonate are highlighted in bold.

### Anemia due to Blood Loss

Significant fetomaternal hemorrhage (FMH) occurs in about 8% of pregnancies. This is an important consideration in the neonates who are anemic at birth. It has been estimated that about 40 mL of FMH would be required to present as anemia at birth. FMH can be diagnosed and quantified from the fetal RBCs in the maternal circulation (Kleihauer-Betke test). Rupture of umbilical cord is seen in preterm precipitous deliveries and if not controlled immediately with clamping can exsanguinate the neonate. Postnatal blood loss from sampling is probably the most important cause of anemia in neonatal intensive care unit candidates. Blood loss into various body compartments (cephalohematomas, subgaleal bleed, sub-arachnoid hemorrhage, and hepatic rupture) may occur in traumatic deliveries, instrumentation, and perinatal asphyxia and may result in large amount of blood loss.

#### BOX 2 Etiological factors for anemia in a neonate

##### Blood loss

- **Fetal:** Feto-maternal bleed, twin-twin transfusion, hemorrhage following amniocentesis
- **Placental:** Placenta previa, placental abruption, placental laceration, velamentous cord insertion, accidental placental incision during cesarean section, vasa previa, placental chorioangioma
- **Umbilical:** Cord rupture with precipitous delivery, cord hematoma
- **Neonatal:** Blood collections: cephalohematoma, subgaleal hemorrhage, intracranial bleed; hepatic or splenic rupture; retroperitoneal hemorrhage; blood-letting for investigations

##### Hemolysis

- **Immune:** Rh incompatibility, ABO or minor blood group incompatibility, autoimmune hemolytic anemia, lupus erythematosus
- **Infections:** Bacterial, Viral-CMV, toxoplasma, syphilis, rubella, herpes, malaria, DIC, microangiopathic anemia
- **Red cell membrane disorders:** Hereditary spherocytosis, elliptocytosis, stomatocytosis, pyropoikilocytosis
- **Red cell enzyme deficiencies:** G6PD deficiency, pyruvate kinase deficiency, hexokinase deficiency
- **Hemoglobinopathies:** Alfa thalassemia, gamma thalassemia
- **Miscellaneous:** Hypothyroidism, vitamin E deficiency

##### Failure of production

- **Physiological:** Anemia of the newborn, anemia of prematurity, late anemia of hemolytic disease
- **Constitutional:** Diamond-Blackfan, Shwachman-Diamond, Pearson syndrome, Congenital dyserythropoietic anemia, Fanconi anemia, TAR syndrome
- **Acquired:** Aplastic anemia, infection (CMV, rubella, toxoplasma, bacterial sepsis), anemia associated with bronchopulmonary dysplasia
- **Nutritional:** Iron deficiency, folate deficiency, vitamin B<sub>12</sub>
- **Bone marrow infiltration:** Neuroblastoma, congenital leukemia, storage disorders, histiocytosis

**Abbreviations:** TAR, thrombocytopenia and absent radii; CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase.

## Hemolytic Anemia

Hemolysis is characterized by increased destruction of RBCs, resulting in progressive anemia and unconjugated hyperbilirubinemia, evidence of extramedullary hematopoiesis in the form of hepatosplenomegaly and in rare circumstances subcutaneous erythropoiesis—*blueberry muffin* like maculopapular lesions. Immune hemolysis is mediated by antibodies, which coat fetal RBCs and result in their sequestration and destruction in the spleen. In Rh incompatibility, the Rh negative mother gets sensitized to Rh positive RBC, which may occur through abortions, fetal diagnostic studies like chorionic villus sampling or amniocentesis, FMH, fetal manipulations like internal or external podalic inversion performed to change an unfavorable presentation of the fetus, as well as during exposure to Rh positive cells during mismatched blood transfusion. The prevalence of this condition has been estimated to be about 385/100,000 births in South Asia as compared to 2.5/100,000 births in developed countries. ABO incompatibility is usually a mild disease, with less than 10% of affected babies manifesting clinically with jaundice and anemia. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is another important cause of anemia during infancy. The prevalence of this condition is estimated at less than 20% for the South Asian region. However, there is a wide regional variation within our country, with Northern part of the country having prevalence of 15–20%, while the Southern states having prevalence of less than 5%. G6PD deficiency predominantly presents in the neonatal period as severe hyperbilirubinemia or prolonged jaundice. Alpha thalassemia usually causes hydrops and in utero demise, however, cases presenting in neonatal period are known. Intrauterine infections causing anemia usually are associated with other clinical manifestations such as growth retardation, microcephaly, bleeding tendency, cardiac disease, jaundice, etc., which help in diagnosis.

## Hypoplastic Anemia

These are among the rarer causes of anemia in the neonate. These usually do not present at birth as the neonatal RBCs have a survival of around 2 months, after which period they usually manifest. The characteristic hallmark is the reticulocytopenia despite severe anemia. The majority of hypoplastic anemia cases are due to acquired conditions and infections. Mechanisms involved are cytokine-mediated suppression of normal erythropoiesis and direct damage to progenitor cells. However, few primary congenital hypoplastic anemia can present in early infancy such as transient erythroblastopenia of infancy, which is the most common variety, and is characterized by anemia, reticulocytopenia, and resolves spontaneously by 1 year of age.

## CLINICAL FEATURES

Clinical features of anemia in a neonate (**Table 1**) depend on the following factors—duration over which anemia has developed, severity of anemia, and postnatal age at presentation. Acute anemia is most commonly due to significant amount of blood loss and may present with circulatory compromise, sudden collapse and listlessness, limpness, and signs of respiratory failure such as gasping respiratory efforts or apnea. It is important to remember that due to equal volume of plasma loss, the hemoglobin and hematocrit remains unchanged till initial 4–6 hours period of gradual hemodilution. Thus, acute blood loss is one clinical condition where blood needs to be transfused despite normal or near normal hematocrit values. Reticulocytosis ensues after 2–3 days which heralds compensatory bone marrow hyperplasia. On the other hand, fetus and neonates usually adequately compensate chronic blood loss and does not result in a catastrophic event. However, it results in growth failure and decreased basal

**Table 1** Clinical manifestations of anemia in a neonate

<i>Effects on the fetus</i>	<i>Acute anemia</i>	<i>Chronic/long standing anemia</i>
Fetal growth retardation (FGR)	Moderate to severe pallor	Pallor
Hydrops fetalis	Hypotension	Metabolic acidosis
Congestive cardiac failure	Collapse, coma	Reduced activity, poor feeding
Intrauterine fetal demise	Gasping respiration or Respiratory failure	Poor physical growth
	Seizures	Congestive cardiac failure – tachypnea, tachycardia, hepatomegaly, edema
		Apnea
		Oxygen requirement

**Table 2** Normal values of various hematological indices in newborns and infants

<i>Age</i>	<i>RBC (million/uL)</i>	<i>Hemoglobin (g/dL)</i>	<i>Hematocrit (%)</i>	<i>MCV (fL)</i>	<i>MCH (pg/g)</i>	<i>MCHC (%)</i>	<i>RDW</i>
0–3 days	4.0–5.9	14.5–20.5	45–61	95–115	31–37	29–37	< 18
4–9 days	3.9–5.7	13.5–19.5	42–60	88–112	28–36	28–38	< 18
10–14 days	3.6–5.5	12.5–18.5	39–57	86–110	28–36	28–38	< 17
15–30 days	3.0–4.8	10.0–16.0	31–49	85–108	26–34	30–36	< 17
1–6 months	3.0–4.3	9.5–12.9	29–42	74–96	25–35	30–36	< 16.5
7–24 months	3.7–4.9	10.5–12.8	33–38	70–84	23–30	31–37	< 16

*Abbreviations:* RBC, red blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width.

metabolic rate manifesting as poor feeding and lethargy to cut down energy expenditure. If this continues uncorrected, it may result in a state of high output cardiac failure.

Symptoms of anemia that suggest inadequate tissue oxygenation are an increase in oxygen requirement, tachycardia, apnea, and poor weight gain. However, these indicators nonspecific and do not correlate well to hemoglobin levels or respond consistently to RBC transfusions.

## EVALUATION OF ANEMIA

Definition of anemia should ideally involve erythrocyte mass measurement, the best measure of anemia. In adults, it correlates directly with hemoglobin values, which can be used as a valid means of determining anemia. However, in infants, the correlation between erythrocyte mass and hemoglobin values is poor and extremely wide variations in the erythrocyte mass values for any given hematocrit values have been observed. Moreover, capillary hematocrit is often a poor reflection of the circulating erythrocyte mass in newborn infants. This is particularly true in ill infants, in whom a poor peripheral circulation may exaggerate capillary and venous hematocrit differences. For all practical purposes, hemoglobin or a hematocrit value measured from a venous blood sample should be the ideal sample for defining and monitoring anemia (**Table 2**).

The general approach to anemia in a neonate is based on the same principles used in the evaluation of older children (**Table 3**). The most important question that comes to the mind is whether the low hemoglobin level is due to decreased RBC production, shortened RBC survival or a combination of these two processes. Blood loss is another important consideration for anemia in neonates, especially preterm neonates. This classic approach is however complicated by a hemoglobin concentration that undergoes constant physiologic change during the first few weeks of life (**Table 2**). Moreover, source of blood and site of sampling can also influence the hemoglobin levels in neonates—capillary samples can vary as large as 1.5 g/dL from the true hemoglobin levels and can also be significantly higher than the venous blood sample values (see above).

It is important to first determine whether the low hemoglobin level can be explained by blood loss from sampling. Cumulative losses, particularly in ill preterm neonates, may be extremely large, and correct interpretation of rapid changes in hemoglobin level can be made only if careful attention is paid to the exact volumes blood sampled and transfused. Anemia resulting from decreased RBC production develops slowly allowing physiologic compensation. Consequently the infant may be having surprisingly few clinical signs of anemia other than pallor. In contrast, a newborn with anemia caused by RBC destruction or acute blood loss often appears acutely ill. Hemolytic anemia usually is accompanied by jaundice and less frequently, enlargement of spleen. The reticulocyte count is elevated and nucleated RBCs may persist in the peripheral blood beyond the first few days of life. Additional laboratory tests can be added once the distinction between decreased RBC production and shortened RBC survival is made. If hemolysis is suspected, additional work-up towards a specific diagnosis such as hemoglobin electrophoresis for hemoglobin H or measurement of enzyme levels for erythrocyte metabolic abnormalities may be planned.

The efficiency of the diagnostic search can be greatly enhanced by *detailed maternal and family history*. The history of febrile illness with rash in mid pregnancy should prompt early investigation for a viral origin for neonatal anemia. A history of several family members with neonatal jaundice and anemia cured by splenectomy should direct the investigation towards membrane disorders such as spherocytosis. Age at anemia is first noticed is also of diagnostic value. Marked anemia at birth is usually due to hemorrhage or severe alloimmunization. Anemia manifesting itself in the first 2 days of life is usually due to external or internal hemorrhages, but anemia appearing after 48 hours of life is usually hemolytic and more commonly is associated with jaundice.

Apart from history, *general physical examination* can many times yield important diagnostic clues. For example, infection associated anemia is usually associated with other abnormalities of the primary disorder, which can be identified on examination and can offer clues to diagnosis. Additionally, severity of anemia should be thoroughly assessed before planning for detailed evaluation.



A well-term neonate with venous hemoglobin of 14.5 g/dL is unlikely to have a serious hematologic disorder and the collection of numerous blood samples for a variety of investigations would lead to sampling loss and further decrease in hemoglobin without improving the overall diagnostic yield.

The clinician must tailor the *investigations* and do them in a proper order that takes him/her towards the diagnosis. Moreover, neonatal hematological indices vary from children and adult values as well as on different postnatal age and these must be kept in mind while interpreting tests (**Table 2**). A proposal of different tiers of investigations to approach anemia in a neonate has been described below, and a flow diagram for approach is given in **Flow chart 1**.

*Tier 1:*

- Hemoglobin, hematocrit, peripheral blood smear examination, reticulocyte count
- *RBC indices:* Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RCDW)
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Blood group, direct antiglobulin test (DAT)
- Total and conjugated fraction of serum bilirubin (in the presence of jaundice).

*Tier 2:*

- TORCH group of infections: paired mother infant serology
- Kleihauer-Betke test (KBT), Apt-Downey test
- *Sepsis work-up:* TLC, ANC, CRP, Blood and CSF cultures
- *Imaging:* Intracranial bleed, intracranial calcifications, hydrocephalus, intraperitoneal bleed
- *Intravascular hemolysis:* Plasma and urine hemoglobin.

*Tier 3: Rare etiologies*

- Hemoglobin electrophoresis
- *Bone marrow aspiration:* Hypoplastic anemia, storage disorders
- Vitamin E levels

*Miscellaneous:*

- *Iron studies:* Ferritin, transferrin saturation, protoporphyrin levels, serum iron, Iron binding capacity
- *Advanced imaging:* Cardiac and liver iron stores
- *Near infrared spectroscopy:* Cerebral oxygenation.

## SPECIAL NOTE ABOUT FEW INVESTIGATIONS

### Complete Hemogram

The peripheral blood picture in neonates is difficult to interpret as anisopoikilocytosis (different sizes and shapes of RBCs) are normally seen as are schistocytes and burr cells. However, presence of certain forms such as spherocytes (seen in hereditary spherocytosis, ABO incompatibility), Heinz bodies and bite cells (seen in G6PD deficiency, thalassemia) are reasonably specific. RBC indices provide clues such as whether the clinician is dealing with microcytic hypochromic anemia or a normocytic anemia, the causes of which are different, as shown later in the algorithm. The normal values of hematological indices in various age groups are given in **Table 2**.

### G6PD Deficiency Status

The prevalence of G6PD deficiency varies across different states and this test must be considered as a tier 1 investigation in regions with high prevalence. It is done in whole blood and dye reduction tests are used. However, it must be borne in mind that G6PD is a function of the age of the RBCs. During active hemolysis, the peripheral blood may contain majority of younger erythrocytes (neocytes), which may show an intermediate or even a normal G6PD enzyme levels. Hence, in cases where it is strongly suspected, it is recommended that the test may be repeated after about 2–3 months.

### Direct Antiglobulin Test

This test is used to detect antibody coated RBCs, which is a marker of immune hemolytic anemia. The test is performed in whole blood; the RBCs are washed to remove the plasma; mixed with antihuman globulin and if RBCs are coated with antibodies, they aggregate. However, this test may give false negatives if the antibody titer is very high (pro-zone phenomenon). In such cases, the test may be repeated with serial dilutions to negate the effect of antibody excess.

### Kleihauer-Betke Test

This test is performed on maternal blood to identify fetal erythrocytes and is used to detect FMH. It takes advantage of the differential resistance of fetal hemoglobin to acid elution. A standard blood smear is prepared from the maternal blood and stained with citric acid-phosphate buffer, which denatures the adult hemoglobin selectively. Subsequent staining with Shepard's method stains the fetal hemoglobin rose pink color, while the maternal RBCs are seen as ghost cells with eluted hemoglobin. Quantification can be made as to the amount of FMH. For this, the smear prepared is viewed, the fetal and adult RBCs are counted till a total of 2,000 cells are counted. Percent of fetal RBCs are given by  $[(\text{Fetal RBC})/(\text{Total RBC counted (2000)}) \times 100]$ . The amount of FMH is calculated by multiplying the percent of fetal RBC's by 50 (considering maternal blood volume as 5000 mL). For example, if in total 2,150 RBCs counted, there are 20 fetal RBCs, the percent of fetal RBCs will be 0.9, and the amount of FMH will be around 45 mL. The test needs to be performed soon after birth as with advancing time and with small quantities of fetal blood seeped in to the maternal circulation, the fetal cells may be cleared from maternal circulation.

### Apt and Downey Test

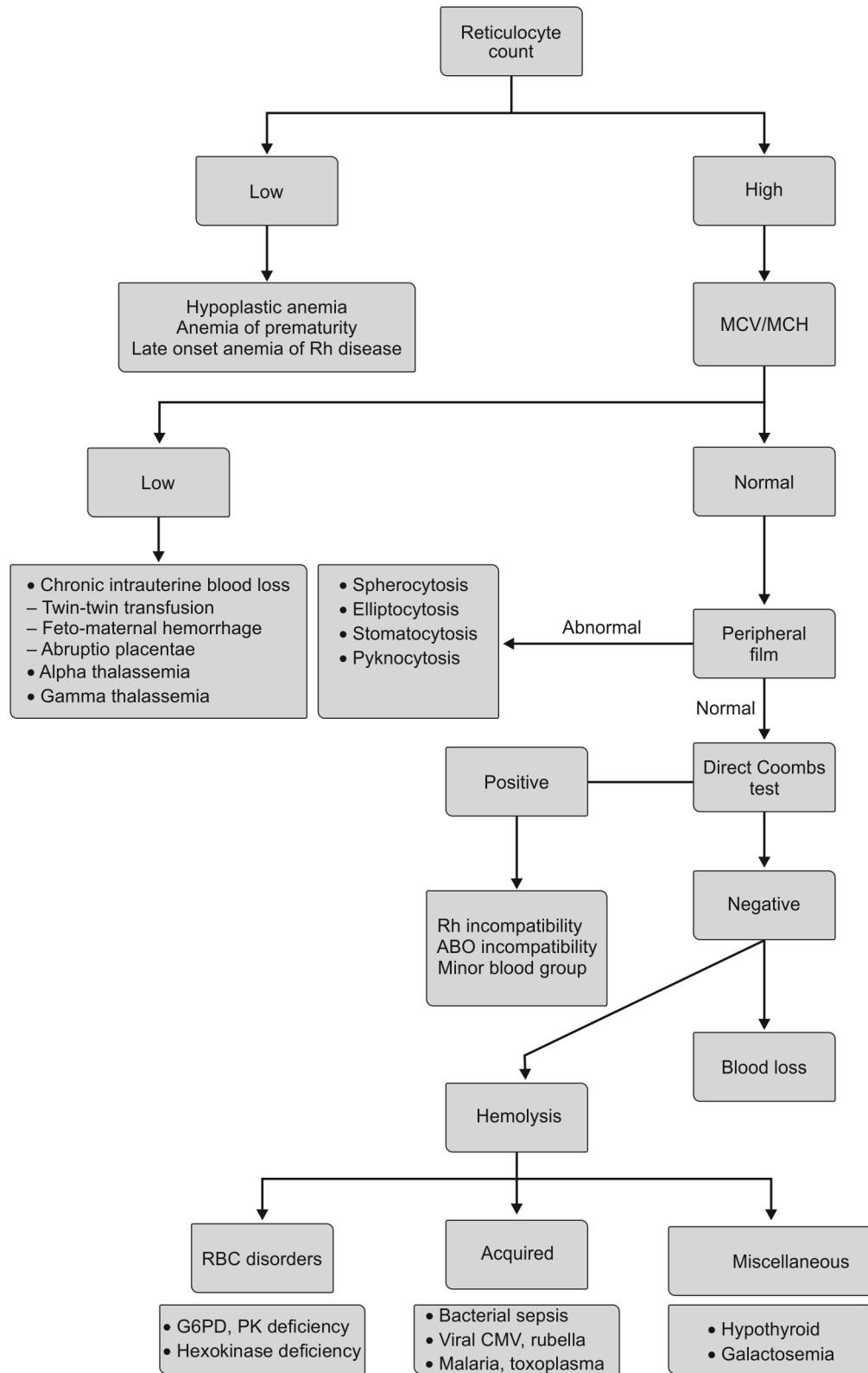
Occasionally an infant may have gastrointestinal bleeding associated with anemia. If this happens close to delivery, it is essential to differentiate this from swallowed maternal blood during delivery. Apt and Downey test is based on the resistance of fetal hemoglobin to alkali denaturation. The principle is similar to KBT in that after alkali treatment, the survived fetal hemoglobin gives a pink color while the denatured maternal hemoglobin gives a yellow brown color. This however, is only a qualitative test.

### Iron Studies

The major disadvantage of using hemoglobin and hematocrit is that they are affected much late; by which time the body iron stores would have significantly reduced. Reticulocyte count is also highly variable, especially during the initial few days, and peripheral blood picture as stated can normally have many abnormal looking cells.

- *Ferritin:* Around 10–15% of iron in the body is stored as ferritin and hemosiderin, primarily in the bone marrow and liver. A small fraction of this is detected in the plasma, the concentration of which is proportional to the body iron store. Around 1 mL of blood needs to be collected in EDTA or heparinated vial. The test can be performed on serum as well as plasma. The samples need to be stored at 2–8°C for shorter use. However, they can be stored at -20°C for 6–9 months and at -80°C till 3 years. The normal values in various age groups are as follows; Neonates 25–200 µg/L, 1–5 months 50–200 µg/L, 6 month–15 years 7–140 µg/L.
- Similarly other tests such as serum iron, total iron binding capacity, transferrin saturation give a better estimate of body's iron status and efficiency of erythropoiesis. However, these tests are not very sensitive during the perinatal period and hence are not used routinely.



**Flow chart 1** Algorithmic approach to anemia in the neonate

**Abbreviations:** MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; CMV, cytomegalovirus; RBC, red blood cells; G6PD, glucose-6-phosphate dehydrogenase deficiency; PK, pyruvate kinase.

**Table 3** History and clinical clues for anemia in a neonate

Feature/clue	Possibilities to be considered
Maternal and paternal blood group <ul style="list-style-type: none"> <li>• Mother blood group negative</li> <li>• Mother O+, husband A/B/AB</li> </ul>	Rh incompatibility ABO incompatibility
Maternal drug history <ul style="list-style-type: none"> <li>• Anticonvulsants (Phenobarbitone, phenytoin, carbamazepine)</li> <li>• Smoking</li> </ul>	Hemorrhagic disease (Blood loss) Increased incidence of placenta previa, abruption (Blood loss)
Maternal fever with rash in first or second trimester	Intrauterine infections
Maternal obstetric illness <ul style="list-style-type: none"> <li>• Placenta previa, abruption</li> <li>• Multiple pregnancy</li> </ul>	Blood loss Fetofetal transfusion (Blood loss)
Maternal procedures <ul style="list-style-type: none"> <li>• Amniocentesis, podalic version</li> </ul>	Fetomaternal bleed (Blood loss)
Events during delivery <ul style="list-style-type: none"> <li>• Precipitous delivery</li> <li>• Accidental placental incision</li> <li>• Instrumental delivery</li> </ul>	Cord rupture (Blood loss) Blood loss Blood loss
Maternal nutritional deficiencies <ul style="list-style-type: none"> <li>• Iron, folate</li> </ul>	Decreased fetal iron stores (early onset anemia of infancy)
Previous losses in mother with hydrops	Isoimmunization, storage disorders, skeletal dysplasias, intrauterine infections
Family history of jaundice, anemia, gall stones	Hemolytic disorders
Time at which anemia was noticed <ul style="list-style-type: none"> <li>• Fetal/at birth</li> <li>• Within first 7 days</li> <li>• 7 day–28 days</li> <li>• After 28 days</li> </ul>	Rh isoimmunization, fetofetal transfusion, storage disorders, skeletal dysplasias, antepartum hemorrhage Rh isoimmunization, intracranial blood loss, birth trauma, hemolytic disorders Sampling losses, intrauterine infections, sepsis, hemolytic disorders, bone marrow infiltrative disorders Anemia of prematurity, anemia of infancy, iron deficiency, congenital hypoplastic anemias
General examination <ul style="list-style-type: none"> <li>• Small for date</li> <li>• Failure to thrive</li> <li>• Microcephaly</li> <li>• Jaundice</li> </ul>	Maternal malnutrition, Intrauterine infections Chronic anemia Intrauterine infections Hemolytic disorders, sepsis, intrauterine infections, congenital dyserythropoietic anemia, histiocytosis
<ul style="list-style-type: none"> <li>• Blueberry muffins</li> <li>• Petechiae</li> <li>• Skeletal abnormalities</li> </ul>	Extramedullary hematopoiesis, nonspecific Sepsis, intrauterine infections, bone marrow infiltration, histiocytosis Skeletal dysplasias, storage disorders, Diamond-Blackfan, Fanconi anemia
Systemic examination <ul style="list-style-type: none"> <li>• Hepatomegaly and/or splenomegaly</li> </ul>	Hemolytic disorders, intrauterine infections, storage disorders, sepsis, histiocytosis

## MANAGEMENT OF ANEMIA

The modalities used in the management of anemia include blood transfusion; iron supplementation; erythropoietin therapy; and immunoglobulin for immune hemolytic anemia.

### Blood Transfusion

Blood transfusion is one of the important modalities for acute management of anemia in neonates. However, transfusion of blood has been implicated as the reason for various complications, possibly due to the oxidative stress, increased viscosity and yet to be identified immune dysregulation related factors that put the newborn at risk. Recently described entities like transfusion associated lung injury (TRALI) and transfusion associated necrotizing enterocolitis (TRANEC) are serious complications, if proven, would lead to even more stringent use of blood products. While deciding to transfuse whole blood or packed red cells, the following aspects have to be considered—when to transfuse, how much to transfuse, how fast to transfuse, blood requirements, technique of transfusion and how to assess the response.

### When to Transfuse

The transfusion need has traditionally been related to hemoglobin/hematocrit (Hct) values in relation to the reference ranges of hemoglobin or Hct at different postnatal ages, and to the clinical status of the newborn. Clinical indicators are nonspecific and do not correlate well with hemoglobin levels or respond consistently to RBC transfusions. Absence of ready availability of biochemical parameters as well as inconsistent evidence favoring them makes them less attractive assessment indicators. Hence, it is recommended that hemoglobin or Hct levels form the primary indicators for deciding the need of pRBC transfusion (**Table 4**). However, decision-making has to take into consideration the clinical status of the newborn such as presence of severe cardiovascular diseases, or symptoms of anemia.

### How Much and how Fast to Transfuse?

Most infants are transfused 10 or 15 mL/kg of pRBCs, depending upon the cardiovascular status. Packed red cells contain 2 mL RBCs in every 3 mL volume. Hence, every 10 mL/kg of pRBC transfusion

**Table 4** Guidelines for blood transfusion in anemia in neonates

<b>Group A: Asymptomatic</b>	Hct $\leq$ 20%; reticulocytes $<$ 100000/ $\mu$ L
<b>Group B:</b> <ul style="list-style-type: none"> <li>• Weight gain <math>&lt;</math> 10 g/day while receiving <math>\geq</math> 100 kcal/kg/day</li> <li>• Significant apnea or bradycardia</li> <li>• Tachypnea or tachycardia</li> <li>• <math>&lt;</math> 35% hood oxygen with CPAP/IMV with Paw <math>&lt;</math> 6 cm H<sub>2</sub>O</li> <li>• Surgery</li> </ul>	Hct $\leq$ 30%
<b>Group C:</b> <ul style="list-style-type: none"> <li>• <math>&gt;</math> 35% hood oxygen</li> <li>• CPAP/IMV with Paw <math>\geq</math> 6–8 cm H<sub>2</sub>O</li> </ul>	

results in a hemoglobin rise of about 3 g/dL and a hematocrit rise of about 10%. Small volume pRBC aliquots may be transfused without warming particularly if the transfusion is given slowly over two to three hours. A controlled blood warmer should be used for large volume transfusions, particularly exchange transfusions. All blood components must be filtered before transfusion. The standard 120–170  $\mu$  pore-size filter is adequate for red cells, plasma, and platelets. Third-generation leukodepletion filters with “ultra-filtration” capability of removing 99.9% of white blood cells by mechanical sieving and cell adhesion have been recommended to decrease transmission of cytomegalovirus and other viruses harbored in leukocytes and to decrease the incidence of alloimmunization. Leukodepletion preferably should be carried out in the laboratory within a few hours of blood collection, rather than by using bedside filters.

### Partial Exchange Transfusion (PET)

PET using packed RBCs is used to correct severe anemia and improve oxygenation in critically ill hydropic infants with severe HDN until they can be stabilized sufficiently to undergo a complete double-volume exchange transfusion. In cases of anemia, a modified calculation would be helpful.

$[(\text{Desired} - \text{Patient Hct}) / (\text{pRBC} - \text{Patient Hct})] \times \text{weight (kg)} \times \text{blood volume (80–100 mL/kg)}$

Hct – hematocrit, pRBC – packed RBC

### Iron Therapy

Term neonates have sufficient iron stores to sustain erythropoiesis for 4–6 months. However, preterm neonates are at risk for early iron deficiency. Although stores are sufficient for first 2 months, however, early enteral iron supplementation starting at around 2 weeks of age, with a dose of 2–3 mg/kg daily has been shown to improve their RBC indices and iron stores measured by ferritin at 6 months of age and the effect persisted till 12 months. The current American Academy of Pediatrics (AAP) recommendation is to begin iron supplementation in all breastfed full-term infants at 4–6 months through iron-containing complementary foods. If iron cannot be provided through dietary sources, elemental iron at 1 mg/kg/day should be used after 6 months.

### Erythropoietin

Erythropoietin (EPO) can be given *early* (before the infant reaches eight days of age) or *late* in order to prevent or decrease the use of pRBC transfusions. The benefit of exogenous EPO to stimulate RBC production and overcome anemia of prematurity is still being debated, despite numerous multicenter trials. Given the

current evidence, neither *early* nor *late* rEPO can be routinely recommended for preterm infants.

### Placental Transfusion for Autologous Transfusion

Delaying cord clamping from 60s to 3 min, milking/stripping the cord and holding the newly born infant well below the vaginal introitus/placenta immediately after delivery of the baby but before the expulsion of the placenta has been shown to reduce the need for blood transfusion and improve the iron stores at 6 months of age. Hence, delaying cord clamping at least up to 60s from the birth of the baby is currently recommended in term neonates considering its short-term benefits.

### Intravenous Immunoglobulin

Immune hemolysis due to Rh and ABO blood group incompatibilities may be reduced and prevented by using intravenous administration of IVIG. Even though the mechanisms by which immunoglobulin prevent hemolysis are unclear, it seems to reduce hemolysis by competitively binding with the splenic site and preventing extravascular hemolysis. Conventionally it is administered in a dose ranging from 400 g to 1000 g/kg body weight. Even though many previous studies reported that Ig administration is beneficial, a recent meta-analysis showed no benefit of Ig therapy in Rh hemolytic disease, either in preventing exchange transfusions or reducing the peak serum bilirubin, especially following a sensitivity analysis of studies with a low risk of bias. Hence, administration of Ig for immune hemolysis should be considered on a case-by-case basis till further evidence comes in.

## POLYCYTHEMIA

The incidence of polycythemia varies from 1–5% of all infants born at term. The incidence varies based on the definition of polycythemia and hyperviscosity, which in turn have varied based on the source of blood sample and the age of the infant at the time of measurement. In many studies, a hematocrit value of 65% and above has been diagnostic for polycythemia. Based on population data from many sources, it has now been accepted that polycythemia should be defined as a hematocrit value of  $\geq$  65% from a large, freely flowing peripheral vein. *Hyperviscosity* has been defined as a value of more than two standard deviations from the mean. Viscosity, as defined by Poiseuille, is the ratio of shear stress to shear rate, as demonstrated by the formula:

$$\eta = (p-p')r^4 \pi / 8lQ = \text{shear stress/shear rate}$$

$\eta$  is blood viscosity (dynes/s/cm<sup>2</sup>),  $p-p'$  is the pressure gradient along the blood vessel,  $r$  is the radius,  $l$  is the length of the blood vessel and  $Q$  is blood flow.

### PATHOGENESIS

Several factors influence the hematocrit of the neonate in the perinatal period (**Table 5**). Placental transfusion at birth, i.e., transfer of blood from the placenta to the baby has been shown to increase both the infant blood volume and the RBC volume. Placental transfusion can be achieved by delaying cord clamping after the birth of the baby. Studies have shown that a delay of 60 sec to 180 sec results in an additional transfer of blood of 20–30 mL/kg equivalent of infants body weight. Others have also shown an increase in RBC volume in preterm infants below 35 weeks gestation. However, none of these studies have shown that placental transfusion per se leads to polycythemia; even though this factor in combination with the other above-mentioned factors can increase the risk of polycythemia. The other factor, which determines the neonatal hematocrit, is intrauterine hypoxia. Both acute as well as

**Table 5** Factors that predispose polycythemia and hyperviscosity

<i>Polycythemia</i>	<i>Hyperviscosity</i>
<ul style="list-style-type: none"> <li>• Timing of cord clamping</li> <li>• Distance of baby below the vaginal introitus at birth</li> <li>• Intrauterine growth</li> <li>• Fetal hypoxia</li> <li>• Site of sampling</li> <li>• Postnatal age</li> <li>• Altitude</li> </ul>	<ul style="list-style-type: none"> <li>• Hematocrit</li> <li>• Red cell deformity</li> <li>• White blood cells—size and deformity</li> <li>• Vessel size—capillaries &gt; arteries &gt; great arteries</li> <li>• Blood pH—increases with blood pH &lt; 7.00</li> <li>• Fibrinogen, platelets and plasma proteins—less contribution</li> </ul>

chronic hypoxias have been shown to result in higher hematocrits at birth. Acute hypoxia results in placental transfusion, the volume of which is proportionate to the duration the stay of the fetus in utero. On the other hand, chronic hypoxia results in an increase in erythropoiesis in the fetus and thus elevates the hematocrit values. For similar reasons, babies born at higher altitude have higher hematocrits.

The hematocrit of the neonate increases soon after birth due to shifting of intravascular volume to the extravascular space during delivery. The peak value is reached around 4–6 hours after birth. Thereafter, due to resifting of fluid into the intravascular space from the interstitial space, the hematocrit reaches its birth value around 12–24 hours of life and thereafter remains stable. The sampling site can also affect the hematocrit values. In studies comparing three sites, capillary, peripheral venous and umbilical venous, the highest hematocrits were observed with capillary blood followed by peripheral venous and umbilical venous blood. Dehydration, by decreasing the plasma volume, can also result in hemoconcentration and polycythemia.

## ETIOLOGY

There are three major categories of etiologies or clinical scenarios in which polycythemia and hyperviscosity may be observed (**Box 3**). These include chronic fetal hypoxia, acute fetal hypoxia/asphyxia and delayed cord clamping at birth. Other less common causes and associations include maternal-fetal hemorrhage, fetofetal transfusion and chromosomal abnormalities.

## CLINICAL FEATURES

The hyperviscosity associated with polycythemia results in decreased organ blood flow, especially to vital organs and leads to increased oxygen extraction to maintain tissue oxygenation. The symptoms of polycythemia depend upon the severity of hyperviscosity, organ blood flow, etiology of polycythemia, and associated clinical conditions. For instance, a small for gestational age (SGA) infant with perinatal asphyxia may have polycythemia; however, several of the clinical manifestations can be explained by either SGA or polycythemia or asphyxia or their combination. This dilemma daunts the clinician and is important to consider if partial exchange is to be undertaken, as symptoms may not improve in such scenario.

The clinical manifestations of polycythemia are variable (**Box 4**). One author reported that cyanosis, plethora, tremulousness, hyperbilirubinemia and abnormal blood smear examination as the most common manifestations of polycythemia. Another author reported plethora and lethargy/poor feeding as common manifestations of polycythemia. However, a large majority of neonates were asymptomatic despite being diagnosed as polycythemic, underscoring the importance of routine monitoring in high-risk neonates to identify such neonates. The hyperviscosity results in elevation of pulmonary resistance and intrapulmonary

### BOX 3 Etiologies and associations of polycythemia

Acute hypoxia—perinatal asphyxia

Chronic hypoxia

- Maternal pre-eclampsia
- Infant of diabetic mother
- Intrauterine growth restriction
- Neonatal thyrotoxicosis
- Placental insufficiency
- High altitude
- Maternal smoking

Delayed cord clamping

Intrauterine transfusion

- Maternal-fetal
- Feto-fetal

Syndromes

- Trisomy 13,18,21
- Beckwith-Wiedemann syndrome

### BOX 4 Common clinical manifestations of polycythemia and their frequencies

- Cyanosis (89%)
- Plethora (63–83%)
- Cardiomegaly (85%)
- Tremulousness/jittery (67%)
- Lethargy/poor feeding (55%)
- Thrombocytopenia (25–40%)
- Hypoglycemia (27–40%)
- Respiratory distress (25%)

shunting, resulting in cyanosis, tachypnea and plethora on chest X-ray. Although cardiomegaly may be seen, it is not clear whether it is primarily due to polycythemia or due to associated complication like hypoxia/asphyxia. Hyperviscosity may also lead to a decrease in splanchnic blood flow and intestinal ischemia and increase the risk of necrotizing enterocolitis (NEC). Another important concern with polycythemia is reduction in cerebral blood flow and its long-term consequences. Many reports have associated symptoms like poor feeding, lethargy, tremors and seizures to polycythemia and hyperviscosity. However, there is no evidence as of now that treatment of polycythemia leads to reduction or prevention from such symptoms. Hypoglycemia is another manifestation of polycythemia and probably is due to the increased glucose consumption due to increased RBC mass.

## MANAGEMENT

Management of polycythemia includes general supportive therapy and specific therapy that includes measures to decrease the RBC volume or to increase the plasma volume. High-risk neonates (**Box 3**) should be routinely monitored for elevated hematocrit. This is especially applicable for small for date neonates, neonates who have suffered perinatal asphyxia and infants of diabetic mothers. In these high-risk neonates, hematocrit should be monitored at 2, 6, and 12 hours of age and thereafter if clinically indicated. Associated conditions such as hypoglycemia, respiratory distress, seizures, and circulatory compromise should be managed with specific therapies such as glucose infusion, respiratory support, anti-epileptics and vasoactive agents. Routine fluid supplementation based on the assumption of dehydration is not recommended. However, if clinical signs indicate dehydration and associated hemoconcentration, appropriate fluid relaxation and treatment of dehydration is mandated.

Partial exchange transfusion (PET) helps in reducing the hematocrit and relieves the symptoms. However, it should not be done routinely as it is not beneficial in improvement of long-term



neurological outcome. Colloidal and crystalloids appear to have equal efficacy in PET. The current indications of PET are:

- a. Any symptomatic neonate with a venous hematocrit of  $\geq 65\%$  where the symptoms are strongly attributable to polycythemia.
- b. Venous hematocrit  $\geq 75\%$  irrespective of the presence or absence of symptoms.

To determine the volume to be exchanged the following formula can be used:

$$\text{Volume (in mL)} = [(\text{Observed Hct} - \text{Desired Hct}) / (\text{Observed Hct})] \times \text{Blood volume (in mL/kg)}$$

Where the desired Hct is usually assumed as 50–55% and the blood volume is assumed as:

For  $< 1$  kg:  $100 \text{ mL} \times \text{body weight}$ ;  $1\text{--}2$  kg:  $90 \text{ mL} \times \text{body weight}$ ;  
For  $> 2$  kg:  $80 \text{ mL} \times \text{body weight}$

### IN A NUTSHELL

1. Anemia in the newborn is primarily due to blood loss and hemolysis.
2. Phlebotomy losses are an important cause of anemia in a sick newborn.
3. Blood transfusions should be used sparingly since they are associated with risks; in asymptomatic newborns blood transfusion should be considered only when hematocrit are less than 20%.
4. Chronic intrauterine hypoxia (as in late onset fetal growth restriction) is an important cause of polycythemia in newborns.
5. Partial exchange transfusion in newborns with polycythemia should be considered only in symptomatic neonates (symptoms attributable to polycythemia).

### MORE ON THIS TOPIC

- Gross GP, Hathaway WE, McGaughey HR. Hyperviscosity in the neonate. *J Pediatr*. 1973;82:1004-12.
- Jaime-Perez JC, Herrera-Garza JL, Gomez-Almaguer D. Suboptimal fetal iron acquisition under a maternal environment. *Arch Med Res*. 2005;36:598-602.
- Kasat K, Hendricks-Muñoz KD, Mally PV. Neonatal red blood cell transfusions: searching for better guidelines. *Blood Transfus*. 2011;9:86-94.
- Kennedy M, Firpo M, Choi K, et al. A common precursor for primitive erythropoiesis and definitive haematopoiesis. *Nature*. 1997;386:488-93.
- Lin JC, Strauss RG, Kulhavy JC, et al. Phlebotomy overdraw in the neonatal intensive care nursery. *Pediatrics*. 2000;106:E19.
- McDonald SJ, Middleton P. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev*. 2013;2:CD004074.
- Ozek E. Partial exchange transfusion to prevent neurodevelopmental disability in infants with polycythemia. *Cochrane Database Syst Rev*. 2010;20:CD005089.
- Rabe H, Diaz-Rossello JL, Duley L, Dowswell T. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev*. 2012;8:CD003248.
- Ramamurthy RS, Brans YW. Neonatal polycythemia. I. Criteria for diagnosis and treatment. *Pediatrics*. 1981;68:168-74.
- Ramasethu J, Luban NL. Red cell transfusions in the newborn. *Semin Neonatol*. 1999;4:5-16.

## Chapter 14.7

# The Bleeding Neonate

Arun Kumar

Pediatricians are faced from time to time with potentially life-threatening bleeding in infants. A systematic approach with appropriate laboratory support should lead to a successful outcome in the majority of infants. This chapter will provide readers with an overview of this topic from a clinician's viewpoint. The focus would be on the neonate presumed to have abnormal hemostasis. It will not delve into details of site specific bleeding such as intracranial or pulmonary hemorrhage. Thrombosis in the newborn is also considered beyond its scope. While the broad principles of treatment are discussed, these would ultimately be governed by local policies and resources.

## EPIDEMIOLOGY

There is paucity of information on the prevalence of bleeding episodes in neonates. In a prospective study on prevalence in a multicentric study in the UK, Australia and the USA, bleeding occurred in 25% of infants and was most common in preterm infants. Eleven percent infants had major or severe bleeds, 1% moderate and 13% minor bleeds. Of the 11 babies within the major bleeding group, two infants developed rectal hemorrhage, two had pulmonary hemorrhages and seven had intracranial hemorrhage. In the severe group of five infants, three had pulmonary hemorrhage and two had subaponeurotic bleeds with intracranial hemorrhages. One percent infants developed moderate bleeds (both had intraventricular hemorrhage without ventricular dilatation). Thirteen percent infants developed minor episodes with bleeding from the nasogastric tube being the most common source. Intracranial hemorrhage was also a commonly observed form of bleeding and 17% infants developing this in some form.

In developing countries, severe sepsis and hypoxic injury are not uncommon, and are often accompanied by bleeding from associated disseminated intravascular coagulation (DIC) and liver dysfunction. Also, prophylactic vitamin K may not be used consistently and hemorrhagic disease of the newborn remains an important cause. The prevalence of conditions associated with thrombocytopenia does not vary significantly across the globe. Coagulation disorders are relatively uncommon but more prevalent in communities with high prevalence of consanguinity.

## PHYSIOLOGY OF COAGULATION

The concentration of vitamin K-dependent coagulation factors (II, VII, IX, X) and contact factors (XI, XII, prekallikrein and high molecular weight kininogen) is low in neonates and gradually increases with age and gestation. The activated partial thromboplastin time is prolonged in neonates due to decreased plasma concentrations of the contact factors. Prothrombin time (PT) is also prolonged reflecting decreased plasma levels of vitamin K-dependent factors. The level of factors V, VIII and XIII are normal. Plasma concentrations of fibrinogen may be raised but thrombin C time is prolonged, due to the presence of *fetal* fibrinogen which has different properties to normal fibrinogen. Platelet counts are similar to adult ranges. Bleeding time is shorter in healthy neonates probably because of high hematocrit and increased concentrations and enhanced function of von Willebrand factor (vWF) and higher levels of vWF large multimers. The capacity of newborns to generate thrombin, dependent upon plasma concentrations of procoagulants, is reduced. Thus, the theoretically increased risk

of bleeding from decreased coagulation factors is balanced by the protective effects of physiologic deficiencies of the inhibitors of coagulation, as well as by the decreased capacity of the fibrinolytic system in infants. This implies that an abnormal result on tests of coagulation may not necessarily require treatment and needs interpretation in the clinical context.

## ETIOLOGY

Most bleeding in neonates is secondary to other disease processes. In a minority, the problem emanates from congenital defects in hemostasis. The causes could broadly be classified into the following categories:

- Thrombocytopenia, or rarely, disorders of platelet function
- Vitamin K deficiency
- Disseminated intravascular coagulation
- Liver cell failure
- Coagulopathies
- Iatrogenic
- Perinatal hemorrhage
- Congenital anomalies including vascular malformations.

Thrombocytopenia and vitamin K deficiency are discussed separately in this textbook. A brief discussion of some of the other causes as follows:

## Disseminated Intravascular Coagulation

This is commonly encountered with severe sepsis, hypoxia, hypotension, acidosis or hypothermia. There is activation of the coagulation cascade with consumption of platelets and coagulation factors, and secondary activation of fibrinolysis. The clinical presentation typically is bleeding from multiple sites including heel pricks and sites of insertion of intravenous lines. Laboratory tests will reveal a low platelet count, prolonged prothrombin and partial thromboplastin times, and decreased fibrinogen levels, with schizocytes in a peripheral blood smear. D-dimers are elevated but not diagnostic as these can be elevated in healthy neonates with no evidence of coagulopathy.

## Treatment

It comprises elimination of the trigger factor, with replacement of factors using fresh frozen plasma (FFP) and platelet concentrate as required. Packed cells may be indicated if the infant is anemic. A recommended approach is to maintain the platelet count more than  $50 \times 10^9/L$  ( $100 \times 10^9/L$  if ventilated, with recent surgical sites or actively bleeding), PT less than and equal to 3 seconds above the upper limit of normal and the fibrinogen more than 1 g/L. Although inhibiting the activation of the coagulation system with prophylactic dosing of heparin (5–10 U/kg/hour) has been considered, trials of anticoagulation in neonates have not been conclusive and the risk of bleeding may be increased. There is little experience with using antithrombin III in neonates.

## Liver Cell Failure

This is seen in neonates secondary to infection, including bacterial sepsis, neonatal herpes simplex virus (HSV) infection, other viral infections, primary liver disease or hypoxic injury, or inborn errors of metabolism. Neonatal HSV infection is an emerging important cause and this diagnosis should always be considered in any unwell infant presenting with a prolonged PT, jaundice and raised liver enzymes that may also be encephalopathic. Treatment consists of addressing the cause and correction of the coagulopathy, if there is bleeding, with vitamin K, FFP or cryoprecipitate. If a diagnosis of HSV is considered, intravenous acyclovir 20 mg/kg/dose 8 hourly should be commenced immediately pending the results of HSV polymerase chain reaction on blood and cerebrospinal fluid samples.

## Coagulation Disorders

These are relatively uncommon but can cause significant hemorrhage. Hemophilia A and B are the most frequently encountered conditions. Other disorders such as afibrinogenemia and deficiencies of other factors are rare but need to be considered in the differential diagnosis. von Willebrand disease only unusually presents in the neonatal period because of their higher vWF factor levels.

### Hemophilia

Hemophilia A and B are X-linked disorders characterized by deficiency of coagulation factors VIII and IX, respectively. Hemophilia A occurs in 1 in 5,000 live male births, and is about four times as common as hemophilia B. As awareness has increased and prenatal diagnosis has become available, diagnosis during the neonatal period has increased significantly. The sites of neonatal bleeding included circumcision site (45.49%), intracranial bleeding (17.69%), heel pricks (14.8%) and venipuncture sites (3.61%).

Where a family history is available, strategies available for management in pregnancy include preimplantation diagnosis, and offering fetal sexing to couples who wish to consider this option, either by chorionic villus sampling or ultrasound. There is also the option for third-trimester amniocentesis, as this may allow the diagnosis of an unaffected pregnancy. There is controversy regarding the merits of normal delivery versus an elective cesarean section. UK guidelines recommend that this should be informed by both obstetric and hemostatic factors, including maternal morbidity with cesarean section for hemophilia B carriers. Data from the Universal Data Collection Cohort suggests that when infants were grouped by presence or absence of family history, intracranial hemorrhage occurred more in vaginal births than cesarean births.

Invasive monitoring with scalp electrodes and fetal scalp blood sampling should be avoided as should application of obstetric forceps and ventouse extraction. On delivery, a sample of cord blood collected carefully without contamination from maternal blood, or a peripheral venous blood sample should be processed as soon as possible for coagulation screen and coagulation factor assay. The diagnosis of severe and moderate hemophilia can also be confirmed in the neonatal period. However, confirmation of mildly affected cases could be problematic due to overlap with the normal range necessitating repeat testing at around 6 months of age. These infants should not have any arterial stabs, and heel pricks should be kept at a minimum. Intramuscular injections should be avoided and vitamin K can be given orally. Circumcision if requested should be performed only with adequate preparation.

*Acute management of the bleeding* Infant requires recombinant factor VIII or IX as applicable to be administered as soon as possible. There is little information on the pharmacokinetics of replacement therapy in neonates and treatment is based on guidelines for older children. Guidelines published by the World Federation of Hemophilia on the Internet constitute an excellent resource and also include advice on duration of therapy where there are resource constraints.

If recombinant factor concentrate is not available, highly purified virally inactivated plasma derived factor VIII or IX products can be administered. Cryoprecipitate should only be used if factor concentrates are not available. If the diagnosis is not known, FFP, 15–25 mL/kg can be administered. The administration of desmopressin [1-deamino-8-D-arginine vasopressin (DDAVP)] may result in dilutional hyponatremia with consequent seizures, and should not be used for the treatment of neonates with mild hemophilia A. Those with suspected intracranial bleeding on ultrasound scan will usually need a CT or MRI scan of the head to establish the diagnosis.

Following confirmation of diagnosis, short-term prophylactic replacement therapy should be given in neonates at increased

risk of bleeding, e.g., following traumatic delivery, instrumental delivery, or a prolonged second stage of labor, and considered following preterm delivery. Children and neonates with severe hemophilia who have had a spontaneous central nervous system bleed should continue long-term prophylaxis.

### Other Coagulation Disorders

Congenital deficiencies of fibrinogen, prothrombin, factors V, VII, XI and XIII are very rare but can be encountered in communities with high prevalence of consanguinity. These can present with cord bleeding (especially fibrinogen and factor XIII deficiency) or intracranial hemorrhage. Treatment is with the appropriate concentrate where available including fibrinogen, recombinant factor VIIa, and factor XIII. Cryoprecipitate or FFP are alternatives. For factor II and X deficiencies, there are no specific concentrates available and prothrombin complex concentrates are the treatment of choice. Factor V deficiency can be isolated or coexist with factor VIII deficiency. Treatment is with FFP and factor VIII concentrates if applicable. Alternatives to these products are cryoprecipitate or FFP. Alpha 2-antiplasmin deficiency is treated with tranexamic acid or epsilon aminocaproic acid (EACA) but there is no neonatal data available for its use.

### Iatrogenic Bleeding

Disastrous bleeding can occur in neonates from dislodged arterial and umbilical lines. Recombinant tissue plasminogen activator used for thrombolysis in neonates has an associated risk of mild to severe bleeding. There is a significant risk of hemorrhagic complications after extracorporeal membrane oxygenation and cardiopulmonary bypass in neonates undergoing corrective heart surgery. These are secondary to anticoagulation, activation of the coagulation and fibrinolytic systems with consumption of coagulation factors, together with dilutional thrombocytopenia. Management includes careful monitoring of heparinization, replacement therapy with hemostatic factors and platelets, and use of drugs such as EACA and recombinant factor VIIa. A detailed discussion on this complex subject is beyond the scope of this chapter.

### Hemorrhage in the Perinatal Period

Massive fetal bleeding may result following placenta previa, placental abruption or incision of the placenta at cesarean section. Another potential problem is vasa previa. Accidental hemorrhage can occur following slippage of a cord clamp. Rupture of the umbilical cord and hematomas into the cord can occasionally lead to severe neonatal anemia with a high perinatal mortality rate. Fetomaternal hemorrhage can occur spontaneously and may be increased by invasive procedures such as fetal blood sampling and cesarean section.

## CLINICAL FEATURES

In addition to bleeding, the affected neonate may have other features indicating the etiology including the following:

- Petechiae, suggestive of low platelets.
- Ecchymosis, indicating a coagulopathy.
- Bleeding from umbilicus, circumcision site, large subgaleal bleeding, all indicating a possible coagulopathy.
- Oral mucous membrane bleeding, or an ooze rather than active bleeding from any site, suggestive of thrombocytopenia. Intracranial hemorrhage is usually associated with prematurity, traumatic delivery, arteriovenous malformations, and secondary to coagulopathies or thrombocytopenia.
- Jaundice, due to liver dysfunction.
- Signs of sepsis, including poor capillary refill and sclerema, full anterior fontanel.

- Blisters over presenting part, site of insertion of scalp electrodes or elsewhere, and seizures in HSV infection.
- Hepatosplenomegaly, in congenital infection.

A relatively well infant with bleeding could have immune thrombocytopenia, vitamin K deficiency, an inherited coagulation factor deficiency, or bleeding from anatomic lesions such as hemangioma. A sick infant with bleeding may have DIC, sepsis or liver failure.

## DIFFERENTIAL DIAGNOSIS

Some entities can masquerade as neonatal bleeding. Pinkish-orange urate crystals deposited from urine into the nappies of normal babies could be misinterpreted as bleeding. Sometimes, the newborn will swallow large quantities of maternal blood especially in the setting of antepartum hemorrhage and then either vomit dark brown maternal blood or pass large quantities of tarry stools. These infants would be clinically very well and laboratory tests would all come back as normal. An Apt test could help differentiate fetal from maternal blood but it is not reliable and persistent bleeding would merit investigation.

## APPROACH TO DIAGNOSIS

In the history, particular attention must be paid to birth details, risk factors for sepsis, use of instruments to augment labor, maternal drugs or illnesses during pregnancy, history of genital herpes, family history of coagulation disorders, and any previously affected siblings. A history of consanguinity would increase the risk of autosomal recessive conditions. Where there is prior information available indicating the possibility of a bleeding disorder in the neonate, meticulous planning of the care in labor and postnatal periods is essential. Physical examination covering the points as mentioned previously would assist in arriving at a possible diagnosis.

## Investigations

If there is clinically significant bleeding, the following tests would need to be performed as soon as possible: full blood count, peripheral blood smear, coagulation screening, PT, partial thromboplastin time, fibrinogen, thrombin clotting time, and blood for group and crossmatching.

Ideally, the sample for coagulation should be taken from a free flowing vein and it is important to ensure that the right volume of blood is collected to maintain the correct ratio with the anticoagulant in the sample bottle. Sometimes, the sample may be taken from an arterial line particularly in the neonatal intensive care unit setting. This is acceptable as long as sufficient blood has been drawn into a syringe beforehand to minimize heparin contamination, and the laboratory is informed about this, as they may be able to perform a reptilase time to help interpretation in the event of heparin contamination.

If a lumbar puncture is contemplated due to concerns with sepsis, this should not be performed until a coagulopathy has been excluded or corrected, and platelet count is above  $100 \times 10^9/L$ . A bedside ultrasound scan of the head helps to check for intracranial hemorrhage. This test is not reliable and if there is strong clinical suspicion, a CT or MRI scan may be required. A blood gas analyzer may be able to measure hemoglobin to help diagnose anemia rapidly. Similarly, if laboratory samples cannot be processed swiftly, a laboratory centrifuge if available would help with quick estimation of packed cell volume.

## Interpretation of Coagulation Tests

The normal values for full blood count and coagulation screen are different in newborn babies and also vary with age and gestation. **Table 1** gives accepted values for these parameters from widely

quoted sources in the literature. **Table 2** is a general guide to interpreting the results.

A number of studies have confirmed that age-related reference ranges for coagulation assays in the healthy population are analyzer and reagent dependent, yet many laboratories compare their pediatric results to either their adult reference range or to published pediatric reference ranges. Neither of these options is satisfactory. Be especially wary of overinterpreting borderline abnormal results and always discuss with an expert hematologist first.

If no abnormality is found in these tests and the infant is bleeding, rarer causes may need to be considered such as factor XIII deficiency,  $\alpha_2$ -antiplasmin deficiency or a platelet function disorder.

## MANAGEMENT

Sometimes, bleeding is mild and the laboratory parameters are stable. A typical example is amounts of hemorrhagic gastric aspirates from the nasogastric tube after perinatal stress, which can be managed expectantly or with a short course of H<sub>2</sub>-receptor antagonists. If bleeding is significant, time is of the essence for clinical intervention and is essential to maintain active liaison with the laboratory and hematology services.

While a member of the team collects information from the parents to help establish the diagnosis, other members should concentrate on examining the infant, ensuring that there is no life-threatening situation that requires immediate assistance. In the context of bleeding, checking for hemodynamic stability is of paramount importance.

Rapid intravenous access must be obtained, using an umbilical venous catheter if peripheral cannulation proves difficult. If the infant is actively bleeding and in shock, an intraosseous needle could be used to obtain access. After the relevant blood samples are collected, an initial bolus of 0.9% saline 10 mL/kg body weight may be needed if there are concerns about a slow capillary refill time. If the infant is pale and shocked at birth and born in a setting of possible severe bleeding, such as placenta previa, immediate transfusion of O-negative blood, 10–20 mL/kg as a slow intravenous push may be given without cross matching. Emergency *flying squad* blood units are usually kept in many delivery suites for obstetric hemorrhage and could be used for the newborn. You would need to follow local blood banking policies in this regard. In a less urgent situation, start treatment for possible associated illnesses such as sepsis while awaiting results of blood tests and administer further treatment based on the results. Initiate supportive treatment as indicated by the infant's condition. Once results of initial tests become available, appropriate therapy for the bleeding diathesis can be given.

1. *Vitamin K<sub>1</sub>*, 1 mg intravenously for vitamin K deficiency. Intramuscular injections should be avoided in any bleeding diathesis.
2. *Packed cell transfusion*, 10–20 mL/kg bodyweight given over 4 hours for significant hemorrhage. If profuse, proportionately larger volumes may be required more quickly. Blood for transfusion needs to be crossmatched with mothers' serum. In addition to routine screening for hepatitis B, syphilis and HIV, blood for neonatal transfusions should be obtained from cytomegalovirus negative donors and should also be leukodepleted. Blood from related donors especially parents should be avoided as it could pose potential immunological risks and a greater likelihood of graft versus host disease. Irradiated blood is indicated when the infants have received intrauterine transfusions or are known to be immunocompromised.
3. *Fresh frozen plasma* obtained from screened donors, is used where rapid correction of coagulation defects is desired as in bleeding associated with vitamin K deficiency, DIC and in coagulation deficiencies where factor concentrate is not available. One infusion of 12–15 mL/kg infused at the rate



of 10–20 mL/kg/hour with careful monitoring for acute transfusion reactions or circulatory overload.

4. *Platelet concentrates* are indicated in clinically significant thrombocytopenia which is discussed in a separate chapter. A platelet concentrate obtained from one donor is suspended in 50–75 mL of plasma. The dose is 10–20 mL/kg, which would be expected to increase the platelet count by  $100 \times 10^9/L$ . In sick neonates, however, such increases in platelet numbers are seldom seen due to rapid consumption or sequestration. It should be given as soon as possible usually at a rate of 10–20 mL/kg/hour.
5. *Factor VIII or IX concentrates* are indicated in hemophilia. Details regarding dosage of these concentrates appear in a reference provided elsewhere in the text.
6. *Cryoprecipitate* is used as a more concentrated source of fibrinogen than FFP and is primarily indicated when the fibrinogen level is less than 0.8–1.0 g/L in the presence of bleeding from acquired or congenital hypofibrinogenemia. The dose is 5–10 mL/kg of body weight.
7. *Exchange transfusion* can be performed in DIC especially if associated with sepsis.
8. *Whole blood* is used principally for exchange transfusions and possibly for resuscitation in hypovolemic states.
9. *Recombinant activated factor VII (rFVIIa)* is a novel therapeutic alternative for bleeding associated with coagulation factor deficiencies. Use in neonates is based solely on case reports, case series, and prospective uncontrolled studies. In most cases, treatment was effective in controlling hemorrhage. Doses of 40–300 µg/kg were used, but further investigation of neonatal rFVIIa pharmacokinetics is required to determine an optimal dose. The

safety of rFVIIa in neonates remains a concern as thrombotic complications have been observed. In the majority of these reports, rFVIIa was used as a desperate final measure, after standard measures had failed to control life-threatening hemorrhage.

The laboratory tests may need to be repeated 8–12 hourly until stable. If bleeding is severe in areas such as the gut, or in the brain, urgent consultation with a pediatric surgeon or neurosurgeon would be needed to plan management. Bleeding in the setting of severe liver failure may need the input of a pediatric hepatology team. Bleeding from the lung (pulmonary hemorrhage) requires intubation and ventilation, or manipulation of ventilator settings to control pulmonary edema in addition to treatment of coagulopathy. A dose of surfactant may help to improve pulmonary function.

The use of all blood products requires to be balanced with potential risks. If large amounts of blood are transfused, this by itself can carry the risk of further hemostatic and metabolic complications which require to be anticipated and managed.

## OUTCOME AND COMPLICATIONS

Most episodes of bleeding can be managed effectively. Sometimes, bleeding may be torrential and unresponsive to treatment as with a congenital vascular malformation. Intracranial hemorrhage carries a guarded prognosis with risk of long-term neurological handicap. Neonatal HSV infection with liver failure also carries a poor prognosis. The outcome for conditions such as alloimmune thrombocytopenia is excellent but those with congenital coagulopathies require a lifetime of follow-up and treatment.

**Table 1** Results of hemostasis screening tests in bleeding disorders

PT	APTT	TT	Fibrinogen	Platelets	Diagnosis
↑	↑	↑	↓	↓	Disseminated intravascular coagulation
↑	↑	N	N	N	Vitamin K deficiency bleeding
N	↑	N	N	N	Hemophilia A, B, C
↑	N	N	N	N	Factor VII deficiency
N	N	N	N	↓	Thrombocytopenia
↑	↑	N	N	N	Factor V, X deficiency
↑	↑	↑	N/↓	N/↓	Liver disease
N	N	N	N	N	Factor XIII deficiency*
					Qualitative platelet disorder, alpha 2-antiplasmin deficiency
↑	↑	↑	Absent	N	Afibrinogenemia
N/↑	↑	↑	N	N	Heparin contamination**

\*Diagnosis requires clot solubility test

\*\*Reptilase time is prolonged in disseminated intravascular coagulation but not with heparin contamination

Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; N, normal; ↑, increase; ↓, decrease.

**Table 2** Normal values for hemostasis screening tests in the newborn\*

Test	30–36 Weeks gestation	30–36 Weeks gestation	Term infant	Term infant
	Day 1	Day 30	Day 1	Day 30
Prothrombin time(s)	Mean: 13 Range: 10.6–16.2	Mean: 11.8 Range: 10.0–13.6	13.0 ± 1.43	11.8 ± 1.25
Activated partial thromboplastin time(s)	Mean: 53.6 Range: 27.5–79.4	Mean: 44.7 Range: 26.9–62.5	42.9 ± 5.8	40.4 ± 7.42
Thrombin clotting time(s)	Mean: 24.8 Range: 19.2–30.4	Mean: 24.4 Range: 18.8–29.9	23.5 ± 2.38	24.3 ± 2.44
Fibrinogen (g/L)	Mean: 2.43 Range: 1.50–3.73	Mean: 2.54 Range: 1.50–4.14	2.83 ± 0.58	2.70 ± 0.54
Platelet count ( × 10 <sup>9</sup> /L)	Range: 150–400	Range: 150–400	Range: 150–400	Range: 150–400

\*Data from Andrew M, et al. All infants received vitamin K at birth

## PREVENTION

Universal administration of vitamin K in newborn infants would be a cost-effective strategy for prevention of severe bleeding. Wherever possible, careful planning prior to delivery of high-risk infants would invariably improve the outcome. Genetic counseling should be arranged for couples of infants affected with inheritable coagulation disorders. Preimplantation genetic diagnosis is available for hemophilia and prenatal diagnosis is possible for several congenital coagulopathies allowing parents the option for termination or proceeding toward early intervention and therapy.

### IN A NUTSHELL

1. Neonatal bleeding is usually secondary to other medical conditions, but could be due to a primary problem with hemostasis.
2. Laboratory ranges for neonatal coagulation parameters differ from other age groups.
3. Liaison with hematology is vital to ensure correct interpretation of test results, and appropriate management, especially the use of blood products.
4. Wherever possible, an antenatal plan for management of the high-risk infant would ensure smooth delivery of care.

## MORE ON THIS TOPIC

- Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full term infant. *Blood*. 1987;70:165-72.
- Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the health premature infant. *Blood*. 1988;72:1651-7.
- Bolton-Maggs PHB, Perry DJ, Chalmers EA, et al. The rare coagulation disorders—review with guidelines for management from the United Kingdom Hemophilia Centre Doctors' Organisation. *Hemophilia*. 2004;10:593-628.
- Kenet G, Chan AKC, Soucie JM, Kulkarni R. Bleeding disorders in neonates. *Hemophilia*. 2010;16:168-74.
- Kenet G. Bleeding in the neonate. *Thromb Res*. 2007;119:S82-4.
- Richards M, Williams M, Chalmers E, et al. A United Kingdom Hemophilia Centre Doctors' Organization guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe hemophilia A. *Brit J Haematol*. 2010;149:498-507.
- Saxonhouse MA, Manco-Johnson MJ. The evaluation and management of neonatal coagulation disorders. *Semin Perinatol*. 2009;33:52-65.
- Venkatesh V, Curley A, Khan R, et al. A novel approach to standardised recording of bleeding in a high-risk neonatal population. *Arch Dis Child Fetal Neonatal Ed*. 2013;98:F260-3.

## Chapter 14.8

# Hemorrhagic Disease of the Newborn

JN Sharma

The term hemorrhagic disease of newborn (HDN) was first coined in 1894 by Townsend, who first described the picture of bleeding from multiple sites in otherwise healthy infants in the absence of trauma, asphyxia, or infection on days 1–5 of life. The link between vitamin K and spontaneous hemorrhage was first reported in 1929. Recognition of the association between vitamin K deficiency and hemorrhagic disease of newborn quickly followed, with subsequent treatment of HDN with vitamin K. The original term hemorrhagic disease of newborn was replaced with the term vitamin K deficiency bleeding (VKDB) in 1999, because the former entity included conditions with bleeding due to other causes.

### PATHOPHYSIOLOGY

None of the coagulation factors cross the placenta from the mother to the fetus. At birth, the concentration of vitamin K dependent factors (Factors II, V, VII, IX and X) and contact factors (factor XI and factor XII) are reduced to about 50% of normal adult values and are further lower in preterm infants.

Vitamin K is required for gamma carboxylation of glutamic acid residues of the protein precursors of the factors II, VII, IX and X which are synthesized in the liver. These protein precursors are termed as PIVKA (proteins induced in vitamin K absence). It is only after gamma carboxylation that these proteins acquire the ability to chelate calcium and to be subsequently activated during coagulation. This action of vitamin K is limited in preterm. Moreover, precursor proteins themselves are deficient in newborn, often below 30% of adult value, as the immature liver is not capable of optimal synthesis of many precursor proteins.

Vitamin K facilitates post-transcriptional carboxylation of factors II, VII, IX and X. In the absence of carboxylation, such factors form PIVKA. It is a sensitive marker of vitamin K status.

A moderate degree of decrease in factors II, VII, IX and X normally occurs in all newborn infants by 48–72 hours after birth. The levels gradually return to normal birth levels by 7–10 days of age. This transient deficiency of vitamin K is due to lack of transplacental transfer of free vitamin K and absence of normal intestinal bacterial flora in the first few days of life which is responsible for the synthesis of vitamin K. There occurs an accentuation and prolongation of this deficiency between the second and seventh days of life resulting in spontaneous and prolonged bleeding. This is frequently seen in preterm and rarely in term infants. Breastmilk is a poor source of vitamin K and hemorrhagic complications are more frequent in exclusively breastfed babies.

### ETIOLOGY

Vitamin K deficiency bleeding is a bleeding disorder which results from the deficiency of vitamin K-dependent coagulation factors viz. factor V, factor VII, factor IX and factor X. Vitamin K is essential for alpha-carboxylation of these factors which converts them to active forms. The newborn has relative vitamin K deficiency for the following reasons:

- Low vitamin K stores at birth
- Poor placental transfer of vitamin K
- Low levels of vitamin K in breastmilk
- Sterility of gut

The intake of vitamin K in exclusively breastfed babies is less than 5 microgram/L in comparison to formula fed infants whose intake is 50 mg/L. Hence VKDB is exceedingly rare in formula fed infants. On rare occasions, deficiency of vitamin K dependent coagulation factors is due to a genetic defect of vitamin K metabolism. Affected infants may present with bleeding in the intrauterine or early neonatal period.

### CLINICAL MANIFESTATION

#### Early HDN

Early HDN occurs as a result of in utero severe vitamin K deficiency precipitated by maternal intake of drugs like phenytoin, and phenobarbitone. These drugs given during pregnancy interfere with vitamin K metabolism and may cause severe deficiency of vitamin K dependent coagulation factors viz. factors II, VII, IX and X in the fetus. In early HDN, onset of bleeding may occur in utero or within 24 hours of birth. Bleeding is usually severe and life-threatening in the form of concealed hemorrhage in the cranium, thorax and abdomen. Large ecchymosis, subcutaneous hemorrhage, external bleeding may also occur. The prothrombin time (PT) is prolonged. Bleeding is usually corrected by administration of vitamin K but response may be delayed or poor in some cases. Such a situation necessitates administration of fresh frozen plasma (FFP).

#### Classical HDN

This is the most common form. It is a result of severe deficiency of vitamin K. Vitamin K stores at birth is very small and rapidly depleted. Breastmilk contains small amount of vitamin K. The amount of milk during the first few days cannot supply adequate amount of vitamin K. In addition, colonization of gut which is necessary for endogenous synthesis of vitamin K is delayed. Hence, breastfed babies can develop bleeding due to severe transient deficiency of prothrombin, factors VII, IX and X. Onset of bleeding usually occurs between the second and fourth day of life, may occur from 1 day to 7 days. The bleeding may be in the form of umbilical stump hemorrhage, hematemesis and/or melena, ecchymosis, epistaxis, subgaleal hemorrhage, bleeding from puncture sites and intracranial hemorrhage. The PT and activated partial thromboplastin time (APTT) are very prolonged. The platelet count, thrombin time and fibrinogen level are normal. The factors II, VII, IX and X are significantly decreased. Administration of vitamin K results in cessation of bleeding, improvement of coagulation defect within a few hours.

#### Late HDN

In late HDN, the onset of bleeding is after the first week, may be between second and sixteenth weeks. Bleeding can occur from any site but more commonly from intracranial vessels, mucous membranes, skin and gastrointestinal tract (GIT). Intracranial bleed may be a devastating complication which is seen in about one-third of cases. Late HDN is often associated with vitamin K malabsorption as seen in biliary atresia and other hepatobiliary disorders.

### DIFFERENTIAL DIAGNOSIS

Other forms of bleeding may be clinically indistinguishable from hemorrhagic disease of newborn responsive to vitamin K. These forms are neither prevented nor successfully treated with vitamin K. It may be emphasized that any of the congenital defects in coagulation can result in a clinical pattern identical to hemorrhagic disease of newborn. The conditions include the following:

*Congenital defects in blood coagulation (viz. factor VIII and IX deficiency)* In 5–35% of cases of congenital deficiency of factor

VIII and IX may present with bleeding in the neonatal period in the form of umbilical cord bleeding, melena, and postcircumcision bleeding. These conditions do not respond to vitamin K but requires FFP or specific factor replacement.

**Disseminated intravascular coagulopathy (DIC)** Neonates affected with disseminated intravascular coagulopathy are usually preterm. It is a disorder that results in consumption of clotting factors, platelets and anticoagulant proteins resulting in widespread intravascular deposition of fibrin leading to tissue ischemia and necrosis, generalized hemorrhagic state and microangiopathic hemolytic anemia. DIC frequently accompanies a severe systemic disease. It may be triggered by a life-threatening process viz. hypoxia, acidosis, infection, tissue necrosis, shock and endothelial damage.

The clinical manifestations include bleeding from venipuncture sites and surgical incision. It is the common initial presentation. There may be petechiae, ecchymosis in skin. The effect of thrombosis and ischemia include large areas of infarction in skin and subcutaneous tissue, renal failure, hemolysis and anemia. There can be life-threatening bleeding viz. intra-cranial bleed which necessitates treatment with FFP and blood transfusions. The laboratory findings include low hemoglobin and severely decreased platelet count. The prune belly syndrome shows fragmented RBCs, burr cells, helmet shaped RBCs. The PT, APTT, thrombin time are prolonged. The fibrin degraded products are present in blood. The levels of protein C and S are low.

**Swallowed maternal blood syndrome** It is characterized by passage of blood or bloody stool usually on the second or third day of life. It may be confused with gastrointestinal bleed. The blood may be swallowed by the infant during delivery or from a fissure in the mother's nipple. Differentiation from gastrointestinal hemorrhage can be done by Apt test.

**Apt test** A blood stained diaper or some grossly bloody stool is rinsed with a suitable amount of water to obtain a distinctly pink supernatant hemoglobin solution. The mixture is centrifuged and the supernatant fluid is decanted. To 5 parts of this fluid one part of 1% sodium hydroxide is added. Within 1–2 min a color reaction takes place. A yellow brown color indicates maternal blood. A persistent pink color indicates presence of fetal hemoglobin and it is infant's blood.

**Subcutaneous ecchymosis in preterm neonate** Widespread subcutaneous ecchymosis in preterm infants at or immediately after birth is apparently a result of fragile superficial blood vessels. Occasionally an infant is born with petechiae limited to face, head and neck. It is probably as a result of venous obstruction by nuchal cord or sudden increase in intrathoracic pressure during delivery.

## LABORATORY DIAGNOSIS

A prolonged PT with international normalized ratio greater than 3.5 in presence of normal fibrinogen level and platelet count is highly suggestive of vitamin K deficiency. Infants with liver disease usually also have vitamin K independent coagulation factors. With DIC there is deficiency of coagulation factors, a low platelet count and elevated levels of fibrin degradation products. Hereditary coagulation factor deficiency can be excluded by single factor analysis.

## MANAGEMENT

The management includes supportive treatment with blood component therapy and administration of vitamin K in appropriate doses as indicated. An infant with hemorrhagic disease of newborn

may present with or without shock depending on the severity of bleeding.

## Infant in Shock

If there is significant hemorrhage and the infant is in shock, it will present with cold peripheries, tachycardia, capillary refill time more than 3 sec and a blood pressure less than 35 mm Hg. However, it should be noted that the hemoglobin level may not fall for 2–3 hours. Further, the blood pressure also may not fall initially until potentially life-threatening blood loss has occurred.

An infant in shock requires a rapid transfusion of 15–20 mL/kg of uncross matched O-negative blood or 10–20 mL/kg of normal saline over 5–15 min. If there are no signs of recovery from shock another bolus should be given over 15–20 min. The blood pressure and central venous pressure (CVP) should be monitored. The aim is to achieve blood pressure more than 40 mm Hg (in term infants) and CVP less than 8 cm H<sub>2</sub>O. If necessary a further transfusion should be given cross matched against maternal blood, 10–30 mL/kg over 2–3 hour accompanied by 1–2 mg/kg furosemide IV.

## Infant not in Shock

If the infant is not in shock, and not given vitamin K at birth, it should be given immediately as follows:

- (i) In classical HDN, 1–2 mg IV
- (ii) In early HDN, 2 mg IV
- (iii) In late HDN, 1 mg IV and then every week.

The infant may need a transfusion with packed red cells 10 mL/kg over 2–3 hours with 2 mg/kg furosemide IV, to raise hemoglobin to 10–12 g/dL. It needs mention that 10 mL/kg of packed red cells will raise hemoglobin by 2–3 g/dL or the hematocrit by 10%.

All critically ill infants with weight less than 1,500 g should be given IV FFP, 10 mL/kg if PT and partial thromboplastin time (PTT) are prolonged.

In classical HDN, after administration of vitamin K, a rise in coagulation factor levels and function occurs within 2 hours of therapy. Complete correction occurs within 24 hours. Vitamin K should not be given IM because large hematomas may form at the site of injection. Intravenous vitamin K should be given slowly because it may induce anaphylactic reaction. In infants with moderate to severe bleeding, FFP 10–15 mL/kg should be administered in addition to vitamin K. In severe bleeding, 2–3 doses of vitamin K may be required.

In infants with early HDN, if the mother is treated with phenytoin, phenobarbitone, INH, salicylates, delivery should be by cesarean section to avoid trauma. The baby should be given vitamin K at postpartum and the dose repeated after 24 hours. FFP administration may be required if fresh bleeding occurs. The platelet, PT, PTT should be monitored. In Late HDN, the underlying condition should be treated. Weekly vitamin K should be given for the first 3 months after birth or till the underlying disorder is controlled.

## PREVENTION

Hemorrhagic disease of newborn due to vitamin K deficiency can be prevented by administration of vitamin K, 1 mg IM, to newborn babies immediately after birth. It is safe and is not associated with an increased risk of childhood cancer. However, it is not uniformly effective in prophylaxis in the preterm. In the preterm, IV dose of 0.2–0.4 mg/kg has been advocated. A recent study showed that intravenous administration of 0.2–0.4 mg/kg vitamin K results in vitamin K plasma levels comparable to after IM injection in the term. Effectiveness of oral vitamin K has not been established; hence not recommended for routine use. Pregnant women



receiving oral anticonvulsant therapy should be given about 10–20 mg/day of vitamin K orally for 15–30 days before delivery to prevent overt vitamin K deficiency in their infants after birth.

### IN A NUTSHELL

1. Hemorrhagic disease of the newborn (HDN) is due to vitamin K deficiency.
2. HDN has three presentations, early (within 24 hours); classical (1–14 days) and late (after 2 weeks). Classical is the most common form.
3. Detection of PIVKA (proteins induced in vitamin K absence) in blood is most confirmatory of HDN.
4. Intracranial hemorrhage can be a devastating complication of HDN.
5. Vitamin K at birth can prevent HDN and should be given to all newborns at birth.

### MORE ON THIS TOPIC

- Andrew M, Paes B, Milner R, et al. Development of the coagulation system in the full term infant. *Blood*. 1987;70:165-72.
- Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the healthy premature infant. *Blood*. 1988;72:1651-7.
- Buchman CR. Coagulation disorders in neonates. *Ped Clin N Am*. 1986;33:203-20.
- Greer FR, Marshall S, Cherry J, et al. Vitamin K status of lactating mothers, human milk, and breastfeeding infants. *Pediatrics*. 1991;88:751-6.
- Loughman PM, McDougall P. Epidemiology of late onset hemorrhagic disease. A pooled data analysis. *J Pediatr Child Health*. 1993;29:177-81.
- Oldenburg J, von Brederlow B, Fregin A, et al. Congenital deficiency of vitamin K dependent coagulation factors in two families presents as a genetic defect of vitamin K-epoxide-reductase-complex. *Thromb Haemostat*. 2000;84:937-41.
- von Kries R, Hanawa Y. Neonatal vitamin K prophylaxis. Report of Scientific and Standardization Committee on Perinatal Haemostasis. *Thrombo Haemost*. 1993;69:293-5.

## Chapter 14.9

Thrombocytopenia  
in the Newborn

Pradeep Sharma

Nearly 1% of term neonates and 20–35% of preterm neonates have platelet counts less than 150,000/ $\mu$ L. Recent data suggests a lower normal limit of 120,000/ $\mu$ L for preterm neonates during the first few days of life. In a series of more than 11,000 neonatal intensive care unit patients with severe thrombocytopenia (platelet count less than 50,000/ $\mu$ L at two or more occasions) occurred in 2.4% of overall admitted neonates and 14% in extremely low birth weight neonates.

## ETIOLOGY

The primary causal factors soon after birth are intrauterine growth restriction, maternal hypertension whereas later on sepsis and necrotizing enterocolitis are responsible for thrombocytopenia. Other factors are maternal immune thrombocytopenia (ITP) and neonatal alloimmune thrombocytopenia (NAIT, **Table 1**).

**Table 1** Classification of neonatal thrombocytopenia

Early onset (<72 hours)	Placental insufficiency
	Perinatal asphyxia
	Congenital and perinatal infections
	Alloimmune thrombocytopenia
	Autoimmune thrombocytopenia
Late onset (>72 hours)	Thrombosis
	Late onset sepsis
	Necrotizing enterocolitis
	Catheter related thrombosis

## PATHOPHYSIOLOGY

Thrombocytopenia in the first few days after birth is often due to placental insufficiency, perinatal hypoxia and antenatal/perinatal infection with reduced megakaryopoiesis. After 72 hours of birth, severe thrombocytopenia in sick preterm newborns is often due to sepsis or necrotizing enterocolitis. There is cytokine release with suppression of platelet production and increased consumption.

Maternally derived antibodies can cause early thrombocytopenia by immune destruction of platelets. These antibodies may also cause platelet dysfunction leading to increased bleeding tendency. NAIT should be suspected when an otherwise healthy newborn presents with severe thrombocytopenia within 48 hours of birth. Serological testing can confirm maternal antihuman platelet antigen-1a (anti-HPA-1a) or anti-HPA-5b platelet antibodies.

Maternal ITP is another cause of neonatal thrombocytopenia suspected in otherwise healthy newborn. The platelet antibodies cross the placenta to the fetal circulation. The maternal platelet count should be checked if thrombocytopenia is unexpected in a newborn. The platelet count will increase within a week but sometimes may take up to 2 months. Intracranial hemorrhage is less commonly seen than in NAIT.

## CLINICAL MANIFESTATIONS

The main clinical concern for neonates with severe thrombocytopenia is major bleeding especially intraventricular and periventricular hemorrhage (IVH-PVH). In a prospective study across seven neonatal units, 169 neonates with platelet count less than 60,000/ $\mu$ L were enrolled. Major hemorrhage occurred in 13% of severely thrombocytopenic patients (IVH 53%, pulmonary 26%, renal 11%). The majority (84%) who had a major hemorrhage were born at less than 30 weeks gestation.

## Platelet Count and Bleeding

There is no relationship between the lowest platelet count and serious bleeding like pulmonary hemorrhage and intraventricular hemorrhage (IVH) although there is a higher incidence of cutaneous bleeds and gastrointestinal hemorrhage. There may be factors other than thrombocytopenia linked to the pathogenesis of these severe types of bleedings. Some studies have shown lower platelet counts in preterm neonates with IVH but it remains unclear whether thrombocytopenia caused IVH or occurred after IVH due to consumptive mechanisms. The close temporal relationship between thrombocytopenia and bleeding in sick neonates does not in itself establish cause and effect relationship nor does it provide justification for giving platelet transfusion to attempt correction of low platelet counts.

## EVALUATION

The evaluation should be started with examination of the placenta for multiple hemangiomas. Ask the mother for a history of previous bleeding that might suggest a diagnosis of maternal ITP, ingestion of drugs that might cause thrombocytopenia in the mother and the infant (e.g., quinidine, quinine); previous siblings affected with purpura, suggesting either immune or inherited thrombocytopenia and skin rash or exposure to rubella during pregnancy. Serologic evidence of congenital infections should be sought (e.g., syphilis, cytomegalovirus, herpes virus, toxoplasmosis). A normal maternal count differentiates alloimmunization from maternal ITP.

The newborn should be examined for hepatosplenomegaly and congenital anomalies suggestive of intrauterine infections. Jaundice with hepatosplenomegaly suggests infectious or hemolytic process. Deformity and shortening of the forearms suggest bilateral absence of the radii with associated amegakaryocytic thrombocytopenia. A single large hemangioma or multiple smaller hemangiomas point to possible platelet trapping and bruises should be searched for internal hemangiomas.

Complete blood count should include hemoglobin, leukocyte count, platelet count and blood smear. Anemia may be associated from blood loss, concurrent hemolysis or marrow infiltration by congenital leukemia. Mild leukocytosis may be there in infection or blood loss but if this exceeds 50,000/ $\mu$ L, it may point to congenital leukemia. In case of persistent thrombocytopenia with no cause identified, bone marrow examination should be considered.

## TREATMENT

## Platelet Transfusions

Two types of platelet products are available: pooled platelets derived from whole-blood donations and apheresis platelets collected by cell separation techniques. Splits of units of platelet concentrates may be prepared for neonatal use. After production, platelet concentrates are stored in plasma in incubators at 20–24°C for 5 days or more depending on use of bacterial screening methods. Platelets must be agitated during storage before transfusion. The recommended dose varies between 10 mL/kg and 20 mL/kg.

### Evidence of Efficacy

Platelet transfusion in a bleeding severely thrombocytopenic newborn has become a standard of care. The role of prophylactic platelet transfusions to keep the platelet count above a certain threshold in a nonbleeding patient is not supported by evidence. The guidelines and recommendations for neonatal platelet transfusion are based on consensus and show differences between countries and hospitals. The consensus based on expert opinions advise transfusing platelets in nonbleeding patients if platelet count is below 20,000/ $\mu$ L. This arbitrary figure is not based on any evidence and the clinician can use his own judgment depending upon the sickness of the patient and the trend in platelet counts. There is a large randomized trial running in the UK, the Netherlands and Ireland. The platelets for neonatal transfusion study 2 is underway comparing a threshold of 50,000/ $\mu$ L with 25,000/ $\mu$ L in neonates with gestational age less than 34 weeks. The primary outcome will be death or major bleed in the first 28 study days.

### Risks of Platelet Transfusions

Platelets are biological agents and are associated with risks. Data from the United Kingdom's Serious Hazards of Transfusion (SHOT) national hemovigilance scheme have shown a disproportionate number of overall adverse events in neonates compared with adult and pediatric population. Platelets are the blood component most likely to be contaminated by bacteria as they are stored at room temperature. It is highly likely that there is under-recognition of adverse events in infants who are already sick from other causes. There has been no relationship between lowest platelet count and mortality, however direct relationship has been observed between the number of transfusions and mortality although mortality cannot be directly ascribed to platelets. It is explained in part by the fact that sick patients need more platelet transfusions but partly by adverse effects of platelet transfusions.

### IN A NUTSHELL

1. Fetal growth restriction and maternal hypertension are common causes of early onset thrombocytopenia in the newborn, while sepsis is an important cause of late onset thrombocytopenia.
2. There is little evidence to support the degree of thrombocytopenia with major bleeds like pulmonary hemorrhage and intraventricular bleeds.
3. In nonbleeding neonates platelet transfusions should be considered only when platelet counts are less than 20,000/ $\text{mm}^3$ .

### MORE ON THIS TOPIC

- Baer VL, Lambert DK, Henry E, Christensen RD. Severe thrombocytopenia in the NICU. *Pediatrics*. 2009;124:e1095-100.
- Christensen RD, Henry E, Wiedmeier SE, et al. Thrombocytopenia among extremely low birth weight neonates: data from a multihospital healthcare system. 2006;26:348-53.
- Gunnink SF, Vlug R, Fijnvandraat K, et al. Neonatal thrombocytopenia: etiology, management and outcome. *Expert Rev Hematol*. 2014;7:387-95.
- Homans A. Thrombocytopenia in the neonate. *Pediatr Clin North Am*. 1996;43:737-56.
- Murray NA, Howarth LJ, McCloy MP, et al. Platelet transfusion in the management of severe thrombocytopenia in neonatal intensive care unit (NICU) patients. *Transfus Med*. 2002;12:35-41.
- Roberts I, Murray NA. Neonatal thrombocytopenia: causes and management. *Arch Dis Child Fetal Neonatal Ed*. 2003;88:F359-64.
- Roberts I, Stanworth S, Murray NA. Thrombocytopenia in the neonate. *Blood Rev*. 2008;22:173-86.
- Sola MC. Evaluation and treatment of severe and prolonged thrombocytopenia in neonates. *Clin Perinatol*. 2004;31:1-14.
- Stanworth SJ. Thrombocytopenia, bleeding and use of platelet transfusions in sick neonates. *Hematology Am Soc Hematol Educ Program*. 2012;2012: 512-6.

## Chapter 14.10

# Cyanosis in the Newborn

K Anil Kuruvilla, Vijay Gupta

Cyanosis is bluish discoloration of the tissues that results when the absolute level of deoxygenated hemoglobin in the capillary bed exceeds 3 g/dL. The appearance of cyanosis depends upon the absolute concentration of reduced hemoglobin rather than the ratio of deoxygenated to oxyhemoglobin. Before understanding the basic pathophysiology related to newborn cyanosis, one should understand oxygen transport and a few other terminologies:

## OXYGEN TRANSPORT

Oxygen is found in the body in three different states: (1) Oxygen in the airway of the respiratory tract; (2) Oxygen dissolved in the plasma; and (3) Oxygen bound to hemoglobin. The amount of oxygen which can be dissolved in plasma depends on the solubility coefficient of oxygen (i.e., 0.3 mL oxygen per 100 mL plasma per 100 mm Hg PaO<sub>2</sub>). Each 1 g of hemoglobin can combine to 1.34 mL of O<sub>2</sub> at 38°C. Each gram can bind to 1.39 mL oxygen under physiological conditions but not all hemoglobin is available for binding.

## Oxygen Carrying Capacity

The capacity of hemoglobin to carry the maximal amount of oxygen is 1.34 mL/g hemoglobin. Hence, the amount of oxygen in the arterial blood at any given point of time known as *oxygen content* can be calculated by the formula:

$$\text{CaO}_2 = (1.34 \times \text{Hb\%} \times \text{SaO}_2) + (0.003 \times \text{PaO}_2)$$

where CaO<sub>2</sub> = oxygen content, Hb% = hemoglobin concentration, SaO<sub>2</sub> = arterial oxygen saturation, PaO<sub>2</sub> = partial pressure of oxygen in arterial blood.

## Saturation (SaO<sub>2</sub>)

It is the proportion of hemoglobin in a blood sample that is saturated with oxygen at a given partial pressure. Pulse oximetry provides an excellent noninvasive and continuous assessment of oxygen saturation. This is different from PaO<sub>2</sub>, which is the partial pressure of oxygen in the artery.

At any given arterial oxygen saturation, blood having increased hemoglobin concentration will have higher oxygen content and can carry more oxygen as compared to blood having lower hemoglobin concentration. Hypoxia may be present in severe anemia caused by low oxygen content (low hemoglobin), although PaO<sub>2</sub> may be normal. Hypoxemia is caused by low PaO<sub>2</sub>, and its relationship to hypoxia is dependent on blood flow, hemoglobin concentration, and the affinity of hemoglobin to oxygen. Thus, an infant could be normoxemic but could still be hypoxic because of severe anemia, poor perfusion, or conditions in which hemoglobin is tightly bound to oxygen (increased affinity of hemoglobin to oxygen). As cyanosis is dependent upon the absolute concentration of reduced hemoglobin, hypoxemia may or may not correlate with the degree of cyanosis.

## ETIOPATHOGENESIS

The causes of cyanosis in newborn can be pulmonary, cardiovascular, neurologic, or hematologic in origin (**Table 1**). Cyanosis can be the result of one of the following pathologic mechanisms:

- Alveolar hypoventilation*: Neurologic illness, e.g., apnea of prematurity, neuromuscular disorders, central nervous system (CNS) dysfunction.
- Ventilation-perfusion mismatch*: Pneumonia, atelectasis

- Right to left shunt*:
  - Intracardiac (e.g., Tetralogy of Fallot)
  - Intrapulmonary (e.g., perfusion of nonventilated areas of the lung)
- Diffusion impairment*: Interference with alveolar-arterial diffusion (e.g., pulmonary edema)
- Abnormal hemoglobin*: With decreased oxygen affinity (e.g., methemoglobinemia).

## METHEMOGLOBINEMIA

Methemoglobin results from oxidation of hemoglobin molecules from the normal ferrous to ferric state. Normal methemoglobin levels are less than 1%, which is kept in check by the enzyme within the red blood cells (methemoglobin reductase). Newborn infants having increased fetal hemoglobin are more susceptible to methemoglobinemia due to easy oxidation of fetal hemoglobin to ferric state as compared to adult hemoglobin.

## Pathology

The altered heme molecule in ferric state is unable to bind to oxygen, with increased oxygen affinity of remaining normal hemoglobin molecule, resulting in decreased oxygen release to tissues. The risk factors for methemoglobinemia include increased oxygen stress; administration of topical anesthetics (prilocaine), antibiotics (sulfonamides), metoclopramide, nitrite or nitrates containing products (inhaled nitric oxide); cytochrome b5 reductase deficiency; and abnormal hemoglobin resistant to reduction (hemoglobin-M).

## Presentation

Newborn infant presents with slate-gray cyanotic appearance with no respiratory distress. Arterial blood appears chocolate brown on exposure to room air with normal PaO<sub>2</sub> levels. Pulse oximetry may show higher saturations rather than true levels of oxyhemoglobin. The severity of hypoxia is quite out of proportion to the degree of cyanosis.

## FACTORS DETERMINING DETECTION OF CYANOSIS

There are several factors that determine the clinical detection of cyanosis in the newborn. These include the hemoglobin concentration, conditions affecting the oxygen dissociation curve, fetal hemoglobin, and skin pigmentation.

## Hemoglobin Concentration

The detection of cyanosis is earlier in a polycythemic child as compared to an anemic child, as the appearance of the cyanosis depends on the absolute concentration of reduced hemoglobin ( $\geq 3\text{ g/dL}$ ) rather than relative concentrations of oxygenated or deoxygenated hemoglobin. As shown in **Figure 1**, patient A becomes cyanotic at 88% SaO<sub>2</sub> being polycythemic (Hb = 25%) as compared to patient E who appears cyanotic when saturation falls below 57% (being anemic Hb = 7 g/dL). Though all patients have the same amount of reduced hemoglobin (3 g/dL), the appearance of cyanosis differs in all patients (from A to E) depending upon the total hemoglobin concentrations.

## Oxyhemoglobin Dissociation Curve

Arterial oxygen saturation when plotted against the partial pressure of oxygen forms the oxyhemoglobin dissociation curve which is nonlinear or sigmoid shaped. The partial pressure of oxygen at which the hemoglobin is 50% saturated is called as P<sub>50</sub>. The oxygen dissociation curve shifts to the left with increase of fetal hemoglobin and decrease in H<sup>+</sup>, CO<sub>2</sub>, temperature and 2,3 DPG;



**Table 1** Causes for cyanosis in the newborn period

<b>Pulmonary lesions (Intrapulmonary right to left shunt)</b>	
Primary parenchymal diseases	Respiratory distress syndrome/hyaline membrane disease Transient tachypnea of newborn Aspiration syndromes (e.g., meconium, blood) Pneumonia Pulmonary hemorrhage Pulmonary edema
Anatomic airway obstruction	Choanal atresia Laryngeal web Pierre Robin syndrome Tracheal stenosis Absent pulmonary valve syndrome Pulmonary sling
Congenital defects	Tracheo-esophageal fistula (TEF) Congenital diaphragmatic hernia (CDH) Hypoplastic lung Cystic adenomatoid malformation Pulmonary sequestration
Extrinsic compression of lungs	Bronchogenic cyst Air leak syndrome (pneumothorax, pneumomediastinum) Chylothorax/Pleural effusion Thoracic dystrophies or dysplasias Pulmonary interstitial or lobar emphysema
Persistent pulmonary hypertension	
<b>Primary cardiac lesion*</b>	
Decreased pulmonary blood flow (Intracardiac right to left shunt)	Critical pulmonary stenosis, tricuspid atresia Pulmonary atresia/intact ventricular septum Tetralogy of Fallot Ebstein anomaly Total anomalous pulmonary venous connection with obstruction
Normal or increased pulmonary blood flow (Intracardiac mixing)	Hypoplastic left heart syndrome Transposition of great arteries Truncus arteriosus Tetralogy of Fallot/pulmonary atresia Complete atrioventricular canal Total anomalous pulmonary venous connection without obstruction Other single ventricle complexes
<b>Hypoventilation</b>	
	Central nervous system lesions Neuromuscular disease Hoffman disease Congenital myotonic dystrophy Sedation Sepsis Pulmonary arteriovenous malformation
<b>Hematological</b>	
	Polycythemia/ hyperviscosity syndromes Methemoglobinemia Sulfhemoglobinemia
<b>Neurological</b>	
	Central nervous system dysfunction Drug-induced depression of respiratory drive Postasphyxial cerebral dysfunction Intraventricular hemorrhage Subarachnoid hemorrhage Subdural hematoma Meningitis/encephalitis Seizures Hypoglycemia Phrenic nerve paralysis

\*Common cardiac causes of cyanosis in newborn can be remembered by 5Ts (Transposition of great artery (TGA), Tetralogy of Fallot (TOF), total anomalous pulmonary venous connection, truncus arteriosus and tricuspid atresia).

it shifts to the right with increase in  $H^+$ ,  $CO_2$ , temperature and 2,3 DPG and decrease in fetal hemoglobin. Hence, physiological factors which shift the oxygen dissociation curve to the left may produce significant fall in  $PaO_2$  for a given  $SaO_2$  as compared to factors which shift the curve to the right (**Fig. 2**).

### Conditions Affecting the Oxygen Dissociation Curve

The binding of oxygen to hemoglobin is dependent on various physiological factors. Factors that decrease oxygen affinity of hemoglobin include acidosis, increased temperature, increased level of 2,3 diphosphoglycerate (2,3 DPG) and hypercarbia. Factors that increase oxygen affinity of hemoglobin include alkalosis, decreased temperature, decreased level of 2,3 diphosphoglycerate (2,3 DPG), increased fetal hemoglobin and hypocarbia.

Newborn infants having higher levels of fetal hemoglobin as compared to their adult counterparts will shift the curve to left. Hence for a presumed  $SaO_2$  of 50%, if the  $PaO_2$  in adult is around 30 mm Hg, it will be almost 20 mm Hg in neonates (**Fig. 2**). Hence, newborn infants having higher fetal hemoglobin levels will be more hypoxemic as compared to infants or adult counterparts with decreased fetal hemoglobin levels. Hence, cyanosis will be detected at lower  $PaO_2$  in newborns who have more of fetal hemoglobin and less 2,3 DPG levels as compared to their older counterparts. As  $PaO_2$  is the main driving force in tissue oxygenation, low  $PaO_2$  levels will adversely affect tissue oxygenation and result in hypoxia.

Similarly, other factors like 2,3 DPG, temperature,  $H^+$  concentration, and  $CO_2$  which are common in sick newborns affect the oxyhemoglobin dissociation in a similar fashion (**Fig. 2**). Conditions which shift the oxygen dissociation curve to the left decreases the concentration of deoxygenated hemoglobin at a given  $PaO_2$ , and lowers the  $PaO_2$  at which cyanosis first appears. As shown in **Figure 2**, for a given  $PaO_2$  of 20 mm Hg,  $SaO_2$  in newborn is almost 50% as compared to almost 25% for adults. In contrast, acidosis, hyperthermia, or increased concentrations of adult hemoglobin shift the oxyhemoglobin dissociation curve to the right, thereby lowering oxygen affinity. As a result, for a given  $PaO_2$ , these conditions increase oxygen delivery to the tissues resulting in a greater concentration of deoxygenated hemoglobin, thus promoting the appearance of cyanosis at a much higher  $PaO_2$  levels (**Fig. 2**).

## CLINICAL PRESENTATION

### Peripheral Cyanosis

It is the bluish discoloration of extremities, but not the mucous membranes and tongue. It is due to increased oxygen extraction by the tissues that results from sluggish movement of blood through the capillary circulation. It is a transient finding in newborn (acrocyanosis) which usually resolves in 24–48 hours time. Other causes of cyanosis may include vasomotor instability (e.g., sepsis), vasoconstriction (sepsis, exposure to cold), venous obstruction, elevated venous pressure, polycythemia, and low cardiac output.

### Central Cyanosis

It is caused by reduced systemic arterial oxygen saturation. Normal newborn after birth may have central cyanosis and attain a preductal saturation of 80–85% and 85–95% only at 5 and 10 min, respectively. A markedly higher oxygen content in the upper (appearing pink) versus the lower part of the body or limbs (appearing blue) due to persisting right to left shunt through the patent ductus results in *differential cyanosis*, e.g., persistent pulmonary hypertension. *Reverse differential cyanosis* is said to exist when there is elevated lower limb saturation as compared to upper limb saturations. It can be seen in newborns having the following cardiac anomalies:

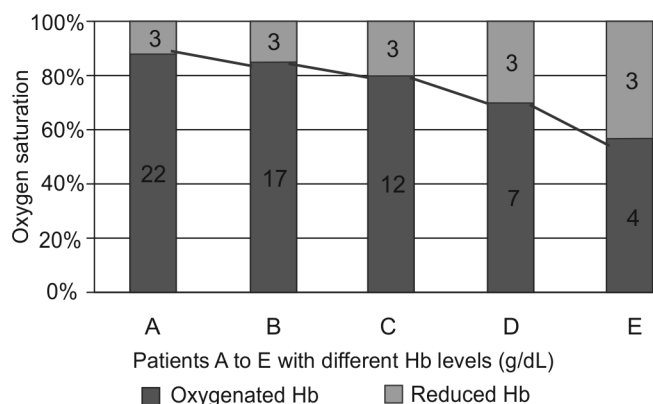
- Transposition of great arteries with abnormal pulmonary—aortic shunt due to left-sided obstructive lesions like

interrupted aortic arch, coarctation of aorta, or suprasystemic pulmonary vascular resistance.

- Total anomalous pulmonary venous connection shunting higher oxygenated right ventricular blood through patent ductus to systemic aorta.

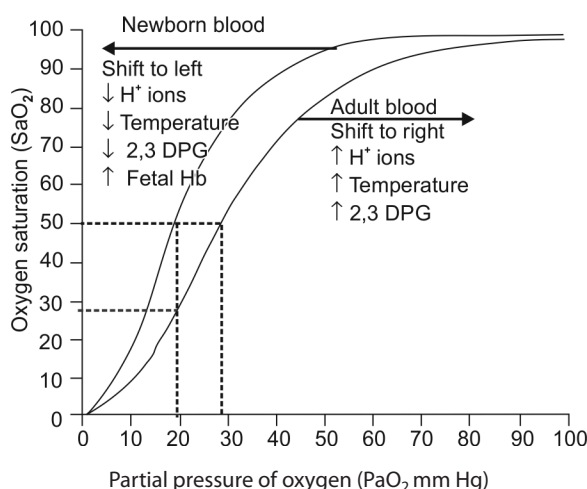
## APPROACH TO CYANOSIS

A systematic approach to neonatal cyanosis starts with a detailed history assessing pregnancy, labor, and newborn risk factors, and physical examination. The possible causes of cyanosis in relation to history, examination and chest X-ray clues are listed in **Table 2**. Arterial blood gases help in determining the oxygenation, ventilation, and acid-base status of the infant. A normal  $PaO_2$  in a neonate with cyanosis should suggest either polycythemia or methemoglobinemia (a useful clue is the presence of a saturation gap—difference in oxygen saturation measured by pulse oximetry and arterial blood gas). An echocardiography would help in diagnosis of structural cardiac lesions or persistent pulmonary hypertension of the newborn (PPHN). Hyperoxia test is perhaps the most sensitive and specific tool in initial evaluation of newborn with suspected critical congenital heart disease.



**Figure 1** Appearance of cyanosis at different  $SaO_2$  levels with differing hemoglobin concentration

Adapted from Lees MH. Cyanosis of the newborn infant. Recognition and clinical evaluation. J Pediatr.1970;77:484-98.



**Figure 2** Oxyhemoglobin dissociation curve

Adapted from Rennie JM. Oxyhemoglobin dissociation curve. In: Rennie and Robertson's Textbook of Neonatology. Elsevier Churchill Livingstone; 2012. p. 1323.

**Table 2** Clues to diagnosis of cyanosis on history, physical examination and radiology

<i>Clues from maternal history</i>	<i>Possible etiology of cyanosis</i>
Diabetes	TTN, HMD, polycythemia, hypoglycemia, congenital heart defects (most common TGA)
Pregnancy induced hypertension	IUGR with increased risk of polycythemia, hypoglycemia
Asthma	TTN
Lupus	Congenital heart block
Drug abuse	Narcotic withdrawal
Lithium intake	Ebstein anomaly
Polyhydramnios	Tracheoesophageal fistula , congenital diaphragmatic hernia
Oligohydramnios	Pulmonary hypoplasia
Previous sibling with respiratory distress	Surfactant protein B deficiency, Group B streptococcal pneumonia
History of congenital heart disease in 1st degree relatives	Increase risk of congenital heart disease
<i>Labor and delivery</i>	
PROM/ PPRM	Sepsis, pneumonia
Chorioamnionitis	Sepsis
Meconium stained amniotic fluid	PPHN, meconium aspiration syndrome
Anesthesia/Analgesia	Respiratory depression, apnea
Cesarean Section	TTN
Perinatal asphyxia	Seizures, severe HIE
Birth trauma	Erb's palsy with phrenic nerve injury
<i>Time of onset of cyanosis</i>	
Onset soon after birth	TTN, HMD, MAS, CDH, CCAM
Onset hours after birth	Cyanotic heart disease
Cyanosis increased on crying	Cyanotic CHD, e.g., Tetralogy of Fallot
Cyanosis decreased with crying	Bilateral choanal atresia
Cyanosis with feeding	Esophageal atresia, severe esophageal reflux
<i>Clues from newborn examination</i>	
Prematurity	Apnea, HMD
Large for gestation	HMD, TTN, hypoglycemia
Small for gestation	Polycythemia, hypoglycemia
Abnormal heart rate	Arrhythmias
Loss of beat to beat variability	Severe sepsis/severe HIE
<i>Upper airway and respiratory system</i>	
Glossoptosis with micrognathia	Pierre-Robin syndrome
Stridulous breathing	Laryngotracheomalacia, subglottic stenosis, vocal cord paralysis
Barrel shaped chest	Meconium aspiration syndrome
Small and narrow appearing thorax	(Jeune's) Asphyxiating thoracic dystrophy
Supraclavicular and suprasternal retractions	Upper airway obstruction (laryngeal web, tracheal stenosis)
Intercostal and subcostal retraction	Diminished lung compliance (Pneumonia, HMD)
Distantly heard breath sounds	Pneumothorax, pleural effusion, atelectasis
Positive thoracic transillumination	Air leak syndrome
<i>Cardiovascular system</i>	
Abnormalities of heart rate	Arrhythmias
Diminished or absent distal pulses	Left sided obstructive lesion ( HLHS, IAA, coarctation of aorta)
Upper limb systolic blood pressure > 10 mm Hg higher than lower limb	Coarctation of aorta, aortic arch hypoplasia and interrupted aortic arch
Preductal and postductal saturation difference >10%	Right to left shunt (e.g. PPHN)
Hyperdynamic precordium	Sizeable left to right shunt

Contd...

Contd...

<i>Clue from examination</i>	<i>Possible etiology of cyanosis</i>
Precordial thrill	Moderate pulmonary or aortic outflow obstruction
Gallop rhythm	Left to right shunt or myocardial dysfunction
Ejection clicks	Pulmonary or aortic valvar stenosis
Single S2	Pulmonary stenosis or atresia, truncus arteriosus
Loud second heart sound with narrow split	Pulmonary hypertension
<i>Abdomen</i>	
Scaphoid abdomen	CDH
Abdominal distension and absent bowel sounds	Sepsis
<i>Central nervous system</i>	
Hypotonia	Severe asphyxia, IEM, sepsis
Hypertonia	Narcotic withdrawal
Seizures	Severe HIE, IEM
Apnea	Apnea of prematurity
<i>Clues from chest X-ray findings</i>	
Bell-shaped thorax	Severe hypotonia, neuromuscular disorder
Air leak	Pneumothorax, pneumomediastinum
Increased parahilar markings, with fluid in the horizontal fissure	TTN
Reticular granular pattern with air bronchogram and low lung volume	HMD
Fluffy infiltrates with areas of patchy atelectasis and hyperinflation	MAS
Honeycomb appearance of lung fields	Pulmonary interstitial emphysema
Opacity of lung field with shift of mediastinum on contralateral side	Pleural effusion or chylothorax
Opacity of lung field with shift of mediastinum on ipsilateral side	Lobar atelectasis
Decreased pulmonary vascular markings	TOF, pulmonary atresia, Ebstein anomaly
Increased pulmonary vascular markings	Truncus arteriosus, transposition of great arteries, obstructed TAPVC, HLHS
Elevation of the right hemi diaphragm > 2 intercostal spaces compared with left side	Diaphragmatic paralysis
Hyperinflated lung	Lobar emphysema, cystic lesions of lungs
Bowel gas in thorax	CDH
<i>Shape of heart</i>	
Normal heart size	Hypoglycemia, polycythemia, sepsis, shock
Small heart size	Hypovolemia, pulmonary interstitial emphysema, congenital lobar emphysema
Boot shaped	TOF, tricuspid atresia
Egg on string	TGA
Large globular heart	Ebstein anomaly
Cardiomegaly	Infant of diabetic mothers, cardiomyopathy, congestive cardiac failure
Snowman sign (Figure of 8)	TAPVC

**Abbreviations:** IUGR, intrauterine growth restriction; CCAM, congenital cystic adenomatoid malformation; PPROM, preterm premature rupture of membranes; PPHN, persistent pulmonary hypertension of the newborn; HIE, hypoxic-ischemic encephalopathy; TTN, transient tachypnea of the newborn; HMD, hyaline membrane disease; MAS, Meconium aspiration syndrome; HLHS, hypoplastic left heart syndrome; CDH, congenital diaphragmatic hernia; TOF, Tetralogy of Fallot; TGA, transposition of the great arteries; TAPVC, total anomalous pulmonary venous connection.



## Hyperoxia Test

To evaluate the possibility of fixed, intracardiac right to left shunt, arterial oxygen tension ( $\text{PaO}_2$ ) should be measured in room air (if tolerated) followed by repeat measurements with the patient receiving 100% inspired oxygen for at least 10–15 min by direct arterial puncture. The  $\text{SaO}_2$  (pulse oximeter) should not be used for the hyperoxia test as 100%  $\text{SpO}_2$  can be obtained with a  $\text{PaO}_2$  ranging from 80 mm Hg to 680 mm Hg. Arterial oxygen tension measurements should be made at both “preductal” and “postductal” sites to rule out the possibility of duct-dependent pulmonary to aortic shunting. An arterial  $\text{PaO}_2$  of more than 250 mm Hg on breathing 100% oxygen ( $\text{FiO}_2 = 1$ ) virtually eliminates the possibility of critical structural cyanotic heart disease and is termed as *passed hyperoxia test*. An arterial  $\text{PaO}_2$  of less than 100 mm Hg (“failed hyperoxia test”) with  $\text{FiO}_2 = 1$  in the absence of clear cut lung disease is virtually diagnostic of cyanotic heart disease with possible intracardiac right to left shunt. Infants who have arterial  $\text{PaO}_2$  between 100 mm Hg and 250 mm Hg with  $\text{FiO}_2 = 1$  may have structural heart disease with complete intracardiac mixing with increased pulmonary blood flow as seen in single ventricular physiology (hypoplastic left heart syndrome).

Neonates who fail a hyperoxia test have a high possibility of critical congenital heart disease with duct dependent systemic or pulmonary blood flow, and should be started on PGE1 (prostaglandin E1) infusion to maintain ductal patency until anatomic definition can be accomplished. Rarely, if a neonate becomes unstable soon after starting PGE1 infusion, obstruction to pulmonary venous return, (TAPVR) or obstruction to left atrial egress (TGA with intact ventricular septum; hypoplastic left heart syndrome with a restrictive foramen ovale or intact atrial septum) should be considered.

With the increased availability of bedside echocardiography in neonatal units, and the risks of exposing babies to 100% oxygen even for a brief time, the hyperoxia test should be used judiciously. **Table 3** provides a summary of findings that would help differentiate pulmonary, cardiac and neurologic causes of cyanosis.

After initial clinical evaluation, chest radiograph, ECG, and laboratory work-up (blood glucose, calcium, CBC, and septic

screen) and echocardiography (where feasible), it should be possible to arrive at an etiology (**Flow chart 1** provides an algorithm for cyanosis evaluation). Management requires initial cardiorespiratory stabilization, assuring hemodynamic stability, oxygen administration, and shifting to a neonatal intensive care unit for further management based on the clinical diagnosis.

### IN A NUTSHELL

1. Cyanosis is bluish discoloration of the tissues that results when the absolute level of reduced hemoglobin exceeds 3 g/dL.
2. Hypoxemia may or may not correlate with the degree of cyanosis.
3. The detection of cyanosis is earlier in a polycythemic child as compared to an anemic child.
4. Factors which shift the oxygen dissociation curve to the left may produce a significant fall in  $\text{PaO}_2$  for a given  $\text{SaO}_2$  as compared to factors which shift the curve to right.
5. Cyanosis will be detected at a lower  $\text{PaO}_2$  in newborns who have more fetal hemoglobin and less 2,3 DPG levels as compared to their older counterparts, hence are more prone for tissue hypoxia.
6. An arterial  $\text{PaO}_2$  of  $< 100$  mm Hg (“failed hyperoxia test”) on breathing 100% oxygen ( $\text{FiO}_2 = 1$ ) in the absence of clear cut lung disease is virtually diagnostic of cyanotic heart disease with possible intracardiac right to left shunt.
7. Neonates who fail a hyperoxia test have a high possibility of critical congenital heart disease with duct dependent systemic or pulmonary blood flow hence should be started on PGE1 infusion.

### MORE ON THIS TOPIC

DiMaio AM, Singh J. The infant with cyanosis in the emergency room. *Pediatr Clin North Am.*1992;39:987-1006.

Driscoll DJ. Evaluation of the cyanotic newborn. *Pediatr Clin North Am.*1990;37:1-3.  
Gomella TL. Neonatology: Management, Procedures, On Call problems,

**Table 3** Differential features of pulmonary, cardiac and neurological causes of cyanosis

Features	Cardiac causes	Pulmonary causes	Neurologic compromise
History	History of CHD in family	Prematurity Meconium aspiration Risk of sepsis	Polyhydramnios Decrease fetal movements Depressed at birth
<i>Respiratory symptoms</i>			
Tachypnea	+	++	-
Chest retractions	-/+*	++	-
Nasal flaring	- /+*	++	Irregular respiration
<i>Cardiovascular signs and symptoms</i>			
Hyperdynamic precordium	++ /-	-	-
Abnormal second heart sound	++	-	-
Murmur	++ /-#	-	-
Abnormal upper limb/lower limb BP	+/-	-	-
Preductal and postductal $\text{SaO}_2$ difference	+/-	-	-
Normal $\text{PaO}_2$ on room air	-	-	+
Hyperoxia test	Failed	Passed	Passed

\*Can present in congestive cardiac failure or pulmonary edema, e.g., Obstructive TAPVC and left sided obstructive lesion.

# Transposition of great artery can present without murmur.

Diseases, and Drugs. 6<sup>th</sup> ed. United States of America: McGraw Hill companies; Cyanosis; 2009;pp.270-4.

Keszler M, Abubakar MK. Physiologic Principles. In: Goldsmith JP, Karotkin EH. Assisted ventilation of the neonate. 5<sup>th</sup> ed. St Louis: Saunders Elsevier; 2011;pp.19-46.

Lees MH. Cyanosis of the newborn infant. Recognition and clinical evaluation. J Pediatr. 1970;77:484-98.

Marino BS, Bird GL, Wernovsky G. Diagnosis and management of the newborn with suspected congenital heart disease. Clin Perinatol. 2001;28:91-136.

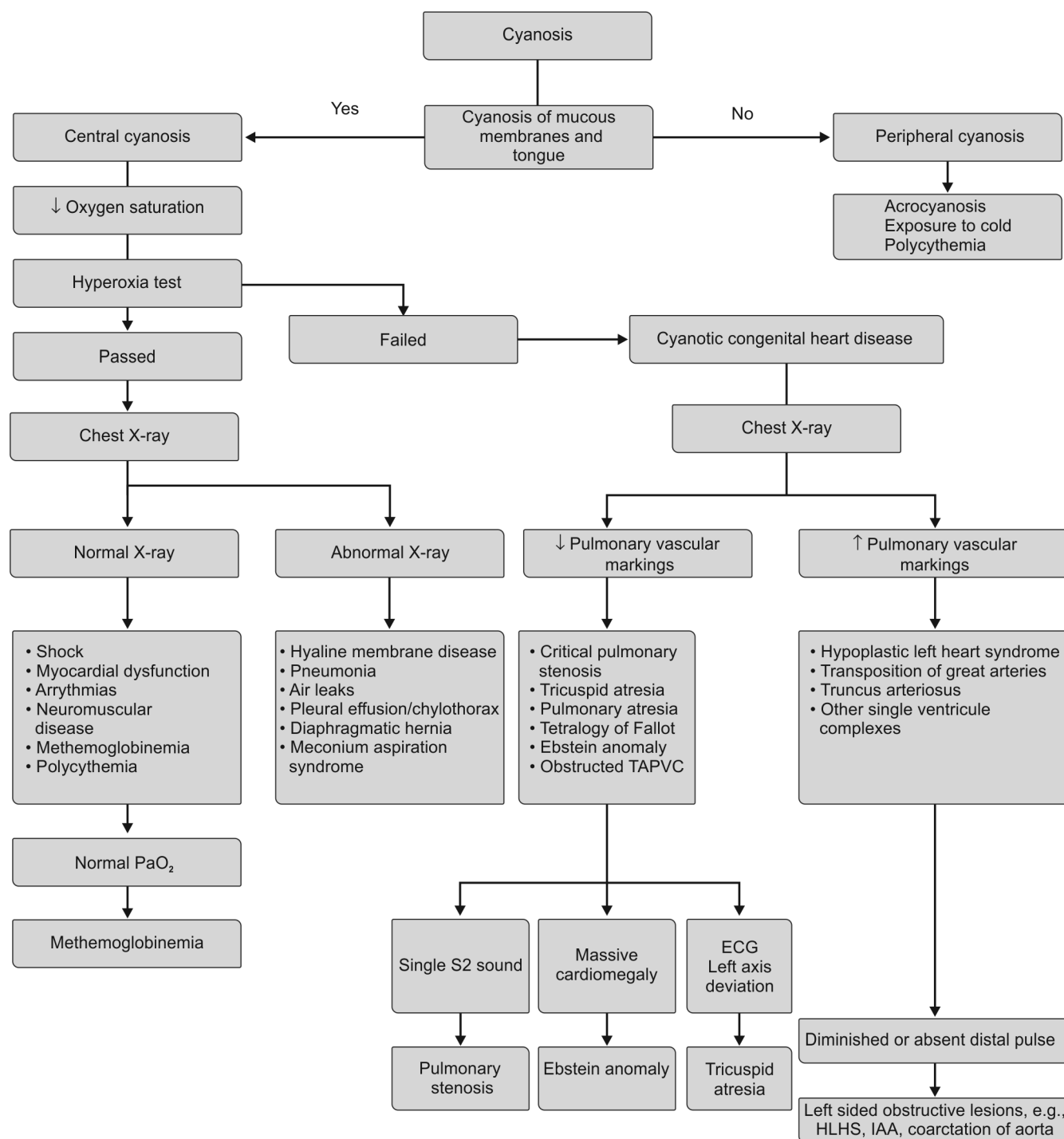
Sasidharan P. An approach to diagnosis and management of cyanosis and tachypnea in term infants. Pediatr Clin North Am. 2004;51:999-1021.

Steinhorn RH. Evaluation and management of the cyanotic neonate. Clin Pediatr Emerg Med. 2008;9:169-75.

Wechsler SB, Wernovsky G. Cardiac disorders. In: Cloherty JP, Eichenwald EC, Hansen AR, Stark AR. Manual of Neonatal care. 7<sup>th</sup> ed. Philadelphia: Wolters Kluwers/Lippincott Williams & Wilkins; 2012;pp.469-528.

Yabek SM. Neonatal cyanosis. Reappraisal of response to 100% oxygen breathing. Am J Dis Child. 1984;138:880-4.

**Flow chart 1** Algorithm to evaluate common causes of newborn cyanosis



Adapted from Stack AM. Cyanosis. In: Textbook of Pediatric Emergency Medicine. 5<sup>th</sup> ed. Fleisher GR, Ludwig S, Henretig FM. Philadelphia: Lippincott, Williams & Wilkins. 2006.

## Chapter 14.11

# Necrotizing Enterocolitis

Krishna Kumar Diwakar

Necrotizing enterocolitis (NEC) as an entity comprising of vomiting, abdominal distension, shock and intestinal hemorrhage was described for the first time by Mizrahi in 1965. NEC affects nearly 15% of very low birth weight (VLBW) infants and is considered a disease almost exclusive to the premature infant. Less than 15% of NEC occurs in late preterm or term infants.

The preterm neonate could be justifiably called the *reluctant enteral feeder*. The premature infant is supposed to be an in utero organism, with all its nutritional requirements being maternally synthesized and routed through the hematogenous channels. A structurally and physiologically immature intestine, when expected to undertake tasks, that it is ill designed for, naturally produces a recipe for damage and catastrophe.

## EPIDEMIOLOGY

The prevalence of NEC varies amongst populations. National Institute of Child Health and Human Development-Neonatal Research Network (NICHD-NRN) study from 2003 to 2007 found that the prevalence of NEC remained high (11%) among very premature infants (born at 22–28 weeks), while it has been observed to be lower in Canada and Europe. Some studies have reported male infants to have the more severe forms of the disease, though these have not been validated by most other studies. Population studies from India on NEC are few in number. In one such report, the incidence of NEC in babies less than 32 weeks gestation was 5.2%. A common scenario in the developing world is that of a VLBW infant, who in addition to being born premature has also been subjected to intrauterine growth retardation. To what extent the in utero compromise enhances the risk of NEC in the

late preterm infant remains unclear. The observation by Australian researchers of the gradual reduction in the prevalence of NEC in the post surfactant era provides impetus to further studies on the causal relationship between various factors and NEC.

## ETIOPATHOGENESIS

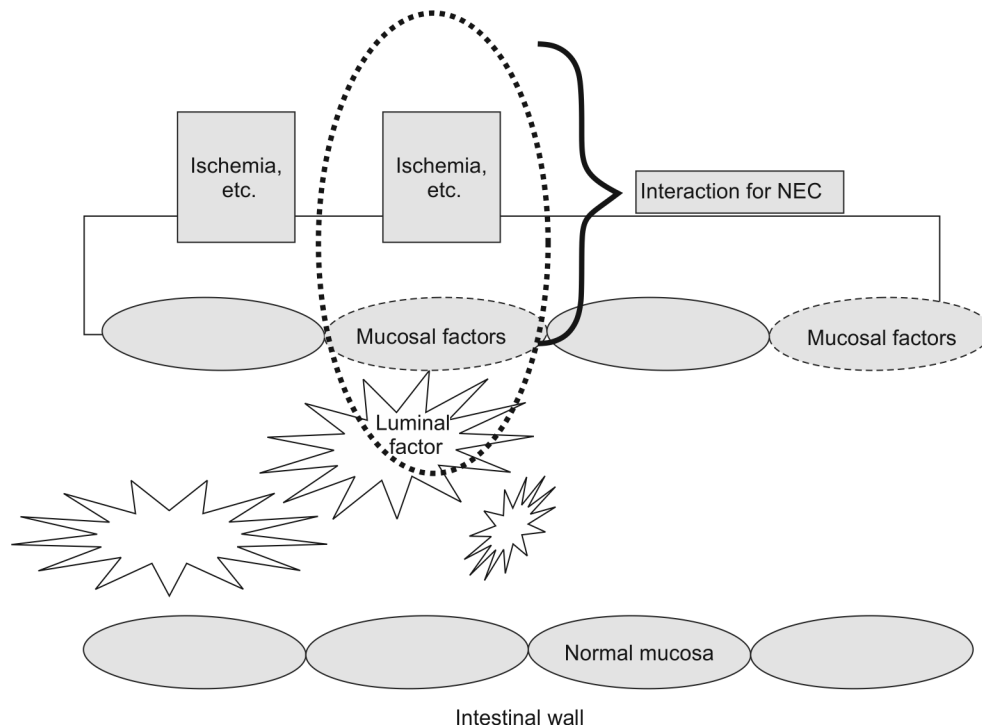
The inherent immaturity of the organ systems under the influence of varying contributory factors results in florid manifestation of NEC. Large epidemiological and more recent clinical studies have shown that previously held beliefs like, low Apgar scores, umbilical catheterizations, episodes of apnea and bradycardia, respiratory distress syndrome, anemia, hypothermia, hypoxic ischemic events, hypotension, indomethacin, etc., are less important as contributory factors for NEC. Exaggerated immunological responses at various stages of the disease contribute to the severity and morbidity of the disease. Complex mechanisms that include dysregulation of chemokines and cytokines like interleukin-6 (IL-6), angiopoietin-2, IL-RII have been observed in patients with NEC.

NEC manifests around the second week of life in preterm infants on oral feeds. It is seen to present earlier in late preterm and term neonates, implying that postmenstrual age (PMA) could influence the pathogenesis of the disease. Irrespective of the initiating mechanisms, the resultant ischemic hemorrhagic necrosis of the intestinal mucosa and the pathological progression of the injury highlight the morbidity of the disease. Prematurity is the single most important risk factor for the occurrence of NEC.

The pathogenesis could be broadly attributed to intestinal mucosal factors, luminal factors and vascular factors (**Fig. 1**). Needless to say, such a classification is an over simplified representation of a complex mechanism.

## Mucosal Factors

The status of the intestinal mucosa influences the normal mechanisms for intestinal epithelial repair. Factors like gestational immaturity, bacterial toxins, and secondary mucosal injury (ischemic or otherwise) have a negative influence on the normal



**Figure 1** Interaction of factors contributing to Necrotizing enterocolitis  
Abbreviation: NEC, necrotizing enterocolitis.

messengers of growth and repair, leading to a preponderance of inflammation, apoptosis and necrosis.

A compromised integrity at every layer of the intestinal mucosa is an inherent limitation of the preterm gut. Goblet cells secrete mucins that help to form a semipermeable barrier of the mucosa. Goblet cells density is increased by epidermal growth factors (EGFs). Lower levels of salivary EGF have been reported in preterm infants who develop NEC. Paneth cells are secretory enterocytes located at the base of the small intestinal crypts that release lysozyme, phospholipase A2, and antimicrobial peptides (defensins and cathelicidins), that help regulate the intestinal bacterial populations. Reduction in the Paneth cell functions seems to enhance the potential of pathogenic bacteria to precipitate NEC. Various inflammatory mediators and mechanisms are also affected by the inherent immaturity of the gut. Platelet-activating factor (PAF), an endogenous mediator is an important augmentor of the inflammatory responses. The enzyme PAF acetylhydrolase (PAF-AH) degrades PAF into the biologically inert lyso-PAF, and restricts uncontrolled progression of inflammatory response. The reduced PAF-AH levels in the neonate contribute to perpetuating PAF activity and aggravating an inflammatory response.

The cellular and molecular immaturity, combined with the diminished immunoglobulin A concentration and lower levels of mucosal enzymes (e.g., pepsin and proteases), and protective agents (lactoferrin) make the premature gut a highly vulnerable organ for bacterial and biochemical injury. The susceptible microenvironment of the gut is further vitiated by a higher gastric pH and decreased small bowel motility facilitates proliferation of pathogenic bacteria.

### Luminal Factors

This should be recognized as an interactive conundrum of substrate, toxins and microbes, with each component facilitating the actions of the other at various stages of the pathogenesis.

It has been claimed that more than 90% of all infants who develop NEC have received milk feeds. Preterm infants fed on formula milk have been observed to be at higher risk for NEC than those on human milk. Despite traditional beliefs, the rates and increments of feed have failed to show any increase in morbidity. Milk provides substrate for bacterial proliferation in the gut. The preterm gut is ill developed to digest and absorb the nutrients available in the feeds. The incompletely digested products (e.g., organic acids, short chain fatty acids, etc.) tend to damage the already vulnerable premature intestinal mucosa. The reduced peristalsis of the premature gut enhances the exposure of the intestinal mucosa to noxious substances.

Proliferating pathogenic bacteria, damage mucosa by their endotoxins and by interacting with the incompletely digested substrate to produce injurious by-products. No incriminating microbial species have been consistently isolated from infants with NEC. Signals from the microbial ligandins like endotoxins interact with the epithelial pattern specific receptors (e.g., toll-like receptors) and result in various mechanisms that could lead to either cytoprotective or destructive (apoptosis or inflammatory) response. Intestinal dilatation in the presence of dysbiosis (abnormal microbial colonization) could distort the normal signal transduction across the intestinal epithelial barrier and alter the pattern of normal growth and repair to that of inflammation, apoptosis and necrosis. Frequent and prolonged use of antibiotics could alter the natural intestinal microbial environment leading to proliferation of pathogenic bacteria.

Probiotics have been considered as a promising tool to promote growth of commensal bacteria in the gut. However, until more robust studies are available about the preferred bacterial strains, standardization of preparation, dosing, timing, duration of

therapy, response at different gestations, etc., probiotics cannot be recommended as a standard of care for preventing NEC.

The antimicrobial property of lactoferrin, is probably due to its iron sequestering property that makes iron unavailable for bacterial growth. Lactoferrin has broad microbicidal activity against gram-positive cocci, gram-negative bacilli, and *Candida* species. VLBW infants have low lactoferrin levels and this deficiency is exacerbated by delay in establishing enteral feeding.

### Vascular Factors

Vascular compromise of the intestinal circulation would certainly complicate an already compromised intestinal environment. Nitric oxide mediated responses have ensured low vascular resistance and high intestinal blood flow. Altered endothelial functions could alter this mechanism resulting in increased vascular resistance with the ensuing ischemic cascade progressing to mucosal necrosis. Though ischemia per se may not be a major triggering factor for NEC it would most certainly compound the morbidity. The earlier concern of umbilical catheters contributing to NEC has been fortunately found to be unsubstantiated.

While packed cell transfusions have been linked to the occurrence with NEC, the exact mechanism for this association is unclear. Transfusion associated NEC has, however, been reported to be associated with higher mortality.

### PATHOLOGY

Terminal ileum and colon are the common sites for NEC though the entire gastrointestinal tract could be affected in severe cases. On gross examination the bowel would appear distended and hemorrhagic. Features depend on the severity and stages of the disease. This would include subserosal collection of gas along the mesenteric border, gangrenous necrosis and perforation in the antimesenteric border. Various stages of healing would manifest as thickening of bowel wall, fibrinous adhesions and areas of stenosis.

Histological findings in NEC are mucosal edema, hemorrhage, and transmural necrosis. Other findings include acute inflammation, secondary bacterial infiltration, and collections of gas. Vascular thrombi are rare.

Spontaneous intestinal perforation (SIP) also called isolated intestinal perforation (IIP) is an entity that occurs earlier than classical NEC with a strong association with postnatal combined use of corticosteroids and indomethacin. This manifests commonly in the antimesenteric border of the terminal ileum. The clinical presentation is rather abrupt and is often a differential diagnosis for NEC. SIP is associated with lower levels of serum inflammatory cytokines and minimal intestinal inflammation and necrosis.

### CLINICAL PRESENTATION

For the caregivers of a preterm infant, there is nothing more satisfying than establishing complete enteral nutrition. Intolerance to feeds, distension or vomiting invariably raises the ubiquitous bogey of NEC. It often manifests in preterm infants by the second week of life, while on oral feeds. The age of onset of NEC is seen to be inversely related to the PMA with the disease manifesting earlier in late preterm and the occasionally term infants. While suspecting, NEC in these groups of infants, history should be sought of problems like perinatal stress that may affect mesenteric blood flow, intestinal anomalies (e.g., aganglionosis or atresia), congenital heart disease or maternal illicit drug use.

Compounding the differential diagnosis is a more recent entrant recognized as SIP or IIP. This is unrelated to feeding and occurs during the early days after birth, unlike the classical NEC that tends to occur around the second week of life. A combined usage of indomethacin and glucocorticoids, has been implicated



in SIP. SIP should be recognized as an entity different from NEC with different pathogenesis and thereby warranting management of strategies different from NEC.

### Clinical Features (Box 1)

The early signs of NEC are no different from that of sepsis. Lethargy, temperature instability, increasing heart rate, changes in perfusion as evidenced by increasing capillary refill time, alteration in glucose homeostasis, etc., are the subtle harbingers of NEC. These features become more profound as the disease progresses.

The initial gastrointestinal symptoms of NEC are subtle and appear no different from those of feed intolerance commonly encountered in most premature infants. It is here that the clinical vigil of the caregiver in detecting the subtle changes in the physiological characteristics like temperature instability pays rich dividends.

Gastric retention greater than 50% of the volume of feeds given over the previous 3–4 hours in a preterm infant, when associated with *unstable physiology* should always be considered as early NEC and therapeutic interventions initiated. While such an approach could lead to some false alarms, it is preferable to error on the side of caution where NEC is concerned. Increasing feed intolerance, bilious/*greenish* aspirates or vomiting, accompanied by progressive abdominal distension in a premature infants are clinical manifestation of the more established stages of NEC. Frank blood in stools (hematochezia), though considered pathognomonic of NEC is not an early sign. Abdomen would be tender, with guarding and occasionally tense. Gentle sensitive palpation could on occasion reveal a mass representing inflamed bowel with associated omental adhesions. Visible discoloration of the abdominal wall is an ominous sign, usually associated with gangrene and perforation of the gut.

Bowel sounds would be diminished to absent. This is a clinical feature useful to differentiate NEC from mechanical intestinal obstruction. Differentiating from paralytic ileus due to other causes, may however be more difficult during the early stages. Depending on the stage of the disease, the differential diagnosis of NEC could range from feed intolerance of the premature infant to SIP or gangrene of the gut due to other causes (**Box 2**).

## INVESTIGATIONS

### Radiological Examination

Plain X-ray of the abdomen could show a variety of presentations, depending on the severity of the disease. In the early stages, distended intestinal loops with thickened intestinal walls better appreciated in the cross-sectional view are the commonest presentation. Many neonatologists prefer to call this *Pre-NEC* stage, though the origin or justification of this terminology is unclear. If an X-ray repeated after a few hours shows a fixed loop of intestine, the suspicion of NEC would be more than justified. The presence of this *sentinel loop*, the so called *thumb print sign* in serial X-rays, represents the *local ileus* of that particular segment of the intestine.

Progression of the clinical stage of the disease is reasonably represented by the radiographic changes. This would range from paucity of intestinal gas shadows and fixed intestinal loop in the initial stages, to the more specific features of gas in the intestinal wall *pneumatosis intestinalis* (**Fig. 2**), and occasionally, gas in the portal vein.

Free-peritoneal gas, the ominous sign of intestinal perforation would be obvious if there is a massive collection. Selective radiological views should be taken when perforation is being sought for. The left lateral decubitus view may reveal gas collection below the diaphragm in relation to the liver, or a cross table view could show gas just beneath the abdominal wall (**Fig. 3**). It must

be remembered that minimal gas in the peritoneum may not be detected on X-ray, and absence of radiological features does not necessarily obviate the role of surgical management in NEC.

### BOX 1 Necrotizing enterocolitis staging based on Bell's stage

#### Stage I (Suspect)

- Clinical
  - *Systemic*: Temperature instability, lethargy, apnea, bradycardia
  - *Gastrointestinal manifestations*: Poor feeding, increasing pregavage residuals, emesis (may be bilious), mild abdominal distension
- Radiograph
  - Abdominal distension with mild ileus

#### Stage II (Definite)

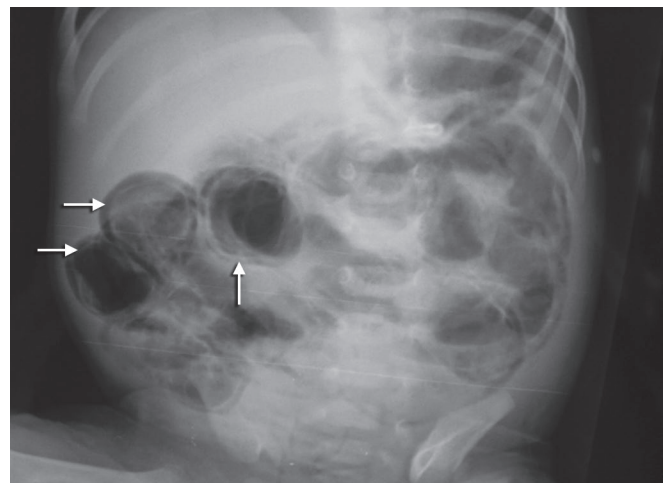
- Clinical
  - All above signs and symptoms plus gastrointestinal bleeding; marked abdominal distension
- Radiograph
  - Significant intestinal distension with ileus, bowel wall edema, peritoneal fluid, unchanging or persistent bowel loops (*sentinel loop*)
  - Pneumatosis intestinalis, portal vein gas

#### Stage III (Advanced)

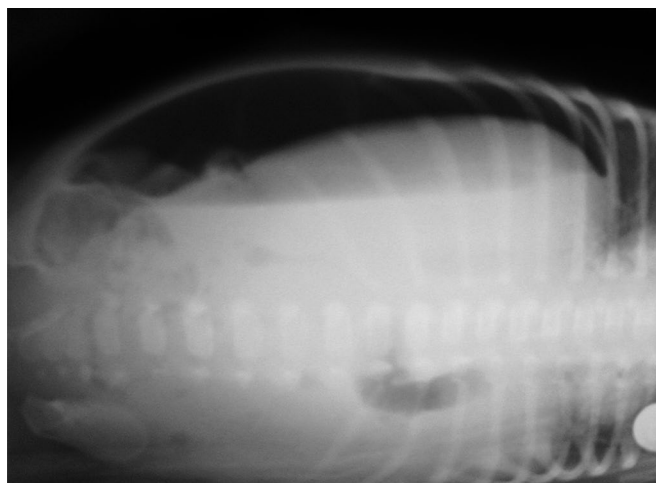
- Clinical
  - Above signs and symptoms plus deterioration of vital signs
  - Features of septic shock or marked gastrointestinal hemorrhage
- Radiograph
  - Earlier features plus pneumoperitoneum.

### BOX 2 Differential diagnosis of necrotizing enterocolitis

- Physiological feed intolerance of prematurity
- Gastroesophageal reflux
- CPAP belly
- Gastric retention/vomiting due to drugs like theophylline
- Malpositioned oro/nasogastric tube (e.g., yellow aspirate from duodenum)
- Paralytic ileus due to sepsis
- Intestinal obstruction due to structural abnormalities of the gastrointestinal tract
- Spontaneous intestinal perforation (syn. isolated intestinal perforation)
- Internal hernia.



**Figure 2** X-ray abdomen showing dilated loops of bowel and intramural gas—*pneumatosis intestinalis* (arrows)



**Figure 3** X-ray abdomen (cross table) showing presence of pneumoperitoneum

The caregiver must realize that NEC is a painful condition. Lifting up the infant vertically for the so called *erect* radiograph must be strongly discouraged. Handling and positioning of the infant must be done with the most gentle and humane touch.

*Ultrasonography* may be used to detect smaller volumes of free peritoneal gas and portal venous gas.

### Hematology

Hemoglobin may be low. Vasoconstriction and hemoconcentration secondary to third spacing of fluid may at times result in falsely reassuring levels of hemoglobin or hematocrit in an otherwise anemic infant. Neutrophilia or neutropenia, with shift to the left and thrombocytopenia are commonly encountered.

### Biochemistry

Metabolic acidosis could be the manifestation of the disease per se or that of acute kidney injury, a not uncommon complication of

NEC. Renal functions and electrolytes must be critically analyzed as the disease progresses. Hyponatremia is considered by many clinicians as an ominous sign.

### MANAGEMENT

Management of NEC starts from the moment the disease entity is suspected. Unfortunately, clinical features alone are far from adequate to diagnose NEC. The staging system described by Bell et al., in 1978 and subsequently refined (**Box 1**) has been used for the systematic description of NEC. However, other causes for perforation like SIP, vitiates the reliability of the Bell's criteria to confirm and grade the severity of NEC. The relative lack of correlation between the clinical presentation, radiological observation and the histopathological findings of the tissue makes the available staging system unreliable for deciding surgical intervention. Despite its limitations, this clinical and radiology based staging system has continued to be a guideline for planning treatment.

Supportive care and antibiotics are initiated, at the slightest suspicion of the disease. Astute clinical, radiological and laboratory evaluations at regular intervals are necessary to confirm the diagnosis of NEC and monitor its progression. Surgical intervention is resorted to if the disease progresses to the advanced stages (**Table 1**).

### Supportive Management

Bowel rest is the most important treatment to be initiated when one is suspecting NEC. The infant should be kept nil by mouth. Abdominal girth should be measured and serially monitored in the same planar circumference. Most experienced neonatal nurses mark parallel lines on the abdomen of the infant to ensure that girth measurement is always along the same path. Total parenteral nutrition is initiated until the infant is back to sustained and complete oral intake—a process best achieved by gradual increments over 7–10 days after clinical and radiological improvement.

*Gastric aspiration* at regular (conventionally 4th hourly) intervals should be done, and the volume and color of the aspirate to be noted. Significant nonbilious gastric residues (more than

**Table 1** Management of necrotizing enterocolitis

Presentation	Intervention	Investigations
Feed intolerance in at-risk infant, mild abdominal distension, some soft signs of sepsis	Keep nil by mouth Intravenous fluids Antibiotics	<i>X-ray abdomen:</i> Nonspecific <i>Blood investigations:</i> complete blood count, blood cultures, renal parameters, electrolytes
<i>Suspected NEC (Bell's stage 1)</i> Decreased activity Thermoregulatory instability Abdominal distension Increased gastric aspirates Sluggish or absent bowel sounds	<i>All the above plus:</i> Fluid resuscitation To consider inotropes TPN may be initiated	<i>X-ray abdomen:</i> Distended intestinal loop Abnormal pattern of intestinal gas Thickened intestinal wall Fixed/sentinel loop of intestine <i>Blood investigations:</i> Same as earlier plus blood gases for metabolic or respiratory acidosis
<i>Definite NEC (Bell's stage 2)</i> Green or yellow aspirates or evidence of gastrointestinal bleeds Tender abdomen, soft mass may be palpable (commonly in right lower quadrant of abdomen) Absent bowel sounds	<i>All the above plus:</i> Inotropes commenced, Supportive ventilation may be initiated	<i>All the above plus:</i> Pneumatosis intestinalis Gas shadow in the portal vein
<i>Advanced NEC (Bell's stage 3)</i> <i>All the above plus:</i> Increased morbidity Circulatory instability and shock Discoloration of abdominal wall	<i>All the above plus:</i> Ventilator support Surgical intervention	<i>X-ray abdomen:</i> Pneumoperitoneum <i>Blood investigations:</i> Same as above

Abbreviations: NEC, necrotizing enterocolitis, TPN, total parenteral nutrition.

1 mL/hour) are replaced with isotonic saline, while bilious residues are best replaced volume for volume by Ringer's lactate solution. As the infant's condition improves, the aspirates become clearer and gradually reduce to negligible levels.

One must remember that with the increasing abdominal girth, the infant would be having third space fluid losses. Additional boluses of saline or ringer lactate may be given over 30–60 min, with strict vigil for fluid overload. The aim is to ensure that perfusion is well-maintained to avoid hypoperfusion of the organs and pre-empt prerenal failure. The erratic dose response of dopamine with the possible risk of mesenteric vasoconstriction due to  $\alpha$ -adrenergic effect even at lower doses, has influenced some units to use alternative inotropic drugs such as epinephrine or even dobutamine when inotropic support is required.

*Ventilator support* may be required if there is acidosis, or progressive abdominal distension hampering normal respiration. This would also provide an opportunity for using narcotic analgesics to alleviate the pain associated with NEC.

*Antibiotics* have been traditionally started in all cases of NEC. The early stages of NEC are often difficult to differentiate from sepsis associated with paralytic ileus. It is also justifiable, as documented bacteremia has been reported in nearly 30% of NEC cases. Gram-negative bacteria like *Enterobacter* spp, *Klebsiella* spp, and *E. coli* constitute majority of bloodstream infections (BSI) in patients with NEC. NEC with concurrent BSI has been found to be associated with higher morbidity and requiring more surgical intervention. Further, the recovery of pathogenic bacteria from peritoneal fluid and the association of NEC with epidemic outbreaks of bacterial infections, justify initiating antibiotics early.

The common practice in most neonatal units, is to use triple drug combination of (1) a penicillin or third-generation cephalosporin; along with (2) an aminoglycoside; and (3) metronidazole. The antibiotics are generally continued till clinical recovery is evident, with the infant tolerating oral feeds usually by 7–14 days.

### Monitoring

All physiological parameters like blood pressure, heart rate, capillary refill time, respiratory parameters, etc., must be regularly evaluated and corrective interventions undertaken. Radiological assessment at 6–8 hourly intervals, is necessary to monitor the progress of the disease. Once clinical and radiological improvement commences, the frequency of these investigations can be reduced. The *pneumatosis intestinalis* tends to disappear over 3–4 days and heralds the gradual recovery process.

Thrombocytopenia and hyponatremia herald ominous outcome. Sudden onset of hyperglycemia is often seen when peritonitis occurs due to transmural spread of inflammation or perforation of viscus. This is often accompanied by deterioration of other physiological parameters. It must be remembered that pneumoperitoneum need not be always radiologically evident.

### Surgical Intervention

The pediatric surgeon is an integral part of the treating team. The timing of surgical intervention is crucial for optimally salvaging the viable bowel. While pneumoperitoneum is an unambiguous decision for surgical intervention, it must be remembered that all perforation may not always be radiologically evident. Therefore, one should be vigilant for other signs of bowel necrosis heralded by deteriorating clinical condition, despite medical management, ascites, palpable mass per abdomen or intestinal obstruction. We have observed a sudden onset of hyperglycemia, in an otherwise euglycemic patient, to be an indicator of peritonitis or perforation.

The specifics of surgical procedures are beyond the purview of this chapter. However, surgical interventions can be summarized as below:

- *Primary peritoneal drainage (PPD)*: This is preferred in critically ill infants below 1,000 g. It can be done under local anesthesia at the bedside.
- *Laparotomy*: There could be different strategies during laparotomy.
- Resecting the necrotic bowel with proximal enterostomy and distal mucus fistula, followed by reanastomosis after 8–12 weeks.
- Resection and primary anastomosis, if only a short segment is involved.
- *Second look approach*: When there is extensive necrosis observed on laparotomy, drains are placed and the abdomen is closed, with the intention of a *relook*. Laparotomy is undertaken again after 2–3 days to enable identification and resection of the segment of the gut that is unambiguously necrotic. The aim is to preserve the maximal length of the viable intestine.

In critically ill preterm infants, the outcome of both PPD and laparotomy has been found to be similar. Proponents for both strategies continue to advocate their preferred method of treatment. Primary peritoneal drainage has not been beneficial when IIP has been the confounding diagnosis.

### COMPLICATIONS

Complications could occur during the acute stage of the disease or may present as late complication. Commonly observed acute complications are:

- Infection linked problems like sepsis, meningitis, peritonitis, abscess formation.
- Disseminated intravascular coagulation.
- Respiratory and cardiovascular—hypotension, shock, and respiratory failure.
- Metabolic complications—metabolic acidosis, hypoglycemia, hyperglycemia, hyponatremia.
- Acute kidney injury.

Complacency after recovery from the acute illness would be ill-advised. While some areas of intestinal narrowing recover, intestinal stricture could persist in 9–36% of NEC. Interestingly, this is unrelated to the severity of the acute disease. Colon is the most common site for stricture formation, though strictures could occur at any part of the intestine or even at multiple sites in the same patient. Risk of developing short bowel syndrome after operative management of NEC was higher in infants below 750 g. As expected, greater percentage of bowel resection and requirement of jejunostomy were associated with a risk for short bowel syndrome. Growth retardation and neurodevelopmental delay have also been reported in infants affected by the more severe forms of NEC.

### IN A NUTSHELL

1. Prematurity is the single most important risk factor for NEC in the newborn.
2. No single clinical sign is pathognomonic of NEC in the newborn; a high index of suspicion is required in sick preterm neonates for NEC.
3. *Pneumatosis intestinalis* is the most classical radiological finding of NEC in newborn.
4. Probiotic therapy has limited role in prevention of NEC.
5. Management of NEC is essentially supportive with intense monitoring for disease progression.

**MORE ON THIS TOPIC**

- Chan KYY, Leung FWL, Lam HS, et al. Immunoregulatory protein profiles of necrotizing enterocolitis versus spontaneous intestinal perforation in preterm infants. *PLoS One*. 2012;7:e36977.
- Gibbs K, Lin J, Holzman IR. Necrotizing enterocolitis: the state of science. *Indian J Pediatr*. 2007;74:67-72.
- Grebenik CR, Sinclair ME. Which inotrope? *Current Paediatr*. 2003;13:6-11.
- Luig M, Lui KJ, NSW & ACT NICUS Group. Epidemiology of necrotizing enterocolitis—Part II: Risks and susceptibility of premature infants during the surfactant era: a regional study. *J Paediatr Child Health*. 2005;41:174-9.
- Markel TA, Engalsted H, Poindexter BB. Predicting disease severity of necrotizing enterocolitis: how to identify infants for future novel therapies. *J Clin Neonatol*. 2014;3:1-9.
- Narang A, Rao R, Bhakoo ON. Neonatal necrotizing enterocolitis an epidemiological study. *Indian Pediatr*. 1993;30:1207-14.
- Neu J, Walker AW. Necrotizing enterocolitis. *NEJM*. 2011;20:255-64.
- Patel BK, Shah JS. Necrotizing enterocolitis in very low birth weight infants: a systemic review. *ISRN Gastroenterol*. 2012;2012:562594.
- Schanler RJ. Management of necrotizing enterocolitis in newborns. From: <http://www.uptodate.com/contents/management-of-necrotizing-enterocolitis-in-newborns> review current. Accessed August 1, 2014.
- Sharma R, Hudak LM. A clinical perspective of necrotizing enterocolitis: past, present, and future. *Clin Perinatol*. 2013;40:27-51.



## Chapter 14.12

# Retinopathy of Prematurity

Ashish Jain, Veeraraja B Sathenahalli,  
Karobi Lahiri Coutinho

Retinopathy of prematurity (ROP), previously known as retrolental fibroplasia is a vasoproliferative disorder of immature developing retina of preterm infants. Its presentation varies from mild, transient changes which regress spontaneously to severe progressive vasoproliferative changes leading to scarring and eventually retinal detachment. ROP is one of the most important preventable causes of childhood blindness in both industrialized and developing countries. Emergence of ROP in recent time can be attributed to the increasing preterm births that get improved and advanced care leading to increased survival, but this comes at a cost of many unwanted consequences among which ROP is one. Hence, world over industrialized countries have witnessed two epidemics of ROP. First in the 40s and 50s, affecting largely premature babies in the US and Europe due to increased use of unregulated oxygen in these babies. However, this epidemic ended with implementation of controlled oxygen administration. Improved understanding of the risk factors for ROP and improving neonatal care with invention of newer modalities of treatment resulting in increased survival rates of premature babies paved way for the second epidemic in 1970s in industrialized countries. Now third epidemic of ROP is occurring in middle-income countries namely Latin America, Former Socialist Economies, India and China. Increasing rate of preterm birth, increased access to health-care facilities, high rates of ROP requiring treatment in these preterm babies and inadequate screening program are contributing factors for the third epidemic. Timely screening, initiation of treatment and proper follow-up can prevent blindness and reduce the morbidity associated with ROP.

## EPIDEMIOLOGY

Retinopathy of prematurity (ROP) causes blindness in almost 50,000 children worldwide. Some of the Indian studies have reported an incidence of 20–50% among screened neonates. However, recent studies report a lower rate of 20–30%. According to early treatment for retinopathy of prematurity study (ETROP) trial, a multicenter trial, 68% of ROP (any stage) was reported among neonates less than 1,250 g, this was comparable to previously reported data by another multicenter trial, cryotherapy-ROP (CRYO-ROP, 65.8%).

## DEFINITION

Retinopathy of prematurity is a disorder of the immature developing retinal vasculature characterized by cessation of the normal progression of newly forming vessels (vasculogenesis), followed by the development of new abnormal blood vessels (neovascularization) which eventually heals by completely involuting with normal vascularization of the retina (regression) or progresses to a chronic phase (cicatrical ROP) with scarring, retinal detachment and visual loss.

## ETIOLOGY

Following risk factors make the immature developing retina of premature infant susceptible to changes responsible for development of ROP.

- Prematurity
- Low birth weight

- Small for gestational age
- Delivery room resuscitation involving chest compression and/or medications
- Respiratory distress syndrome/surfactant therapy/oxygen therapy for more than 24 hours
- Severe intraventricular hemorrhage (IVH, Grade 3 or Grade 4)
- Patent ductus arteriosus requiring pharmacological or surgical closure
- Culture-positive sepsis or culture-negative sepsis treated with antibiotic therapy for more than 5 days
- Documented necrotizing enterocolitis
- Multiple blood transfusions and/or exchange transfusion
- Pneumothorax
- Hypotension requiring vasopressor therapy.

## PATHOGENESIS

Various theories have been proposed for the pathogenesis of ROP. The important ones are the Classical theory and the Gap junction theory.

The *Classical theory* hypothesized that ROP occurred in two phases:

1. *Hyperoxic phase* It occurs immediately after birth due to exposure to hyperoxic environment. This leads to retinal arteriolar constriction, irreversible vaso-obliteration and dissolution of the retinal capillary endothelial cells.
2. *Hypoxic phase* On withdrawal of the hyperoxic environment, an ischemia induced vasoproliferative response was seen, resulting in ROP.

The *Gap Junction theory* is based on the activity of mesenchymal spindle cell precursors of retinal capillaries. The precursor cells migrate from optic disc to the junction between vascular and avascular retina to form a new capillary network. Under hyperoxic conditions, abnormal gap junctions appear between adjacent spindle cells and this interferes with normal cellular migration and vascular formation. The angiogenic factors secreted by these mesenchymal cells may in turn trigger a neovascular response.

The current understanding incorporates both theories. Hence, pathogenesis of ROP can be divided into two sequential phases:

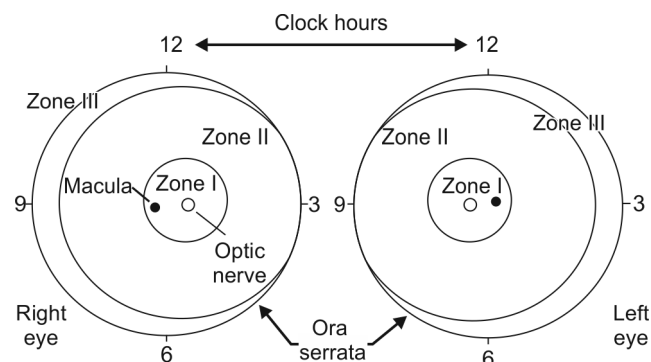
1. *Phase 1 Hyperoxia-vasoconstriction*: This phase is characterized by cessation of vascular endothelial growth factor (VEGF) driven vessel growth because of exposure of the premature infant to hyperoxic condition immediately after birth. The consequent vascular endothelial obliteration results in retinal vessel obliteration.
2. *Phase 2 Hypoxia-vasoproliferation*: On termination of phase of hyperoxia, retinal ischemia occurs, a high metabolic demand of the developing vessels causes hypoxia driven VEGF expression now resulting in neovascularization (hallmark of Phase II ROP). VEGF is a promoter of angiogenesis upregulated by hypoxia. Insulin-like growth factor 1 (IGF-1) is produced by placenta in late second and third trimester by an oxygen-independent mechanism. IGF-1 participates in the regulation of VEGF within the retina. Its absence due to premature birth plays a major role in the pathogenesis of ROP, because VEGF is then produced by the ischemic retina without any regulation, resulting in the abnormal angiogenesis.

## CLASSIFICATION OF RETINOPATHY OF PREMATURE

The international classification of retinopathy of prematurity (ICROP) by Flynn was first published in 1984 and expanded in 1987. The original ICROP dealt with the early phases of the

disorder and was based on several key observations essential in describing the retinopathy. These included (1) the location of retinal involvement by zone, (2) the extent of retinal involvement by clock hour (**Fig. 1**), (3) the stage or severity of retinopathy at the junction of the vascularized and avascular retina, and (4) the presence or absence of dilated and tortuous posterior pole vessels (plus disease). This was revisited in 2005 to include (1) the concept of a more virulent form of retinopathy observed in the tiniest babies [aggressive posterior ROP (AP-ROP)], (2) a description of an intermediate level of plus disease (preplus) between normal posterior pole vessels and frank plus disease, and (3) a practical clinical tool for estimating the extent of zone I in addition to old classification (**Table 1**). The definitions for some of the terms used in the classification are as under:

- **Preplus disease** This spectrum of ROP is characterized by abnormal tortuosity and dilatation of the posterior vessels. The abnormality may not account up to plus disease but demonstrates more venous dilatation and arterial tortuosity than normal. This may progress to plus disease anytime.
- **Aggressive posterior ROP** This is an uncommon, rapidly progressing severe form of ROP previously known as *type II ROP* and *Rush disease*. It is characterized by its posterior location, prominence of plus disease and the ill-defined nature of retinopathy. If untreated, it usually progresses to stage 5 ROP. Most commonly observed in zone I, but may also occur in zone II. Another important feature of AP-ROP is that it usually does not progress through the classic stages 1–3. It may appear as only a flat network of neovascularization at the deceptively featureless junction between vascularized and nonvascularized retina which may be overlooked by an inexperienced observer. The extend is typically circumferential. Use of 20D condensing lens instead of regular 25D or 28D during indirect ophthalmoscopy may help in distinguishing this deceptively featureless neovascularization of AP-ROP.
- **Threshold disease** According to CRYO-ROP study, this is defined as a morphologic change beyond which the incidence of unfavorable outcome is more than 50%. It translates into the presence of stage 3 with plus disease in zone I or zone II, extending in 5 or more contiguous or 8 cumulative clock hours.
- **Prethreshold disease** Presence of less than threshold disease in zone I, or stage 2 plus disease in zone II, or stage 3 (without plus) disease in zone II, or stage 3 plus disease with extent



**Figure 1** Diagram of retina describing the zone and extent of retinopathy of prematurity according to ICROP. The retinal changes observed during screening examinations should be recorded according to the above figure

less than that for threshold disease. Now this is the stage where the laser therapy is considered.

## EARLY IDENTIFICATION AND SCREENING

Retinopathy of prematurity occurs in a sequential nature of progression that depends on the gestational age at birth and the postnatal age of the baby. When these babies are examined by an experienced ophthalmologist on a scheduled basis, the same can be identified before it progresses to a severe stage. Thus, timely screening and treatment has a proven benefit of reducing the risk of visual loss. The goal of an effective ROP screening program is to identify the infants who could benefit from treatment and make appropriate recommendations on the timing of future screening and treatment interventions. Because unchecked ROP can lead to permanent blindness, it is important that all at-risk infants be screened in a timely fashion, recognizing that not all infants require treatment.

## Screening for Retinopathy of Prematurity

### Neonates to be Screened for Retinopathy of Prematurity

The ROP screening should be undertaken in the following at-risk neonates:

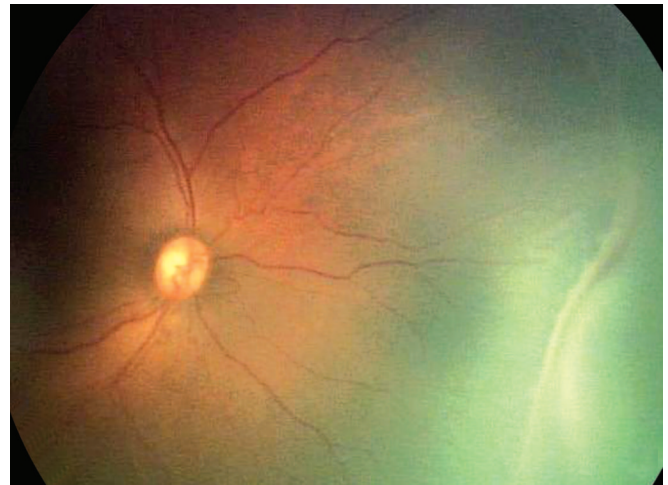
- Neonates with a birth weight of less than and equal to 1,500 g or gestational age of 30 weeks or less (as defined by the attending neonatologist).

**Table 1** International classification of retinopathy of prematurity (ICROP)

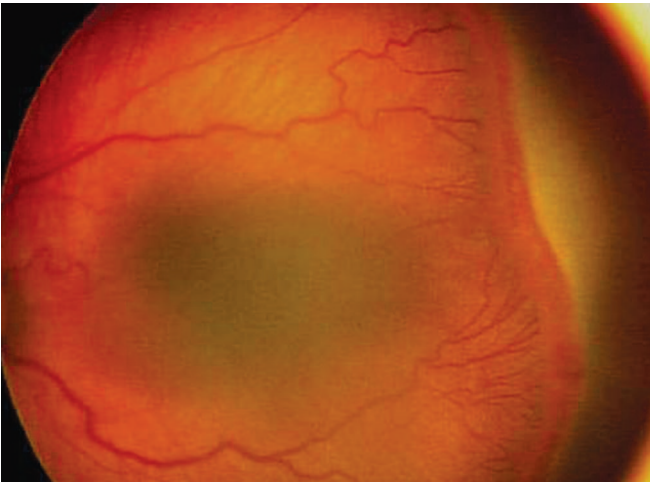
Location	Zone I	Circle with optic nerve at its center and a radius of twice the distance from optic nerve to macula
	Zone II	Concentric circle from edge of zone I to ora serrata nasally and equator temporally
	Zone III	Lateral crescent from zone II to ora serrata temporally
Severity	Stage 1	Presence of thin white demarcation line separating vascular from avascular retina ( <b>Fig. 2</b> )
	Stage 2	Addition of depth and width to the demarcation line of stage 1, so as the line becomes ridge ( <b>Fig. 3</b> )
	Stage 3	Presence of extraretinal fibrovascular proliferation with abnormal vessels and fibrous tissue extending from ridge to vitreous ( <b>Fig. 4</b> )
	Stage 4	Partial retinal detachment not involving macula (4A) and involving macula (4B, <b>Fig. 5</b> )
	Stage 5	Complete retinal detachment ( <b>Fig. 6</b> )
Plus disease	Presence of dilatation and tortuosity of retinal vessels at posterior pole of eye. Also associated with papillary rigidity and vitreous haze	
Extent	Extent of retinopathy of prematurity described in 30° clock hours (a total of 12-hour clock of 30° each)	



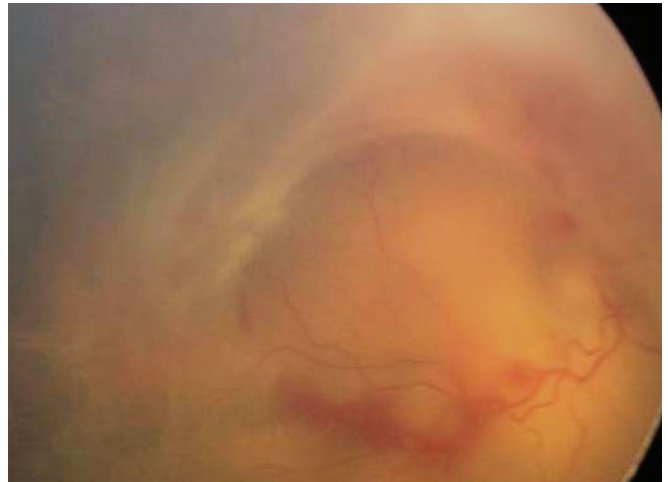
**Figure 2** Stage 1–2 retinopathy of prematurity showing thin white demarcation line separating vascular from avascular retina



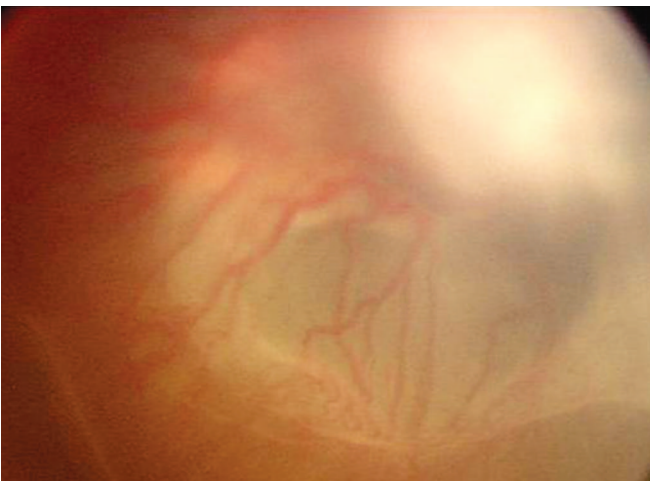
**Figure 3** Stage 2 retinopathy of prematurity; the line becomes ridge



**Figure 4** Stage 3 retinopathy of prematurity showing extraretinal fibrovascular proliferation with abnormal vessels and fibrous tissue extending from ridge to vitreous



**Figure 5** Stage 4B retinopathy of prematurity showing partial retinal detachment involving macula



**Figure 6** Stage 5 retinopathy of prematurity showing complete retinal detachment

- Selected infants with a birth weight between 1,500 g and 2,000 g or gestational age of less than 30 weeks with an unstable clinical course, including those requiring cardiorespiratory support.
- Infants believed by their attending pediatrician or neonatologist to be at high-risk for ROP such as prolonged oxygen therapy, repeated episodes of apnea of prematurity, anemia needing blood transfusion, neonatal sepsis, hypotension and poor weight gain.

The above criteria were laid down by the American Academy of Pediatrics. However, in India the gestation of the neonate is not always known or accurate; in addition, ROP has been reported in larger babies (1,500–2,000 g). Hence, the National Neonatology Forum of India (NNF) recommends screening of neonates less than 34 weeks and/or birth weight less than 1,750 g.

Despite appropriate timing of examinations and treatment, a small number of infants at risk progress to poor outcomes. The initiation of acute-phase ROP screening should be based on the infant's postmenstrual age (PMA, **Table 2**). The onset of serious ROP correlates better with PMA (gestational age at birth plus chronologic age) than with postnatal age. Progression of ROP follows a distinct timeline. Hardly any ROP is detected before 32 weeks of PMA. The median age at detection of stage 1 ROP is



**Table 2** Timing of first eye examination based on gestational age at birth

Gestational age at birth (week)	Age at initial examination (week)	
	Postmenstrual	Chronologic
22	31	9
23	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
Older gestational age, high-risk factors		4

34 weeks. Threshold ROP appears at 34–38 weeks. Vascularization is complete by 44 weeks of gestation. Therefore, critical phase (Window) is between 34 weeks and 38 weeks, when the infant is likely to reach the threshold stage of disease and may require treatment for prevention of blindness.

### First Retinopathy of Prematurity Screen

First screening examination is to be carried at 32 weeks of PMA or 4 weeks of postnatal age, whichever is later. It has been well documented that VLBW babies, may develop early AP-ROP. This is relatively common in Indian babies and needs early screening. Hence, the NNF India recommends that the first screen should be performed not later than 4 weeks of age in neonates more than 28 weeks of gestation. Infants less than 28 weeks or less than 1,200 g should be screened early at 2–3 weeks of age, to enable early identification of AP-ROP.

### Follow-up Retinopathy of Prematurity Screens

Follow-up examinations should be recommended by the examining ophthalmologist on the basis of retinal findings classified according to the revised ICROP. The following schedule is suggested:

#### 1 week or less follow-up:

- *Immature vascularization:* Zone I, no ROP
- Immature retina extends into posterior zone II, near the boundary of zone I
- *Stage 1 or 2 ROP:* Zone I
- *Stage 3 ROP:* Zone II
- The presence or suspected presence of AP-ROP.

#### 1–2 week follow-up:

- *Immature vascularization:* Posterior zone II
- *Stage 2 ROP:* Zone II
- *Unequivocally regressing ROP:* Zone I.

#### 2 weeks follow-up:

- *Stage 1 ROP:* Zone II
- *Immature vascularization:* Zone II, no ROP
- *Unequivocally regressing ROP:* Zone II.

#### 2–3 weeks follow-up:

- *Stage 1 or 2 ROP:* Zone III
- *Regressing ROP:* Zone III.

### Termination of the Retinopathy of Prematurity Screen

The retinal screening examinations may be terminated based on PMA or retinal findings. Findings that suggest that examinations can be terminated include the following:

- Zone III retinal vascularization attained without previous zone I or II ROP (if there is examiner doubt about the zone or if the PMA is less than 35 weeks, confirmatory examinations may be warranted).
- Full retinal vascularization in close proximity to the ora serrata for 360°—that is, the normal distance found in mature retina between the end of vascularization and the ora serrata. This criterion should be used for all cases treated for ROP solely with bevacizumab.
- Postmenstrual age of 50 weeks and no prethreshold disease (defined as stage 3 ROP in zone II, any ROP in zone I) or worse ROP is present.
- Regression of ROP (care must be taken to be sure that there is no abnormal vascular tissue present that is capable of reactivation and progression in zone II or III).

On simplifying the above recommendations, ROP screening should be continued till complete vascularization of retina without any ROP, or if the ROP has shown regression which happens at around 40–44 weeks of PMA.

### Retinopathy of Prematurity Screen Procedure

Screening is best done in the neonatal intensive care unit under supervision of attending pediatrician/neonatologist. Dilatation of pupils is done with phenylephrine 2.5% and tropicamide 0.5–1%. One drop of tropicamide is instilled every 10–15 minutes up to 4 times starting 1 hour before the scheduled time for examination. This is followed by phenylephrine, just one drop before examination. Phenylephrine is available in 10% concentration; it should be diluted 4 times before use in neonates. Repeated instillation of phenylephrine is avoided for the fear of hypotension. If pupils are not dilating despite administration of mydriatic drops, AP-ROP should be suspected.

The examination is done by indirect ophthalmoscopy using 20D or 28/30D lens by an experienced ophthalmologist. A topical anesthetic drop like proparacaine is used to avoid pain during the procedure; a wire speculum is inserted to keep the eyelids apart. The examination progresses from anterior segment to posterior segment. Anterior segment is examined for corneal clarity, anterior chamber depth, pupillary dilation, lens status, and media clarity. Then the posterior pole is visualized to look for plus disease. This is essential because sclera indentation can alter the vascular dilation and tortuosity and cause confusion in interpretation of plus disease. Then the peripheral retina is examined in each clock hour to assess the zone and stage of ROP. Gentle indentation with a pediatric depressor helps to stabilize the globe, visualize the periphery and contrast the details. The findings should be documented after each examination on a ROP chart as per the recommendations of ICROP, mentioning zone, stage and extent in terms of clock hours of any ROP and the presence of any preplus or plus disease. The timing of next visit should also be mentioned at the same time.

Proper precaution should be taken while screening the baby. This includes maintenance of asepsis; the examination should be as brief as possible to avoid short-term effects on blood pressure, heart rate and respiratory function in the premature baby. Discomfort to the baby can be minimized by administering oral sucrose just before examination, pretreatment of the eyes with a topical proparacaine and swaddling the baby. It is better to skip a feed just before the examination as there are chances of vomiting and aspiration.

### RetCam Screening

The use of digital photographic retinal images that are captured and sent for remote interpretation is a developing approach to ROP screening. It has been evaluated as an alternative to indirect ophthalmoscopy screening. The images captured can be stored, transmitted to expert, reviewed, analyzed and sequentially compared over time and are



useful for telemedicine purposes. It has an advantage of eliminating interobserver variability and is also a useful teaching tool. The high cost, lack of trained individuals and diagnostic inaccuracy are the limitations of this novel approach. RetCam in comparison to IO has variable sensitivity but good specificity.

## DIFFERENTIAL DIAGNOSIS

Following diseases mimic ROP:

- Familial exudative vitreoretinopathy
- Persistent hyperplastic primary vitreous/persistent fetal vasculature syndrome
- Norrie disease
- Incontinentia pigmenti
- Osteoporosis-pseudoglioma syndrome.

## MANAGEMENT

Therapy for ROP is directed at treating the underlying pathogenesis by decreasing VEGF levels (specifically VEGF-A), either by completely ablating the peripheral avascular retina that produces the VEGF (LASER therapy/cryotherapy) or by inactivating VEGF by binding it after its production (anti-VEGF therapy).

### Proven Methods (Cryotherapy/LASER therapy)

Standard treatment of ROP in the initial period was by cryotherapy. Treatment of ROP shifted from cryotherapy to light amplification by stimulated emission of radiation (LASER) ablation in 1990s as cryotherapy was very painful, required ventilation during procedure, lacked approach to posterior retina and left a residue of myopia and retinal detachment even after such amount of traumatic procedure. Laser ablation, though a less painful procedure, lacks the other disadvantages of cryotherapy.

Laser ablation involves ablation of peripheral avascular retina so as to prevent the hypoxic drive of retina which produces VEGF causing progression of ROP. This prevents the progression and causes the regression of an established ROP. ROP retina should be avoided as it will cause torrential bleeding inside due to its abnormal vasculature.

According to ETROP, indications of retinal ablation are:

- Zone I, any stage ROP with plus disease
- Zone II, stage 3 ROP without plus disease
- Zone II, stage 2 or 3 ROP with plus disease.

The above stages are included in type I ROP. They include threshold ROP and subset of prethreshold ROP likely to benefit from early treatment.

Type 2 ROP includes:

- Zone I, stage 1 or 2 ROP without plus disease
- Zone II, stage 3 ROP without plus disease.

The above stages require continued serial examinations to follow their progression.

### Newer Strategies (Bevacizumab)

Bevacizumab is a humanized recombinant antibody that inhibits the biological activity of VEGF. It has been widely used for ocular angiogenesis disorders like age-related macular degeneration, proliferative diabetic retinopathy and neovascular glaucoma. An intravitreal injection of bevacizumab demonstrated reduced neovascular activity. In a small case series, when used in stage 3 ROP (acute phase ROP including AP-ROP), it temporarily slowed vasculogenesis and permanently halted angiogenesis. It has the advantage that retinal vessels continued grow as opposed to permanent destruction of the same with laser therapy. But it is yet to be recommended for routine use in neonates with ROP as data regarding serious systemic adverse effects of intravitreal injection are lacking. It may be used only when laser photocoagulation fails and

after taking informed consent from the parents. Another anti-VEGF drug, Pegaptanib sodium is under study and is yet to be studied under large trials before its approval for use. Other newer strategies for treatment of ROP include IGF-I, granulocyte colony stimulating factor, c-Jun-N-terminal kinases (JNK) inhibitors and gene therapy.

## Surgical Management

Surgical management consists of vitreoretinal surgery for the treatment of retinal detachment and includes scleral buckling and vitrectomy.

## SEQUELAE

Timely screening and treatment of ROP reduces vision loss but sequelae can occur even in successfully treated infants. Thus, patients should be followed closely at regular intervals both in the acute stages and in the long-term. Following are the most common sequelae seen in eyes treated for ROP:

- *Visual function:* Reduction in visual acuity is seen. Infants with advanced ROP were found to have visual acuity less than 20/200.
- *Strabismus:* It is seen in up to 40% of babies varying from mildest stages to advanced stages.
- *Myopia:* It is the most common sequelae seen in up to 50% of cases. May cause anisometropia on long run.
- *Amblyopia:* A result of strabismus/anisometropia, frequent screening will help in early identification and requires treatment in the form of refractive correction, occlusion therapy or surgery.
- *Glaucoma:* Seen in advanced stages and is secondary to narrowing of anterior chamber due to retinal contraction causing anterior displacement of lens-iris diaphragm.
- *Retinal detachment:* One of the most common long-term sequelae seen in up to 25% of cases.

## PREVENTION

Retinopathy of prematurity is a preventable disease to a significant extent. The following methods may help in reducing the risk of development of ROP:

- *Judicious oxygen therapy:* Oxygen as drug is a double-edged sword. It should be administered in desired range of concentration to avoid hypoxia and hyperoxia. It is advised that oxygen saturation of the baby should be monitored using pulse oximetry. The oxygen saturation should be maintained between 90% and 93%. PaO<sub>2</sub> should be maintained between 50 mm Hg and 70 mm Hg.
- *Permissive hypercapnia:* Hypocapnia is a risk factor for ROP. By allowing permissive hypercapnia, i.e., 50–60 mm Hg when the pH is above 7.25, a lower ventilatory setting can be maintained minimizing the tendency for progression to chronic lung disease, an oxygen dependent disease.
- *Judicious use of blood transfusions:* Red blood cell (RBC) transfusion is a risk factor as it transfuses adult hemoglobin with low oxygen affinity; it ends up delivering a higher amount of oxygen to retinal tissues causing hyperoxia. Thus packed RBCs should be transmitted only when indicated.
- *Strict clinical monitoring:* Low and high blood pressure are also risk factors for ROP. These situations can be avoided by strict clinical monitoring.
- *Vitamin E supplementation:* Vitamin E deficiency predisposes to ROP. Thus vitamin E supplementation is advised in VLBW babies.
- *Prenatal steroids:* Use of prenatal steroids helps in prevention of ROP by preventing respiratory distress of newborn, IVH and preventing acute illnesses of the preterm infants which are risk factors for ROP.

### IN A NUTSHELL

1. Retinopathy of prematurity, a disorder of immature developing retina, characterized by vasocessation followed by neovascularization, is one of the leading preventable causes of blindness in developing countries.
2. Prematurity and low birth weight are the main risk factors associated with ROP.
3. Vascular endothelial growth factor and IGF-1 play a key role in the pathogenesis of ROP.
4. Babies to be screened are infants with a birth weight of less than and equal to 1,500 g or gestational age of 30 weeks or less (as defined by the attending neonatologist) and selected infants with a birth weight between 1,500 g and 2,000 g or gestational age of more than 30 weeks when associated with risk factors or to be considered when attending neonatologist thinks they are at high-risk.
5. According to Indian literature, first screening examination should be carried at 32 weeks of PMA or 4 weeks of postnatal age, whichever is later.
6. The findings of indirect ophthalmoscope should be recorded and classified according to the recommendations of ICROP.
7. Severity and staging of ROP determine the schedule of follow-up examinations.
8. Retinopathy of prematurity screening should be continued till complete vascularization of retina without any ROP, or if the ROP has shown regression which happens at around 40–44 weeks of PMA.
9. Treatment of ROP mainly aims at reducing the levels of VEGF. Retinal ablation of avascular retina is the mainstay of therapy.
10. Type I ROP, i.e., zone I—any stage ROP with plus disease, zone II—stage 3 ROP without plus disease and zone III—stage 2 or 3 ROP with plus disease are the indications for laser ablation.

### MORE ON THIS TOPIC

- Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. *Arch Ophthalmol*. 2003;121:1684-96.
- Fierston WM, American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, et al. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2013;131:189-95.
- International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol*. 2005;123:991-9.
- Kumar P, Sankar MJ, Deorari A, et al. Risk factors for severe retinopathy of prematurity in preterm low birth weight neonates. *Indian J Pediatr*. 2011;78:812-6.
- Niranjan HS, Benakappa N, Reddy KB, et al. Retinopathy of prematurity promising newer modalities of treatment. *Indian Pediatr*. 2012;49:139-43.
- Pejaver RK, Vinekar A, Bilagi A. National Neonatology Foundation's Evidence Based Clinical Practice Guidelines for Retinopathy of Prematurity, NNF India, Guidelines; 2010.pp.253-62.
- Vinekar A, Dogra MR, Sangtam T, et al. Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: Ten year data from a tertiary care center in a developing country. *Indian J Ophthalmol*. 2007;55:331-6.

## Chapter 14.13

# Neonatal Transport

Neelam Kler, Anup Thakur

Organized emergency neonatal transport systems are an important component of modern perinatal care. The aim of all neonatal transport teams is to transport an infant in a well-stabilized manner and this can be achieved by timely, organized, comprehensive care by the health-care team. Ideally, mothers with identified high-risk pregnancies should deliver in tertiary level perinatal facilities for comprehensive maternal and newborn care. In utero transfer is therefore undoubtedly the safest means of transfer; however problems of prematurity, perinatal illness and congenital malformations are often unanticipated, resulting in a continued need for transfer of these high-risk infants after birth.

Stabilization of newborn before and during transportation has been shown to improve the condition of newborn in terms of temperature, blood glucose, oxygenation and blood pressure. However, most of neonatal transports in our country are self transport without any pretreatment stabilization or care during transport. The consequences of such disorganized transports are often grave with most of these newborns being transported cold, blue and hypoglycemic. 75% of the babies transferred this way have serious clinical implications.

In India, antenatal care is inadequate and majority of the deliveries still occur at home (approximately 60% in rural areas as per National Family Health Survey 3). Thus, the problem of shifting sick neonates born in the community is compounded by a virtually nonexistent neonatal transport system. As a result most of the referred neonates reach the hospital in a critical state with 5-fold higher mortality risk as compared to those delivered in hospital or transferred in stable condition.

## REGIONALIZATION OF NEONATAL HEALTH-CARE

Neonatal transport programs require appropriate referral systems, management structures and trained transport personnel. They need to utilize transport equipment, address transport logistics and have a quality improvement program. Local factors such as geography, population density and organization of perinatal services affect the manner in which different transport programs function. There are various regionalized neonatal transport systems distributed all over the world. Among them, the popular ones are the New South Wales Emergency Transport System (NETS), various regionalized transport systems in United Kingdom and in United States of America. Similarly in India, Tamil Nadu, Madhya Pradesh and Gujarat are the other states where regionalized neonatal transport services are being initiated.

## ORGANIZED VERSUS SELF-TRANSPORT

Organized transport service provides almost the same level of monitoring and the quality of care during the transport that is available in an advanced NICU. Mechanical ventilation, multiple fluid infusion therapy and cardiorespiratory monitoring should be inherent in such services. In India, currently no dedicated neonatal transport service is available and most sick neonates are transferred by their parents or paramedical personnel either in private vehicles or poorly equipped ambulance. There is enough data to suggest that transport by a skilled organized team reduces neonatal mortality and morbidity. In a retrospective analysis done in a regionalized transport network in and around 250 km of Hyderabad, biochemical and temperature disturbances were

more common in babies transported on their own as compared to specialized neonatal transport service. Neonates transported by the hospital team had significantly higher survival as compared to those who came on their own.

## CLINICAL PROFILE OF TRANSPORTED BABIES

Common clinical reasons for transporting neonates include prematurity, hyaline membrane disease, sepsis and birth asphyxia. In India, the onus of transport usually lies with the parents, who are barely informed about the condition of their baby and the indications of transfer. In a recent study in India by Dalal et al., pretransport stabilization was done only in 37% of neonates and hypothermia, hypoxia, poor perfusion, hypoglycemia was observed in 55%, 27.4%, 23.4% and 20.6% of neonates respectively. Singh et al. noted a higher mortality of 56.2% in transported neonates as compared to an overall mortality of 26.3%. The neonates were usually brought to the emergency department wrapped in cotton (24.5%), blanket (25.4%), and quilt (11.8%) or just in towels without any external source to provide warmth. Facility of oxygen therapy was available to only those babies who were brought in ambulances. A secure intravenous access was almost always lacking.

## INDICATIONS OF TRANSPORT

Infants requiring advance medical and/or nursing care exceeding what is available in their current settings will need transfer to a higher health facility. Reasons for transferring infants are: no appropriate local neonatal facilities; unavailability of cot; insufficient appropriate nursing or medical staff—for example, pediatric surgeons, cardiologists, unexpected delivery, and transfers back to local facility (reverse transport). The broad indications for which neonatal transport should be considered are given in **Box 1**.

## TYPES OF TRANSPORT

There is widespread agreement that neonates should have access to facilities appropriate to their care needs. Neonatal transfers can be categorized as follows:

- Intrahospital transport (including delivery suites, theaters).
- To facilitate specialist management of the neonate (movement to a regional center for cardiac, neurological, renal or surgical opinion).

### BOX 1 Indications for transport

- Very low birth weight infants especially below 1,250 g
- Prematurity: Gestational age < 32 weeks
- Respiratory distress or apnea
  - Requiring supplemental Oxygen or mechanical ventilation
- Cyanosis persisting despite oxygen therapy
- Hypoxic ischemic encephalopathy
  - Requiring intubation and assisted ventilation
  - Seizures
  - Multiorgan involvement
- Sepsis with signs of systemic infection
- Jaundice with potential for exchange transfusion
- Active bleeding from any site
- Infant of diabetic mother or hypoglycemia unresponsive to recommended treatment
- Surgical conditions
- Congenital heart disease (antenatal diagnosis or suspected)
- Heart failure or arrhythmia
- Suspected metabolic disorder
- Severe electrolytes abnormalities
- Infants requiring special diagnostic and/or therapeutic service.

- Retrieval from a peripheral hospital for ongoing intensive care within a level 3 unit (when mothers deliver prematurely without warning).
- Returning infants to local neonatal units following care elsewhere (either locally or long distance)—reverse transport.

## MODE OF TRANSPORT

The mode of transport (ground, air) should be determined by the transferring institution in consultation with the referral hospital. The thumb rule is to use *the safest and fastest means of transport that is available*. The vehicle used would depend on the local terrain, condition of the neonate, distance to be traveled, safety and cost. The transport vehicle should be compatible with weather and traffic conditions. Ground transport is useful for distances of 100–120 km, beyond which an aircraft is desirable. However, in places like India where proper ground transport is rarely available, air transport is utopian.

## ORGANIZATION OF TRANSPORT

### Pretransport Stabilization

Prior stabilization and adequate care during transport results in decreased risk of hypothermia, hypoglycemia, poor perfusion and mortality. Available models for pretransport stabilization and care during transport are:

- **STABLE:** Sugar, Temperature, Artificial breathing, Blood pressure, Laboratory work, Emotional support.
- **SAFER:** Sugar, Arterial circulatory support, Family support, Environment, Respiratory support.
- **TOPS:** Temperature, Oxygenation (Airway and Breathing), Perfusion, Sugar.

The following scheme may be followed for stabilization of neonates prior to transport:

### Assessment

Assess the baby and depending on facilities available check for temperature, airway, breathing, circulation and sugar. Identify special needs and circumstances that require additional intervention.

### Temperature

Assess temperature and consider the support required for transfer. Correct hypothermia if present before transport with radiant warmer at stabilization unit or referring center.

### Airway and Breathing

Make sure the airway is patent and secure. Assess airway for presence of any secretions (suction if present) and position of neck (place shoulder roll). Decision for need of intubation should be taken beforehand and a lower threshold for intubation should be used to minimize the need to intervene in transit. If the infant is unstable, has a rising oxygen requirement, has recurrent apnea/recurrent seizure, is on prostaglandin infusion due to duct dependent congenital heart disease, is extremely premature; then intubation and respiratory support is highly likely to be required. If already intubated, the endotracheal tube (ETT) must be correctly positioned and secured. Adequate respiratory support must be given. Surfactant should be administered if indicated.

### Circulation

Stabilize blood pressure, correct perfusion and severe acidosis. Document heart rate, BP, capillary refill time (CRT) and urine output in last 6 hours. Check what fluids baby is getting and assess for the need of fluid bolus and inotropes; adjust infusion of inotropes as per need. Arterial access should be considered in

infants who require repeated blood gas analysis or accurate blood pressure measurement. As portable hand-held arterial blood gas (ABG) machines are usually not used during transport in our country, so it may be acceptable to delay putting an arterial line until reaching the referral center.

### Sugar

Measure and stabilize blood glucose. Secure intravenous access and check the patency of IV cannula. Check sugar with glucometer; if blood glucose less than 40 mg/dL, give 2 mL/kg of 10% dextrose through intravenous line followed by continuous dextrose infusion at the rate of 6–8 mg/kg/min.

### Laboratory Work-up

Check and document all investigations and medications.

### Infection

If sepsis is suspected, give one dose of antibiotics.

### Transport Personnel

Trained transport team capable of monitoring and providing care is ideal. Trained nurse, paramedic or physician at the referring hospital is another alternative. Accredited social health activists from community or basic health facility are also involved in neonatal transfers.

### Equipment

A fully equipped neonatal transport ambulance should be used for transport. Raise the environmental temperature of the vehicle if possible. Ensure doors of vehicle are closed. Ensure doors of transport incubator are closed. If possible improve general comfort for the infant, use mattress that can absorb vibration and avoid sudden acceleration and deceleration of the vehicle.

### Parents' Information and Wishes

Discuss plans with parents and take informed consent. Discuss the condition of the baby and provide emotional support.

### Communication

Ensure the team at the referral unit will have all the necessary information to advance the care of the baby. Ascertain availability of bed, personnel and equipment at the arriving unit.

## Care During Transport

### Temperature Maintenance

Use a transport incubator. Transwarmer mattress is another effective option to keep infants warm. Innovative techniques like Embrace incorporates a phase change material to rapidly stabilize the temperature of an infant suffering from hypothermia. It is inexpensive and costs less than 1% of the cost of a standard incubator, reusable (50 times) and can be used while the baby is held in the mother's arms or during transport. Plastic wraps or bags have been shown to be low cost and effective method for neonatal transport. In resource limited conditions kangaroo mother care (KMC) is an important alternative method, when transport incubators are not available.

### Airway and Breathing

Keep neck of the baby in slight extension position; if airway is unstable, it is better to intubate and transport.

### Circulation

Assess perfusion for warm peripheries, capillary refill time of  $\leq 3$  sec, tone and activity, and blood pressure. Syringe infusion pumps are required to use inotropes with accuracy.



### Check Oxygenation

Continuous pulse oximeter monitoring is preferable; observe for central cyanosis; if possible perform blood gas analysis before and during transfer.

### Communication

Inform about baby's condition and vitals during transport so that adequate manpower and resources are kept ready at the referral unit.

## KEY COMPONENTS OF A TRANSPORT SYSTEM

In India, neonatal health-care delivery and transport systems are unregulated, patchy and not standardized. There is a need for development of Neonatal Transport Systems across the country with at least minimum standards. The key components of a transport system are discussed below:

### Human Resource

An organised neonatal transport service should consist of a *transport team*. A physician with specialty training in neonatology or equivalent expertise should be the *leader* of such a team. Most transport teams in western countries have a neonatal-trained nurse. Other programs use anesthetists, respiratory therapists, paramedics or a combination of these three disciplines. Trained nurses or paramedics for transport services are not available in India. Most units involved in organized neonatal transport utilize the services of residents and fellows working in neonatology for this purpose.

### Vehicle and Equipment

An ideal design of the vehicle and equipment for transport should have consideration of weight, fixation, power and gas requirements.

#### Transport Vehicle

The ambulance used for neonatal transport should, at a minimum, meet the requirements for a basic life support ambulance and must provide:

- Secure fixation of the transport incubator to the cot rails and fastening of other equipment (e.g., oxygen and air tanks, monitoring equipment).
- Independent power source to supplement equipment batteries to guarantee uninterrupted operation of the incubator and other monitoring and supportive equipment.
- Necessary adapters to access the ambulance power source should be readily available.
- Suction apparatus.
- Minimum two seats for transport staff.

#### Incubator Position

Offside mounting of incubator as compared to transverse mounting is quick and easy to load and enables more staff to be seated by the side with clear vision of the baby. Offside mounting is better fixed to the ambulance and provides more straightforward access for re-intubation if needed.

#### Fixation of Equipment

All equipment such as transport incubator, monitors, cylinders, infusion pumps etc. should be secured well enough to withstand sufficient force (10G force in five directions forward, rearward, left, right and vertical) in the event of sudden acceleration or deceleration.

### Speed of Vehicle

Our national guidelines state that speed of the ambulance should not be more than 15–20 km/hour over the posted speed limit.

### Equipment

The transportation of neonates requires several equipment (**Box 2**). These includes power back up, additional air and oxygen cylinders, neonatal ventilators. Some of the commercially available transport systems have ventilators that are integral to the incubator system (examples-Air-Shields Globetrotter TI500, Draeger Medical) or standalone systems (Pneupac® babyPAC™, Smiths Medical). These systems are now capable of functioning well at the full range of rates and inspiratory times required for neonatal practice.

- *Transport incubators* Some of the available transport incubator systems which provide adequate temperature control even in extreme conditions are (Airborne 750i, GE Health-care; Air Shields Globetrotter TI 500, Draeger Medical). A new solution to assist warming during transport is the use of phase-change gel mattresses which very effectively warm infants through release of latent heat of crystallization. It is important to secure the neonate inside the incubator. Neonatal harnesses are now commercially available (Neo-restraint, Paraid Medical) which consists of a series of foam wedges and straps, than can be adjusted to the position and size of the infant within the transport incubator.
- *Syringe infusion pumps* For neonatal transport, syringe infusion pumps are probably the best suited to deliver both maintenance fluids and drug infusions. Most pumps work on 240V power source and many work with an internal rechargeable battery that last for 4 hours.
- *Monitors* A multiparameter monitor is preferable. However, a lightweight portable pulse-oximeter is a good alternative. Pulse oximeters and monitors which use massimo technology would minimize or eliminate motion artefacts.

### Communication and Family Support

The family must be communicated in detail about the following aspects:

- Nature and severity of illness and the need for transport.
- Facilities available at referral hospital including infrastructure, details of key personnel.
- Type and mode of transport and time needed to reach the referral hospital.
- Names and contact numbers of key personnel at referral hospital.
- Possible need for emergency procedures during transport.
- The availability of bed should be asked before starting transport and referred hospital should be informed in advance.

The referring institute/physician has the responsibility to document and communicate to the transport team and the receiving institute (**Fig. 1**).

- Patient demographic details (name, age, sex, gestational age and weight, place and name of referring hospital)
- Reason for transfer
- Detail perinatal history, labor and delivery, neonatal resuscitation
- Current patient status, therapy and laboratory data (e.g., CBC, blood sugar)
- Potential for deterioration and need for advance therapy like mechanical ventilation and exchange transfusion or diagnostic evaluation
- Referral note with provisional diagnosis and treatment given so far
- Consent form from parents.

**BOX 2 Equipment required for neonatal transport***Thermal support equipment and supplies:*

- Transport incubator
- Thermometer and/or temperature monitor and probes
- Plastic wrap, insulating blankets, heat shield

*Respiratory support equipment:*

- Oxygen and air cylinders with appropriate indicators of in-line pressure and gas content
- Flow meters, oxygen tubing and adapters
- Oxygen hood, neonatal size masks and cannula
- Oxygen analyzer, pulse oximeter
- Neonatal positive pressure bags
- Continuous positive airway apparatus: nasal prongs, endotracheal tube
- Mechanical ventilator with back up circuit
- Endotracheal tubes: 2.5, 3.0, 3.5, 4.0 mm
- Laryngoscope with size 00, 0 and 1 blades
- Laryngoscope batteries and extralamps
- Endotracheal tube holders and tape to secure ET tube

*Suction equipment*

- Mucus suction trap, suction catheters (5, 6, 8, 10, 12 F)
- Regulated suction with gauge limiting < 100 mm Hg
- Feeding tube (8 Fr) and 20 mL syringe for orogastric decompression
- Sterile gloves, sterile water for irrigation

*Monitoring equipment*

- Stethoscope, cardiac monitor, pulse oximeter
- Glucometer for blood sugar evaluation

*Infusion equipment*

- Intravenous catheters (24, 26 gauge)
- Syringes (2, 5, 10, 20, 50 mL)
- Splint, transparent dressings or micropore
- Three way stopcocks, IV chamber sets/microdrip sets
- Intravenous administration tubing compatible with infusion pump

*Medications*

- Calcium gluconate 10%
- Epinephrine (1:10000) prefilled syringes, sodium bicarbonate
- Dopamine, dobutamine, morphine, midazolam
- Normal saline, phenobarbitone, surfactant.

The transport team should communicate to the receiving institute the condition of the baby and the probable time at which they are likely to arrive so that they can be received preferably in the emergency area and shifted to NICU. Once the baby is received and stabilized in the receiving unit the transport team should communicate with the referring unit about the condition of the baby.

**SPECIAL CONSIDERATION****Respiratory Distress Syndrome**

Oxygenation, perfusion should be maintained throughout the transport. Depending on degree of respiratory distress, appropriate ventilator support may be provided with oxygen, continuous positive airway pressure (CPAP) or mechanical ventilation. Babies requiring mild to moderate respiratory distress may be transported on nasopharyngeal CPAP as binasal prongs are likely to get dislodged during transport. The endotracheal tube should be firmly secured and position ensured clinically before embarking on transporting a baby with severe respiratory distress on mechanical ventilator. Infants who need high frequency ventilation in transit currently present a problem, as there is no oscillatory ventilation option on commonly available transport ventilators. Clinical teams will usually have to convert oscillation to standard ventilation for transfer, and there is anecdotal experience of using inhaled nitric oxide (iNO) to support this conversion and make transfer possible in very unstable infants.

Date _____	Time _____
Address _____	
Name _____	Mother's Name _____ Father's Name _____
DOB _____	TOB _____ Sex _____
Duration of Pregnancy _____	LMP _____ EDD _____
Antenatal Risk Factor- _____	
Antenatal Steroids (in case of prematurity)- Yes/No _____	
<b>Birth Details</b>	
Mode of Delivery _____	Place of Delivery _____
Apgar 1 min _____	5 min _____ 10 min _____
<b>Resuscitation details</b>	
<b>Short Clinical Course</b>	
<b>Reason for transfer:</b>	
<b>Examination Findings</b>	
Should include following details: <i>Present weight, gestation, Vitals: HR, Respiratory rate, CRT, BP, Temp, SpO<sub>2</sub>, Blood sugar, Ventilatory settings, Ionotropes requirements, ET details, Central line if any and any specific findings</i>	
<b>Medications and IV Fluids</b>	
<b>Investigations with date</b>	
Place to which being referred _____	
Mode of transport _____	Accompanying person _____
Name and Phone number of person at Referral Hospital _____	
Signatures, Name, Date and Time _____	

**Figure 1** Sample referral note and documentation sheet

**Air Leak Syndromes**

Even mild pneumothoraces may worsen during transport. Hence, it is advisable to drain the pneumothorax adequately and preferably keep a chest tube in place before departure.

**Esophageal Atresia**

A continuous suction with the help of two catheters (one attached to suction and the other left open to air—*repolage tube*) should be done during transport in babies with esophageal atresia to prevent pulmonary aspiration.

**Meningomyelocele**

The exposed swelling on the back should be covered with gauze piece soaked in normal saline and baby should lie on the side or prone but not back during transport.

**Abdominal Wall Defects**

Due to increased exposed surface area and the fluid exudation causing evaporation, maintenance of fluid electrolyte balance is very important. The bowel/membranes should be wrapped with a clean plastic film without compressing, twisting and kinking the bowel. Gastric decompression is essential with a size 6 or 8 Fr tube should be done.

**Consideration During Air Transport****High Altitude**

The barometric pressure in a standard airline carrier is 565 mm Hg as compared to 760 mm Hg at sea level resulting in reduction of partial pressure of oxygen. Every effort therefore must be made to maximize oxygen delivery in hypoxic infants. As air expands at high altitude and even benign air leaks at sea level

are likely to become significant, they should be drained before embarking on air transport. Need for supplemental oxygen may increase by 20–30% during air transport.

### Take-off and Landing

Rapid acceleration during take-off and rapid deceleration on landing may cause a sudden change in cerebral perfusion. There is provisional evidence that premature infants undergoing transfer may have a higher incidence of intraventricular bleeding.

### Temperature

There is a temperature drop of 2°C for every 300 m of altitude, and in unheated military helicopters this may put high demands on the transport incubator system. A reliable method of measuring infant temperature during transport must be used. The incubator used for air transport must always have fully charged batteries at the beginning of a transfer. DC power cables suitable for both the aircraft and the ambulance should be taken.

### Noise and Vibration

Vibration is not usually detrimental to the infant, but can dislodge lines and tubes and adversely effect monitoring equipment. Consideration should be given to equipment specifically designed to minimize the effect of movement artefact such as pulse oximetry using Masimo or Oxismart technology. During transport all lines should be secure and visible, particularly arterial lines, to allow observation without the need to open the incubator. Visual rather than audio alarms should be used where possible. The long-term effects of exposure of the newborn infant to excessive sound remain unclear.

## COMPLICATIONS OF TRANSPORT

- Hyperventilation during manual ventilation may cause respiratory alkalosis, cardiac dysrhythmias and hypotension.
- Loss of positive end-expiratory pressure (PEEP)/CPAP may result in hypoxemia.
- Position changes may result in hypotension, hypercarbia and hypoxemia which may increase the chances of intraventricular hemorrhage.
- Equipment failure.
- Inadvertent disconnection of intravenous drugs.
- Movements may cause disconnection from ventilatory support and respiratory compromise.
- Movements may result in accidental extubation.
- Movements may result in accidental removal of vascular access and bleeding.
- Loss of oxygen supply may lead to hypoxemia.

## MEDICOLEGAL ISSUES

Most medicolegal problems are a result of poor communication and provision of inadequate information. The condition of baby, risks involved during transport and financial implications of transport and treatment at the referral center should be discussed with family and documented in the case record. If baby dies during transport:

- The ambulance should be stopped and cardiopulmonary resuscitation should be performed as per neonatal resuscitation program guidelines.
- If baby dies on the way, he/she should be first taken to the higher health facility.
- Casualty admission should be done. Parents should be explained and death certificate made by the medical personnel of higher health-care facility.

- It is the responsibility of transporting team to make death certificate of baby.

## QUALITY MANAGEMENT PROGRAM

Quality assurance is now an integral part of patient care in medicine. In addition to patient care issues, a quality management program should assess all aspects of transport program. This includes management of vehicles, operational and safety issues, training of manpower, maintenance of licensure and establishment of patient care guidelines. The institution providing transport services should have predefined and prospective quality indicators and should follow standards of operation and regional standards of care. Thresholds of compliance for acceptable outcome should be decided and an annual review should be made of the quality assurance process to improve transport services and overall neonatal outcome.

### IN A NUTSHELL

1. Neonatal transport programs require appropriate referral systems, management structures and trained transport personnel. They need to utilize transport equipment, address transport logistics and have a quality improvement program.
2. Infants requiring advance medical and/or nursing care exceeding what is available in their current settings will need transfer to a higher health facility.
3. Prior stabilization and adequate care during transport results in decreased risk of hypoglycemia, acidosis and mortality.
4. The key components of neonatal transport are human resources, vehicles and equipment, communication, family support and documentation.
5. In India, neonatal health-care delivery and transport systems are unregulated, patchy and not standardized. There is a need for development of Neonatal Transport Systems across the country with at least minimum standards.

### MORE ON THIS TOPIC

- Agostino R, Fenton AC, Kollée LAA. Organization of neonatal transport in Europe. *Prenat Neonatal Med.* 1999;4:20-34.
- Bang AT, Bang RA, Baitule SB, et al. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. *Lancet.* 1999;354(9194):1955-61.
- Britto J, Nadel S, Maconochie I, Levin M. Morbidity and severity of illness during inter hospital transfer: impact of a specialized pediatric retrieval team. *BMJ.* 1995;311:836-9.
- Dalal E, Vishal G, Solanki D. Study on neonatal transport at tertiary care centre. *Int J Sci Res.* 2013;2(12).
- Kempley ST, Sinha AK. Thames Regional Perinatal Group. Census of neonatal transfers in London and the South East of England. *Arch Dis Child Fetal Neonatal Ed.* 2004;89(6):F521-6.
- Kumar PP, Kumar CD, Shaik F, et al. Transported neonates by a specialist team - how STABLE are they. *Indian J Pediatr.* 2011;78:860-2.
- Kumar PP, Kumar CD, Venkatlakshmi A. Long distance neonatal transport—the need of the hour. *Indian Pediatr.* 2008;45(11):920.
- Leslie AJ, Stephenson TJ. Audit of neonatal intensive care transport: closing the loop. *Acta Paediatr.* 1997;86:1253-6.
- Mathur NB. Comprehensive neonatal care in India: Experiences in planning and implementation. *J Neonatol.* 2006;20:204-5.
- Mathur NB, Arora D. Role of TOPS (a simplified assessment of neonatal acute physiology) in predicting mortality in transported neonates. *Acta Paediatrica.* 2007;96:172-5.
- Singh H, Singh D, Jain BK. Transport of referred sick neonates: how far from ideal? *Indian Pediatr.* 1996;33:851-3.
- Transporting newborns the SAFER way. National Neonatology Forum of India, PENN India Health Group, University of Pennsylvania, WHO Perinatal Collaborating Center, Illinois, 1999.

## Chapter 14.14

# Follow-Up of the High-Risk Neonate

Shuchita Gupta

The low- and middle-income countries (LMICs) have huge burden of perinatal illnesses like prematurity, intrauterine growth retardation, neonatal encephalopathy, sepsis/meningitis, jaundice and congenital defects. These insults not only result in a high neonatal mortality, but also carry a higher risk of postdischarge mortality and morbidities, including long-term sequelae like poor neurodevelopment and adverse health outcomes like hypertension and cardiovascular disease.

The decline in global neonatal mortality rate by 28% (from 33.2 deaths to 23.9 deaths per 1,000 live births) between 1990 and 2009, suggests that increasing number of infants with perinatal risk factors are now beginning to survive. This is likely to result in increased postdischarge mortality, morbidities requiring hospitalization, and long-term illnesses and disability requiring frequent health-care services. This will not only affect the quality of life of the surviving infants, but also add significantly to the family's socioeconomic burden.

To ensure continuum of care and prevent postneonatal mortality and morbidity, it is mandatory to have a dedicated follow-up program linked to the neonatal units. Monitoring postdischarge outcomes would not only help in early identification and management of problems while still amenable to prevention and/or treatment, but also to counsel and prognosticate parents with respect to specific conditions. Standardized documentation of follow-up data would also allow ascertainment of association between various perinatal risk factors and outcomes and identify previously unidentified problems.

## ESTABLISHING FOLLOW-UP PROGRAM

### Setting

It is imperative that a follow-up program for the high-risk infants be an integral part of the neonatal services. There should be a dedicated clinic along with a multidisciplinary team of trained, skilled and experienced personnel. In small hospitals, if a multidisciplinary team is not available, appropriate referral services should be identified in the region where such infants may be referred for formal evaluation and management.

### Personnel and their Roles

The follow-up team should include a pediatrician/neonatologist, who has the overall responsibility of the follow-up program and he should have adequate knowledge and training in follow-up of high-risk infants. It is his duty to assess the child with regard to growth and nutrition, provide medical management for any continuing or intermittent morbidities, ensure timely immunization, screen for development and neurological intactness and refer for appropriate services as appropriate/as required. It is also his duty to coordinate care, regularly assess child's progress and counsel the family. Other important members include:

- *Clinical psychologist* trained in doing pediatric assessments to perform formal developmental evaluation.
- *Physiotherapist* to provide training exercises to infants with tone abnormalities.
- *Occupational therapist* to work at improving neuromotor coordination and perceptual skills in the infants and train

them in activities of daily living, like feeding, bathing and dressing, which require fine motor function and oro-motor coordination.

- *Special educator* is required to promote developmental potential through an understanding of the special needs of differently-abled children. He/she focuses on behavior, cognitive, social, language, emotional and self-care skills and academic development to promote holistic learning in such children. In resource restricted settings, a person trained in transdisciplinary work may also be considered to provide services expected of the therapists and the special educator combined.
- *Medical social worker* is a desirable member of the follow-up team. This person would assess the family conditions, home environment and parental perspectives, priorities and expectations, which are important to know in order to provide appropriate, individualized care to any infant. A medical social worker may also help families with regard to social and socioeconomic issues and help in rehabilitation of the differently-abled children.
- *Other specialists* like ophthalmologist, audiologist and speech therapist, nutritionist, and pediatric neurologist and geneticists are consulted as per the needs of an individual child.

It might not be possible in all health-care facilities to have a complete team of specialists as outlined above. It is therefore important to have a linkup with specialized services where appropriate referrals may be sought when required.

#### Follow-up Team

Essential members of follow-up team:

- Pediatrician/neonatologist, trained in follow-up of high-risk infants
- Clinical psychologist (trained and experienced in pediatrics)
- Physiotherapist, occupational therapist and special educator (trained and experienced in pediatrics); or a person trained in transdisciplinary work
- Medical social worker.

For specialized referrals in selected cases:

- Ophthalmologist, audiologist and speech therapist, nutritionist, pediatric neurologist and geneticist.

## DISCHARGE PLANNING

Discharge planning should begin early during the infant's hospitalization to ensure successful transition to home care. The following criteria should be fulfilled before discharging any high-risk infant from the hospital:

- Free of any significant medical/surgical illness
- Should not be on injectable drugs (antibiotics/other)
- Should be on full enteral feeds (either direct breastfeeding or by spoon/cup)
- Appropriate micronutrient/multivitamin supplementation has been started, vaccination has been initiated based on postnatal age and parents are confident to take care of the infant at home
- For very low birth weight (VLBW) infants, in addition to above, the following are essential:
  - Should ideally be off caffeine/theophylline and apnea free for at least 5 days prior to discharge
  - Be able to maintain body temperature in an open crib
  - Have had stable weight gain for three consecutive days
  - The discharge weight should be around 1,400 g.

It might be necessary in some resource limited settings to individualize some of the above criteria. In such cases, it would be important to call such infants 3–7 days postdischarge to ensure successful transition of the infant to home care.



*Discharge Summary*

It is very important to provide a detailed discharge summary to all high-risk neonates at discharge which should include details of the perinatal course, investigations, important advice including oral medications, danger signs and follow-up schedule with venue, dates and timing (including dates/time/venue for special visits like neuroimaging, ROP screening, ABR, etc.).

**INITIATING FOLLOW-UP**

A few components of care that have important implications for follow-up, but need to be initiated within the neonatal intensive care unit are as follows:

**Neuroimaging**

Routine screening cranial ultrasonography (CUS) should be performed on all infants less than 30 weeks gestation once between 7 days and 14 days of age and should ideally be repeated between 36 weeks and 40 weeks' postmenstrual age (PMA). This helps to detect lesions such as intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and ventriculomegaly, which are all associated with adverse neurodevelopmental outcome. A routine MRI of all VLBW preterm infants is not presently recommended, even if they have abnormal findings on CUS.

*Abnormalities on Cranial Sonogram*

- Twelve to fifty-one percent of infants with birth weight less than 1,500 g and/or gestation less than 33 weeks have CUS abnormalities. However, major abnormalities such as grades 3 and 4 IVH, cystic PVL and ventriculomegaly, which might alter treatment or provide prognostic information, are more common (20–25%) in infants with gestational age less than 30 weeks.
- Grades 3 and 4 IVH, cystic PVL, and moderate to severe ventriculomegaly on CUS have all been shown to be significantly associated with cerebral palsy at 2–9 years of age in VLBW preterm infants, with almost a tenfold elevation in the risk of adverse outcome.

For term infants, neuroimaging is indicated only if the infant has encephalopathy with a history of birth trauma, low hematocrit, or coagulopathy. In such case, a noncontrast CT should be done first to detect any hemorrhagic lesions. If CT findings are inconclusive, MRI should be performed between 2 days and 8 days to assess the location and extent of injury, wherein the pattern of injury may provide diagnostic and prognostic information.

**Retinopathy of Prematurity Screening**

The first retinopathy of prematurity (ROP) screening for infants less than 32 weeks or 1,500 g and other preterm neonates more than and equal to 32 weeks or birth weight more than and equal to 1,500 g but with risk factors like need of cardiorespiratory support, prolonged oxygen therapy/ventilation, anemia requiring blood transfusion, sepsis and apnea, etc. should be done at 32 weeks postmenstrual age or 1 month of postnatal age, whichever is earlier. If screening detects ROP not requiring treatment, follow-up should be planned according to the location and stage of ROP, and should continue till 40–44 weeks PMA, or till the retinal vessels have matured.

**Metabolic Screening**

Neonatal screening for congenital hypothyroidism, congenital adrenal hyperplasia and glucose-6-phosphate dehydrogenase deficiency is presently being recommended in India, as the screening and treatment is likely to be cost-efficient when compared to the cost of the permanent mental subnormality that would occur in these children if diagnosed late. In view of the

limited facilities available at most centers for routine metabolic screening, a universal screening might not be feasible at present.

**Hearing Screening**

Hearing screening should be performed for all high-risk infants prior to discharge, taking care to do the first screen for premature infants not before 34 weeks PMA, as this might increase the false-positive rates. Either otoacoustic emissions (OAEs) or automated auditory brainstem response (AABR) may be used, but it is important to carry out a two-step screening (two-step AABR or OAE followed by AABR) as this has shown to decrease false-positive results. An AABR should ideally be incorporated for screening of high-risk infants as the risk of auditory neuropathy is high.

**Follow-up Plan for Unresolved Problems**

Management plan for unresolved medical/surgical problems should be formulated prior to discharge in collaboration with the supporting units (e.g., pediatric surgery team for gastrostomy/inguinal hernia, ear, nose and throat team for tracheostomy, cardiology team for congenital heart disease, genetics team for genetic/chromosomal abnormality, etc.).

**Neurological Assessment**

A baseline neurological examination should be done in all high-risk infants prior to discharge, as it has now been shown to be an important predictor for later neurodevelopment.

In general, the predictive ability of isolated neurological signs in the neonatal period is not considered to be very good. However, on comparing a large population of predominantly term infants who later developed cerebral palsy to those who did not, certain neurological abnormalities were found to be particularly valuable predictors for later neurodevelopment (**Table 1**). A combination of neurological abnormalities increases the predictive ability, and clear relationship has been demonstrated between the severity of abnormality on neurological examination at discharge and motor abnormalities at 1–5 years of age (**Table 2**).

**Table 1** Neurological abnormalities: Predictors of later cerebral palsy

Neurological abnormality	Risk of cerebral palsy
Tone abnormality of limb, neck, trunk	12–15 times higher
Diminished activity or cry for more than the first day of life	19–21 times higher
Weak or absent sucking during exam (~48 hours of life)	14 times higher
Need for gavage/tube feeds	16–22 times higher

**Table 2** Abnormal neonatal neurodevelopmental examination and later neuromotor outcome

Grading of abnormality on neurological examination at discharge	Outcome at 1–5 years of age		
	Cerebral palsy	Minor neuromotor dysfunction	Normal motor outcome
None (n = 30)	3%	3%	94%
Subtle (n = 45)	7%	13%	80%
Mild (n = 50)	7%	18%	74%
Definite (n = 57)	33%	26%	42%
Marked (n = 28)	50%	29%	21%

Source: Allen MC, Capute AJ. Neonatal neurodevelopmental examination as a predictor of neuromotor outcome in premature infants. *Pediatrics*. 1989;83:498–506.

There are a variety of neonatal neurological examination tools that have been used across the world with variable predictive abilities for later adverse neurodevelopmental outcomes. The most commonly used tools that have been widely used and validated include the Amiel-Tison neurological examination at term (focuses primarily on neuromotor component including tone and primitive reflexes), Brazelton neurobehavioral examination (focuses on behavior), the Prechtl's assessment (focuses on the observation of general movements), and the Dubowitz examination (encompasses various aspects of neurological function such as behavioral states, tone, primitive reflexes, motility and some aspects of behavior). There is no consensus on which of these tools to be used. A simplified proforma for routine clinical use is depicted at **Figure 1**.

## FOLLOW-UP SCHEDULE

### Frequency of Follow-up

The periodicity and schedule of follow-up of high-risk infants is guided by several factors. These include developmental attainments at a given age, availability and applicability of suitable test instruments at specific ages, need for additional services like immunization, complementary feeding advice, other special services, etc. **Box 1** outlines a follow-up schedule that can be used by most facilities and also adapted and modified to the needs of each setting. But, some of the periods of assessment are critical and are summarized below:

#### 9–12 Months of Age

Most medical issues have been taken care of by 9–12 months of corrected age (CA), and environmental factors are also less influential on performance. At this age, many issues involving motor skills development can be reliably identified. Some neurologic abnormalities that are identified in the first year of life are transient and improve, whereas other may worsen over time. The child's visual and hearing abilities, and emerging early communication skills, like social and nonverbal communication (including vocalizations and gestures), may also be assessed at this age. These may provide clues to early diagnosis of autism (lack of eye contact, orienting to name being called, or pointing).

#### 15–18 Months

Mild motor delays (that remained undetected at 9 month) and delays in communication and language development are often evident by 18 months of age. General formal development assessment in all domains (including gross and fine motor, cognition, receptive and expressive language), social-adaptive assessment as well as behavior and autism screening tools may be

administered at this age. Effective early intervention therapies for motor disorders, delayed language development and autism are also available at this stage.

#### 24–30 Months

By 2–2½ years of age, most motor, language, and cognitive delays may be identified with screening instruments, leading to evaluation of and intervention for those children with delayed development.

#### 5–6 Years

By this age, the preschool skills and school readiness may be assessed. By 6 years of age school achievement and intelligent quotient (IQ) can be assessed; and by 8 years, school performance may be assessed.

#### Calculating Corrected Age

- For any preterm infant less than 37 weeks of gestation, growth and development is assessed as per the CA at least till 2 years of CA.
- Calculate as follows:
  - *Postnatal age*: Age as calculated from the date of birth
  - *Corrected age (CA)*: Age as calculated from expected date of delivery (EDD)

Formula CA (in weeks) = (Postnatal or chronological age in weeks) – (40 – gestational age in weeks).

*Example*: B/o XYZ is born on 27th March, 2014 at gestation of 32 weeks (EDD: 22nd May, 2014), is brought for follow-up visit on 3rd July 2014. Then, the postnatal age of the child as on 3rd July, 2014 would be 14 weeks and CA would be 6 weeks.

*\*The terms postmenstrual or postconceptual age (though the two are slightly different) are frequently used to describe the age of a premature baby till term equivalent age/EDD, beyond which the term CA is used.*

## WHAT SHOULD BE DONE?

This section outlines the assessment that should be carried out during the follow-up visits. **Table 3** provides a checklist for the assessment during various follow-up visits.

### Assessment of Feeding

During each follow-up visit, it is important that feeding is assessed. Feeding should be assessed as per standard guidelines for age (i.e., exclusive breastfeeding for 6 months followed by complementary feeding). During each visit the health-care provider should also ensure compliance with micronutrient/vitamin supplements.

There are no standard guidelines on time of initiation of complementary food for preterm infants, and practices vary among experts. The decision should be guided by the developmental appropriateness of any individual infant, type of feeding being given and the growth trajectory of the infant.

### Growth Monitoring

For term normal birth weight infants, the postnatal growth may be monitored using World Health Organization-Multicenter Growth Reference Study (WHO-MGRS) growth curves, freely available and downloadable from the WHO website (<http://www.who.int/childgrowth/en/>). Monitoring postnatal growth among premature and/or low birth weight (LBW) infants remains a controversial issue with different postnatal charts being available, with their relative merits and demerits.

For term LBW infants, the WHO-MGRS charts may be used. However, it is important to consider here that the WHO-MGRS charts are primarily based on a sample of term, healthy breastfed



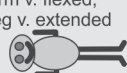
















#### BOX 1 Follow-up schedule for various categories of high-risk infants

##### Very preterm infants (< 32 weeks or < 1,500 g)

- After 3–7 days of discharge to check if the baby has adjusted well in the home environment
- Every 2 weeks until a body weight of 3 kg (6, 10 and 14 weeks—immunization visits to be covered during these visits)
- At 3, 6, 9, 12, 15 and 18 months of corrected age and then every 6 months
- More visits if required

##### Infants with other conditions

- 2 weeks after discharge
- At 6, 10, 14 weeks of age
- At 6, 9, 12, 15 and 18 months of corrected/postnatal age, as applicable; and then every 6 months
- More visits if required.

	Abnormal	Optimal	Abnormal/deviant	Comments
<b>Posture</b> Baby lying supine, look at position of legs mainly but also note arms. May change drawing	Arms and legs extended 	Leg well-flexed but not adducted 	Opisthotonos or arm v. flexed, leg v. extended 	
<b>Arm traction</b> Hold wrist and pull upwards, note flexion at arm and resistance while shoulder lifts off table	Arms remain straight—no resistance 	Arms flex and remain flexed as 	Arms remain flexed when body lifts up 	
<b>Leg traction</b> Hold ankle, pull leg upwards. Look at flexion and resistance as bottom pulled up	Legs straight—no resistance 	Knee flexes—remains flexed when bottom lifts up 	Flexion stays when back+bottom lifts up 	
<b>Head control (1) (extensor tone)</b> Infant sitting upright, encircle chest with both hands holding shoulders. Let head drop forward	No attempt to raise head 	Raises head: remains vertical, wobbles 		
<b>Head control (2) (flexor tone)</b> Infant sitting upright, encircle chest with both hands holding shoulders. Let head drop forward	No attempt or raise head 	Raises head: remains vertical, wobbles 		
<b>Head lag</b> Pull infant to sit by both wrists and support head slightly	Head drops back	Lifts head in line with body 		
<b>Ventral suspension</b> Hold infant horizontally under the abdomen. Look at back, arm and limb position. It looks different—DRAW	Back curved, head and limbshang straight 	Back straight, head in line or above body 		
<b>Body movements</b> Observe during the examination when the infant is awake and quiet	Absent infrequent	Mainly smooth alternating	Cramped, athetoid, jerky, or other abnormal movements, describe	
<b>Tremors and startles</b>		Only occasional	Tremolous always many startles	
<b>MORO</b> Put infant in position shown in diagram. Bring head forward and suddenly let it go back slightly 	No response; full abduction or the arm, extension at the elbow; no adduction 	Full abduction, followed by adduction 	• Minimal adduction or abduction • Difficult to elicit	
<b>Auditory orientation</b> Ability to respond to rattle. Rattle 5 inch/from ear	No response	Brightens, turns to stimuli either side		
<b>Visual orientation</b> Able to track red ball or target	No focusing: tracking $\leq 60$	Good horizontal and vertical tracking		
<b>Alertness</b> Response to visual stimulation	When awake variable response to orientation	Alertness sustained, may use stimulus to come to alert state		
<b>Abnormal signs</b>	<b>Facial palsy</b> Y N	<b>Abnormal eye movements</b> Y N	<b>Sunset sign</b> Y N	<b>Fisted hand</b> Y N
				<b>Clonus</b> Y N

NB: Infants with 2 or items in shaded areas need to be reassessed.

**Figure 1** Simplified proforma for neurological examination of the newborn infant at discharge  
Source: Reproduced with permission. From: Mercuri E, et al. The neurological examination of the newborn baby. Early Human Dev 2005;81:947-56. ©Elsevier.

**How to use:** The items in the first column are always abnormal in a full-term infant. Infants with more than and equal to two items in the first column or showing more than and equal to one of the abnormal signs listed at the end of the proforma should be reassessed. If the abnormal signs persist, a more detailed assessment is required.

**Table 3** Checklist of assessments to be done at various follow-up visits

Assessment	Corrected or postnatal age, as applicable								
	3 months	6 months	9 months	12 months	18 months	24 months	3 years	6 years	8 years
Nutrition and growth	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medical examination and management as required	✓	✓	✓	✓	✓	✓	✓	✓	✓
Immunization	As per postnatal age; decide schedule based on vaccines being given								
Hearing (ABR)	✓	α	Clinical screening at each visit						
Language			✓		✓	α			
Vision			✓	α	α				
Developmental screening	✓	✓	✓	✓	✓	✓	✓	✓	✓
Formal developmental assessment	✓				✓		✓		
Autism and behavior screening					✓	α	α	✓	
Intelligence (IQ)								✓	✓
ADHD/learning disability/others								✓	✓

α If previous test abnormal

Abbreviations: ABR, auditory brainstem response; ADHD, attention deficit hyperactivity disorder.

infants, with only a small proportion of term LBW infants. Therefore, the growth of LBW infants as plotted on the WHO-MGRS charts may not accurately reflect their optimal growth trajectory. It would also be difficult to comment upon the catch up growth, if any, among these infants.

For premature infants, especially those less than 1,500 g at birth, there are various charts available for monitoring postnatal growth—Ehrenkranz's charts, Niklasson's charts and Fenton's charts. It may at present be best to use the latest Fenton charts till preterm infants attain 40 weeks postconceptional age and the WHO-MGRS chart thereafter.

#### Use of Growth Charts in LBW Babies

- Use WHO-MGRS growth charts for term infants and Fenton's growth charts for preterm infants (these merge with WHO-MGRS curves at 50 weeks PMA).
- Alternately, but less preferable, is to be guided by the absolute weight gain till term age and then used WHO-MGRS growth curves.

Remember that the growth of LBW (premature/intrauterine growth restriction) might continue to remain at less than third centile on WHO-MGRS growth curves. If these infants continue to maintain their trajectory and show some catch up growth (using weight for length charts), it might be considered to be adequate.

### Medical Examination and Management of Ongoing/Intermittent Morbidities

At each follow-up visit, a detailed evaluation and management of the infant should be done in accordance with the perinatal history/insults. These may relate to prolonged jaundice due to any cause, recurrent exacerbations of respiratory insufficiency in a child with chronic lung disease, gastroesophageal reflux or other feeding difficulties or inadequate weight gain in a preterm infant, anemia in a baby with Rh immunization, cardiac failure in a baby with congenital heart disease, diagnostic evaluation and intermittent illnesses in a baby born to HIV-positive mother, etc.

### Immunization

The immunization should be done as per the chronological/postnatal age of the child. The national immunization schedule for any country should be taken as the reference for the mandatory

vaccines required to be given to any child. The advice on optional vaccines may be given depending upon the epidemiology of the disease in the particular geographical region and vaccine efficacy and safety. A detailed guideline on the same is beyond the scope of the present chapter and the reader is advised to refer to the section on immunization in this book.

### Hearing Assessment

For any infant who has failed a two-step hearing screening prior to discharge, it is important to ensure that the conventional auditory brainstem response is done by an audiologist during follow-up. Hearing aids, if required, should be fitted by 6 months of age to allow normal acquisition of language.

Infants who have passed a two-step neonatal hearing screening might still be at risk of permanent hearing loss. It is therefore important to track the infants' auditory behavior and communication milestones at each follow-up visit. If any concern arises with regard to the same, it is necessary to refer the infant to a pediatric otorhinolaryngologist for evaluation and further audiological assessment.

### Visual Assessment

Evaluation for vision should continue during all high-risk visits. All parents should be asked age appropriate questions related to visual behavior as detailed in **Table 4**. In children younger than 3 years or in any nonverbal child, vision is assessed by the child's ability to fix and follow objects. A failure to fixate on an object, maintain fixation, and then follow the object in different gaze positions indicates significant visual impairment.

*If poor fix and following is noted binocularly after 3 months of age, a significant bilateral eye or brain abnormality might be present and the child should be referred to a pediatric ophthalmologist or an eye care specialist trained in evaluating and treating pediatric patients.*

In addition, an external penlight evaluation of the lids, conjunctiva, sclera, cornea and iris should be done. Ocular alignment should be seen for any strabismus, pupils should be examined and red reflex test performed. This will help detect opacities in the visual axis, such as cataract and abnormalities of the back of the eye, such



**Table 4** Age-appropriate visual history

Age	Visual behavior
1st month	<i>Does the child</i> looks at the face of the person holding them?
2–3 months	<i>Does the child:</i> Follow moving object (till or past midline)? Look from one person/object to another? Look into the eyes of the person holding them?
4 months	<i>Does the child:</i> Show visual interest to near and distant objects? Responds to full range of colors?
6 months	<i>Does the child:</i> Enjoy looking at mirror? Show sustained visual interest at near and distant objects? Demonstrates hand-eye coordination? Maintains fixation at a stationary fixation on stationary object, even if another moving object is present?
7–12 months	<i>Does the child:</i> Notice small objects such as breadcrumbs? Recognize objects that are partially hidden? Scan eyes around the room to see what is happening?
18 months	<i>Does the child:</i> Point to objects or people using words <i>look</i> or <i>see</i> ? Look for and identify pictures in books?
24–36 months	<i>Does the child:</i> See small pictures well with both eyes? Show ability to arrange similar pictures in groups?

as retinoblastoma or retinal detachment. Presence of nystagmus should also be noted. All children who are found/suspected to have an ocular abnormality should be referred to an ophthalmologist trained in pediatric assessments.

### Neurological Examination

Neurological examination at discharge has been detailed in the previous section. It is important to repeat the neurological examination on follow-up as sequential assessments are more informative than isolated examinations.

Amiel-Tison neurological examination is most useful during follow-up assessments, as it is simple and precise, is based on a fixed set of observations and maneuvers, the results are scored according to the child's age (this is important because cerebral maturation modifies the results with age), and a single tool can be used from birth till 6 years of age.

The Amiel-Tison neurological examination incorporates the following:

- **Observation and interview with parents:** Parents are asked about any episodes of seizures, quality of alertness and attention and any symptoms of hyperexcitability. Child is also observed for alertness and attention and hyperexcitability.
- **Motor development milestones in first 2 years:** The age at acquisition of various developmental milestones is assessed and a delay/absence of the age appropriate milestones is noted.
- **Head growth and craniofacial examination:** Head circumference is evaluated as per the reference growth charts and interpreted in accordance with other growth parameters like length. Head growth profile during the first 2 years of life is also taken into account. Craniofacial examination incorporates examination of anterior fontanel, cranial sutures, shape of the skull and shape of palate.

- **Neurosensory examination:** It includes assessment of hearing, vision and ocular signs like fix and track, nystagmus, eye movements, and presence of strabismus and sunset sign.
- **Passive muscle tone:** The muscle tone at rest is evaluated through resistance to slow stretching/slow passive movements. The angles to be measured are detailed in **Table 5** and the techniques depicted in **Figures 2 to 5**. It is desirable to use a goniometer to measure the various angles as it gives a more reliable estimate. It is however important to note that the resistance to movement as felt by the examiner is equally important though it needs some experience before one may comment on normal/abnormal tone. Hypertonia and hypotonia imply that the range of passive movement is either too limited or too wide for age standards.

**Figure 2** Measuring the adductor angle using goniometer**Figure 3** Measuring popliteal angle

It is important to remember the following points while evaluating passive tone of a child:

- The reference values get modified at three monthly intervals over first 9 months and at less frequent intervals thereafter.
- There is a wide range of normalcy in relation to individual, familial and ethnic variations.
- A complete lack of resistance to stretching might be normal between 9 months and 18 months.
- One should distinguish *physiological hypotonia* from other conditions of congenital hypotonia where resistance to stretching will be very weak from the first few months of life.



**Figure 4** Measuring dorsiflexion angle



**Figure 5** Eliciting the scarf sign

**Table 5** Muscle tone norms (Amiel-Tison)

Age (months)	Adductor angle (Fig. 2)	Popliteal angle (Fig. 3)	Dorsiflexion angle (Fig. 4)	Scarf sign (Fig. 5)
0–3	40°–80°	80°–100°	60°–70°	Elbow does not cross midline
4–6	70°–110°	90°–120°	60°–70°	Elbow crosses midline
7–9	110°–140°	110°–160°	60°–70°	Elbow goes beyond axillary line
10–12	140°–160°	150°–170°	60°–70°	–

*At 40 weeks PMA, there is physiological hypertonia of flexor muscles in all four limbs with subsequent muscular relaxation in the cephalocaudal direction, linked to cerebral maturation. This results in a physiological hypotonia between 9 months and 18 months of age, which can vary in intensity. Later, between 2 years and 6 years of age, there is a slow and progressive increase in resistance to passive stretching, depending on extracerebral factors like muscle mass and strength of articular ligaments which are linked to the physical activity of the child.*

In addition to the above angles to evaluate the passive tone, passive extension and flexion of the body axis, hand and finger movements, and presence/absence of candle stick posture (shoulder girdle retraction due to shortening of trapezius) are also noted and right and left sides of the body are compared for asymmetry.

- **Motor activity:** This includes evaluation of facial expressions (normal, symmetric, varied), drooling, facial paralysis, fasciculations of tongue, spontaneous limb movements, any involuntary movements and dystonia.
- **Deep tendon, cutaneous and primitive reflexes:** The bicipital, patellar and plantar reflexes are assessed. The primitive reflexes, like Moro's, finger grasp, automatic walking and asymmetric tonic neck reflex (ATNR) are seen as they are indicators of subcortical cerebral function, and their persistence beyond 6 months of age is considered pathological. ATNR is particularly important reflex as it needs to be integrated before an infant may initiate midline activities and turning of body.
- **Postural reactions:** Postural reactions appear during the first year of life in response to rapid movements felt by the infant, and help in maintaining balance. Once they appear, they persist throughout life. Their absence after a particular age is considered pathological. The lateral propping reaction (extension of opposite arm when briskly pushed from the other side laterally at shoulder level); should be present by 9 months of age (*Note: this reaction is elicited only after a child*

can sit independently well). The parachute reflex (extension of both upper limbs on head being pushed forward in ventral suspension) should be present by 12 months of age.

- **Qualitative abnormalities in gross motor function and acquired deformities:** Abnormal signs like holding head behind axis, poorly maintained head control due to fatigue, failure to sit due to falling forward/backward, poorly maintained sitting position due to fatigue, excessive extension while standing and lower limb deformities like crossing of legs in extension or scissoring are noted, along with gait of the child.

## Developmental Screening and Assessment

For any infant during follow-up, developmental surveillance is required, which comprises a review of the perinatal risk factors, asking parents about any concerns with regard to development of their child, and eliciting a developmental history. For a high-risk infant, it is necessary that we go a step further and objectively screen them for age appropriate development using standardized developmental screening tests. This is important because these infants are at a higher risk of adverse neurodevelopmental outcomes, and need to be recognized early to be able to benefit through developmental interventions.

Developmental screening should be done using standardized tests at each high-risk visit as repeated and regular screening is more likely than a single screening to identify problems, especially in later developing skills such as language. Any child who fails the screening should be referred for a formal developmental assessment, along with complete medical evaluation. **Table 6** enlists the commonly available and used screening tests in India. The other screening tests available for different domains of development are Modified Checklist for Autism (M-CHAT), Vineland Social Maturity Scale and Vineland Adaptive Behavior Scales, and Child Behavioral Checklist-Language development scale (CBCL-LDS 1½).

**Table 6** Developmental screening tests commonly available in India

Test	Domains assessed	Age range	No. of items	Psychometric properties
Trivandrum development screening test (TDSC)	Gross motor, fine motor, vision/hearing, and personal/social/language	0–6 years	51	Sensitivity: 84.62% Specificity: 90.8% Validated against DDST
Denver developmental screening test-II (DDST-II) or/Denver-II	Gross motor, language, fine motor-adaptive, and personal-social. Also a behavior rating scale	0–6 years	123	Sensitivity: 83% Specificity: 43%
Baroda development screening test (BDST)	Motor and mental	0–30 months	54	Sensitivity and specificity: 65–95%
Bayley infant neurological screener (BINS)	Neurological intactness, receptive functions, expressive functions, and cognitive processes	3–24 months	72	Sensitivity: 65–75% Specificity: 60–80%

The formal developmental assessment tool presently available for use in India and considered to be the gold standard is Development Assessment Scale for Indian Infants (DASII). It is Indian adaptation of Bayley II, and has been standardized on Indian children. It assesses the motor and mental development of children between 0 months and 30 months of age. There are 67 items for assessment of motor development (includes gross and fine motor activities) and 163 items for assessment of mental development (includes cognitive, personal social and language skills). The developmental age of the index child is expressed at 3rd, 50th and 97th percentiles with reference to the study population. Developmental quotients (motor, mental and composite) are calculated using developmental and CA of the index child.

### Duration of Follow-up

Ideally, the follow-up of high-risk infants should be continued till adulthood, but in view of the feasibility in the clinical context, the same should continue at least till 8 years of age. Advice with regard to any increased risk for chronic diseases and maintaining healthy lifestyle with periodic screening should be provided prior to discharge from the high-risk follow-up.

### MORE ON THIS TOPIC

Amiel-Tison C. Update of the Amiel-Tison neurologic assessment for the term neonate or at 40 weeks corrected age. *Pediatr Neurol.* 2002;27:196-212.  
Brazelton TB, Nugent JK. The Neonatal Behavioral Assessment Scale. Cambridge: MacKeith Press; 2011.  
Dubowitz L, Mercuri E, Dubowitz V. An optimality score for the neurologic examination of the term newborn. *J Pediatr.* 1998;133:406-16.  
Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr.* 2013;13:59.

Ment LR, Bada HS, Barnes P, et al. Practice parameter: neuroimaging of the neonate: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2002;58:1726-38.

Mercuri E, Ricci D, Pane M, Baranello G. The neurological examination of the newborn baby. *Early Human Dev.* 2005;81:947-56.

Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. *Lancet.* 2012;379:445-52.

### IN A NUTSHELL

1. It is imperative that a follow-up program for the high-risk infants be an integral part of the neonatal services.
2. The follow-up team is multidisciplinary comprising pediatrician, clinical psychologist, physiotherapist, occupational therapist, special educator, medical social workers and specialist from eye, ENT and genetics /neurology.
3. High-risk infants, especially preterms less than 32 weeks must have a screening CUS, ROP and hearing screening before discharge from the hospital.
4. Critical time periods for assessment of high-risk infants during follow-up are at ages 9–12 months, 15–18 months, 24–30 months and at 5–6 years.
5. For preterm infants, use corrected age when assessing for growth and development up to 2 years of age.
6. For assessing growth of preterm infants, use Fenton's charts till 40 weeks postconception age and the WHO-MGRS thereafter.
7. At each follow-up visit, assess for nutrition, growth, development and any medical problems.



# Section 15 NEONATAL INFECTIONS

**Section Editor** Siddarth Ramji

## Chapter 15.1

### Neonatal Sepsis

*Suman Chaurasia, Ramesh Agarwal*

Neonatal sepsis (NNS) contributes to substantial morbidity and mortality in newborn infants. Approximately, 20% of all neonates suffer from sepsis and about 1% succumb to it. Currently, sepsis accounts for nearly 28% of annual global deaths in the newborn period. Among the survivors, it is responsible for considerable neurodevelopmental sequelae, particularly in preterm infants (cerebral palsy in 10%), and is a cause of significant economic burden to the families, society and the nation at large. In resource poor settings, the costs of hospital-acquired infections divert precious resources that could be utilized for improving the access and quality of healthcare services. Additionally, after the initial admission, re-hospitalizations, long-term chronic illnesses and disabilities further inflate the expenses, often having a lifelong bearing upon the society.

#### DEFINITIONS

Neonatal sepsis refers to systemic infections affecting infants within 28 days of life and is usually of bacterial origin. It basically implies invasion of bloodstream by pathogens and may involve multiple organ systems. In common usage, the term covers bloodstream infections (BSIs) or septicemia, pneumonia, meningitis, urinary tract and bone/joint infections but does not include superficial infections.

**Neonatal sepsis (NNS) is classified in two different ways:**

*Based on culture positivity:*

1. Confirmed or culture positive sepsis—when sepsis is attributed to the pathogen isolated from clinical samples in the laboratory.
2. Clinical or culture negative sepsis—when sepsis is labeled based on clinical and/or other laboratory parameters in case the pathogen was not isolated.

*Based on age at onset:*

1. Early onset sepsis (EOS)—occurrence of sepsis before 72 hours of age.
2. Late onset sepsis (LOS)—occurrence of sepsis at or beyond 72 hours of age.

Healthcare-associated infection (HAI) is another term recently used in the context of NNS. The Centers for Disease Control (CDC) 2013 criteria defines it as any infection within health facility first suspected on or after the 3rd calendar (NOT hospital) day of admission to the facility (the day of hospital admission being calendar day 1). Note that all infections in infants resulting from passage through the birth canal during a hospital delivery are also included in the definition. HAI is further classified into device associated HAI (DA-HAI), which in neonates comprises of central

line associated BSI (CLABSI), umbilical catheter associated BSI (UCBSI), ventilator associated pneumonia (VAP) and catheter associated urinary tract infection (CAUTI).

#### EPIDEMIOLOGY

Neonatal sepsis is a major public health problem globally having high incidence and mortality in developing countries. NNS rates ranged from 6.5–38 per 1,000 live hospital-born babies in developing countries. These figures are 3–20 times higher compared to those in developed countries (1–5 per 1,000 live-births). In the community, NNS ranged from 49 per 1,000 livebirths in rural Guatemala to as high as 170 per 1,000 livebirths as in rural India. National Neonatal Perinatal Database (NNPD; 2002–2003) network in India reported HAI of 4% (67% being EOS, meningitis: 0.3–3%) in intramural and up to 40% in extramural infants.

Neonatal sepsis is commoner in infants with lower birthweight and gestational age. It is ten times commoner in those born with weight less than 1,500 g compared to infants with birthweight greater than or equal to 1,500 g. In the very low birthweight (VLBW) infants in the developing countries septicemia rates alone ranges from 20 to 41%. The data in hospital-days or device-days expressed from developing countries are rare; incidence densities of CLABSI and VAP are reported as 12.2 and 9.0 per thousand respective device days.

Infections in neonates kill nearly 11% of children around the world before their fifth birthday with around 40% (0.3 million) of them occurring in India alone. Of every three newborn casualties due to infections globally, one occurs in India; and approximately 42% of these die within the first week of life. Forty percent of septic infants have long-term sequelae, the most common being cognitive/learning difficulties or developmental delay (74%), cerebral palsy (36%), visual impairment (32%) and hearing impairment (10%). The risk increases further with lower birthweight/gestation age (nearly two-folds in culture positive VLBW infants), and depends also on causative pathogens [nearly fivefold with Gram negative sepsis in extremely low birthweight (ELBW) infants]; however it remains similar for early onset sepsis (EOS) or late onset sepsis (LOS).

#### ETIOLOGY

Major pathogens detected in HAI in developing countries are *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas* spp, *Acinetobacter* spp and *Staphylococcus aureus* (Table 1). The pathogen profile for EOS and LOS is largely identical. These patterns are in sharp contrast to the developed countries where group B streptococci (in term EOS and *E. coli* (in preterm EOS) dominate.

Many of these pathogens harbor high degree of antimicrobial resistance (AMR). Common first line antibiotics (ampicillin and gentamicin) no longer cover over 70% of hospital isolates. The AMR against third generation cephalosporins has soared from nearly 50% to around 80% over a decade in the gram-negative pathogens. Similarly, methicillin resistance, which is linked with broad range



**Table 1** Profile of pathogens of neonatal sepsis

Developing countries	Developed countries
1. <i>Klebsiella pneumoniae</i>	1. Group B streptococci <sup>a</sup>
2. <i>Acinetobacter</i> spp	2. <i>Escherichia coli</i> <sup>a</sup>
3. <i>Escherichia coli</i>	3. Coagulase negative staphylococci <sup>b</sup>
4. <i>Pseudomonas</i> spp	4. <i>Staphylococcus aureus</i>
5. <i>Staphylococcus aureus</i>	5. <i>Enterococcus</i> spp.
	6. <i>Listeria monocytogenes</i>

<sup>a</sup>more common in early onset sepsis; <sup>b</sup>more common in late onset sepsis

of antibiotics resistance in gram-positive pathogens, continues to prevail in over half of hospital isolates. Even the community strains have exhibited remarkable degree of AMR.

High antibiotic usage due to unregulated sale in health and other sectors (agriculture, animal husbandry) are the important reasons for evolution of the AMR epidemic. In fact, antibiotics—the most common drug prescribed in the neonatal intensive care unit (NICU), results in sustained high antibiotic exposure on the microbes—a stress termed as *antibiotic selection pressure*. This pressure coupled with poor hospital infection control practices favor the multidrug resistant pathogens to thrive rampantly in the Indian sub-continent. Recent evidence corroborates resistance elements like mobile genes [e.g., CTX-M15 and New Delhi Metallo-beta-lactamase-1 (NDM-1)] originating in India has high potential to transmit across species and genuses, and spread rapidly throughout the globe. Thus, AMR is fast acquiring universal dimensions requiring concerted efforts at the global level.

## RISK FACTORS

### Early Onset Sepsis

Early onset sepsis (EOS) is believed to be of maternal origin and generally indicate fetal infection (vertical transmission). Three mechanisms have been postulated—organisms are picked up during the passage through the birth canal, microbes ascending from the maternal perineum via a leak in the amniotic membrane (chorioamnionitis), or rarely, transplacental passage. Chorioamnionitis manifests clinically as intrapartum maternal fever (>38°C; essential criterion) plus any two of the following additional risk factors: maternal tachycardia (>100 bpm), fetal tachycardia (>160 bpm), uterine tenderness, and foul smelling liquor. Other important risk factors for EOS are low birthweight or preterm, and prelabor rupture of membranes more than 18–24 hours. Other risk factors reported include prolonged duration of labor (sum of 1st and 2nd stage > 24 hours), single unclean or more than three clean intrapartum vaginal examinations, asphyxia, male gender and not receiving intrapartum antibiotics. There are some 'extreme' risk factors that warrant early treatment: very prolonged rupture of membrane (≥ 72 hours), foul smelling liquor and documented ongoing maternal septicemia.

### Late Onset Sepsis

Late onset sepsis (LOS) is considered to be of environmental origin, the pathogen being acquired through care giving practices in homes and hospitals (horizontal transmission). LOS in the community results from poor hygiene/cord care, bottle feeding and prelacteal feeds. In hospital settings, besides low birthweight (< 2,500 g) or preterm (< 37 weeks), risk factors of LOS include:

- Admission to NICU
- Overcrowding and increased work loads
- Administration of IV fluids including parenteral nutrition
- Mechanical ventilation

- Invasive procedures including presence of central lines
- Unnecessary investigations or medications.

## PATHOGENESIS

Sepsis is believed to be an unusual systemic response to an ordinary infection. The manifestation of sepsis results from a complex interaction among host, pathogen and the environment.

Once a pathogen makes access into the local tissue, pathogen associated molecular patterns (PAMPs) like lipopolysaccharide (LPS—in Gram-negatives), lipoteichoic acid (LTA—in Gram-positive) or other cell wall products are released. PAMPs bind to the immune cells via receptors known as pathogen recognition receptors (PRRs) such as Toll-like receptors. Simultaneously, as a result of local damage, the host tissue release molecules (like high mobility group box-1 [HMGB-1], free DNA/RNA) known as damage associated molecular patterns (DAMPs). These together with PAMPs stimulate the innate immune response, which is generic in nature and is made up of chiefly tissue macrophages and complement systems. The pro-inflammatory response marked by release of cytokines [interleukin-6 (IL-6), interleukin-1-β, tumor necrosis factor-α (TNF-α)] and chemokines (interleukin-8) sets in. These potent molecules not only initiate but also amplify the interaction between the pathogen and host's immune system.

When the pathogen (or its products) is not contained locally and disseminates through the bloodstream, it leads to a systemic reaction via the pro-inflammatory response (systemic inflammatory response syndrome; SIRS). The immune system goes overboard to kill the spread of infection and manifests as clinical signs and symptoms of sepsis. Interestingly, in this wave to neutralize the attack, the overdriven immune system—often producing *cytokine storm*, may harm its own tissues and organ system. Thus, the host institutes the compensatory stage of anti-inflammatory response (CARS) as a possible protective measure.

However, the ensuing balance of pro- and anti-inflammatory is complex and may be associated with multiple organ dysfunctions (MOD)/shock—identified clinically as severe sepsis. It is not fully clear why this switch to CARS occurs in some and not in others. However, pre-existing immune dysfunction has been well recognized as an important determinant of severe sepsis.

As such, the neonatal host is born with underlying immune defect.

- In the innate system, they have decreased capacity of producing IL-6 and TNF-α. Instead, they are highly inducible to produce interleukin-10, an anti-inflammatory cytokine which also provides negative feedback to pro-inflammatory cytokine synthesis. The neutrophils and dendritic cells are not only lesser in number, but also functionally impaired. There is decreased activation of natural killer cells. The complement levels are barely the half of adult levels even at term gestation, implying defective opsonization and impaired bacterial killing.
- In the adaptive immunity, they have blunted pro-inflammatory immune (Th1) responses—an extension of adaptation in the intrauterine life. This signifies decreased cytotoxic function and isotype switching of B-cells leading to reduced cell mediated immunity. Besides, inherent memory deficit from limited pathogen exposure since birth, worsens it. Altogether, these features increase the neonatal susceptibility to intracellular pathogens. Further, neonatal immunoglobulin (except IgG) stores are low even at term, and over 50% of transplacental transfer occur only after 28–32 weeks. The spleen remains immature to handle capsulated organisms till 2 years of age.

With these limitations, the neonatal immune response does not conform to the stereotypical response to microbial invasion and manifests with more nonspecific features clinically compared to older children and adults.

## CLINICAL FEATURES

Neonatal sepsis presents with nonspecific and subtle features, which often overlap with common noninfectious conditions. Therefore, high index of suspicion is crucial for early identification of NNS. In fact, any clinical deterioration, especially of a previously well infant, should be viewed with a strong possibility of sepsis, particularly when other diagnoses are uncertain.

Alteration in feeding pattern is one of the most common findings manifesting as lethargy/poor activity, refusal to suck or unresponsiveness in a neonate who fed well before. In contrast to older children or adults, neonates do not mount fever easily. However, hypothermia ( $< 36.5^{\circ}\text{C}$ ) is a common manifestation, especially in preterm infants. Other features of autonomic system disturbances include: tachycardia or bradycardia, poor perfusion or delayed capillary refill, hypotonia or absent neonatal reflexes, and apnea or gasping respiration. WHO Young Infant Study (YIS) provided useful clinical signs and symptoms for diagnosis (**Table 2**).

Though a systemic condition, NNS often manifests with cluster of findings signaling predominant involvement of one or more organ systems:

- **Central nervous system (CNS):** Irritability, excessive crying, high pitched cry, seizures, bulging fontanelle (however, neonatal meningitis is usually silent).
- **Respiratory:** Tachypnea, retractions, grunting, apnea, cyanosis or increased ventilatory requirements.
- **Gastrointestinal tract:** Feed intolerance, abdominal distension, paralytic ileus, necrotizing enterocolitis, vomiting, diarrhea, jaundice (excessive or mainly conjugated) and hepatomegaly.

Late features include shock, sclerema (hide-like skin), disseminated intravascular coagulation (DIC) and pulmonary hemorrhage. Metabolic derangements may include hypo-/hyperglycemia, metabolic acidosis and hypocalcemia.

Early onset sepsis manifests commonly with respiratory symptoms, often having a fulminant course and less frequently as septicemia or meningitis. LOS presents as generalized septicemia with rapidly downhill presentation or may be localized to one organ system such as bone/joint infections with smoldering course. Evidence does not suggest a difference in the presentations of term versus preterm infants.

## DIFFERENTIAL DIAGNOSIS

Early presentation in sepsis can be confusing. One of the important differential diagnoses for EOS is perinatal asphyxia (findings in favor: difficult labor/birth; need for resuscitation; symptomatic soon after birth). Other common sepsis mimickers are hypoglycemia, temperature instability, respiratory distress syndrome and meconium aspiration syndrome.

## DIAGNOSIS

### Blood Culture

Isolation of pathogens remains the gold standard. It helps in tailoring the treatment based on the antibiogram. A properly

performed blood culture prior to start of antibiotics is a crucial step in the management. However, conventional culture methods (manual) have a long turn-around time and come positive in less than a third of suspected infants. The modern automated systems as BacT/Alert (biomerieux, USA), BACTEC [Beckton Dickinson (BD), USA] and LightCycler SeptiFast (Roche, Germany) have improved the initial reporting time as they detect the growth during initial incubation itself; but, being expensive, these are still unaffordable in most settings. Following important points concerning the blood culture need to be kept in mind:

- **Blood volume:** Nearly two-thirds of infants (0–2 months) with NNS have a colony count of less than 10 CFU/mL. Current evidence suggests optimum volume of blood to be inoculated at least 1 mL. Culture sample obtained from indwelling catheter is not advisable; though, sample drawn during fresh cannulation may be acceptable. Documenting negative bacteremia in a previously culture positive episode is unnecessary.
- **Choice of skin disinfectant:** Povidone-iodine (Betadine; desired concentration: 10%) and chlorhexidine (desired concentration: 2%) offer similar benefit. However, superior results can be expected if either agent is combined with alcohol (Isopropyl alcohol 70%). More importantly, the method of applying the solutions should be adhered strictly. Apply each solution in concentric circles with friction, and allow them to air dry between applications.

## Sepsis Screen

Sepsis screen is the most common test of sepsis work-up as it can be performed at the bedside. It is considered positive when any two or more of the following parameters exceed their cutoffs:

- **Total leukocyte counts (TLC)** less than 5,000/cmm.
- **Absolute neutrophilic count (ANC):** Its cut off is gestational age-specific and should be based on Manroe's and Mouzinho's charts in term and preterm infants, respectively; roughly less than 1,800/cmm in term babies.
- **Immature to total neutrophil ratio (I:T ratio):** 0.2 or more.
- **Micro-ESR ( $\mu\text{ESR}$ ):** Measured as fall in mm in first hour; 3+ age in days in the first week of life or more than 15 mm if older.
- **C-reactive protein (CRP):** It is the most popular and widely studied biomarker of sepsis. A cutoff of more than 10 mg/L or 1 mg/dL is widely accepted. However, commonly used latex agglutination qualitative test kits have a lower cutoff of 6 to 8 mg/L. A positive CRP test with these kits should be repeated using one part of the CRP reagent with two parts of serum that would effectively give a cutoff of more than 12 or 16 mg/L. A quantitative CRP has a higher cost but provides actual values and therefore is more meaningful.

Out of the indices in the sepsis screen, the most sensitive index is I:T ratio and most specific the CRP, but as a panel, none of them have good positive predictive value (PPV; 7–77%); though the negative predictive value (NPV) approaches nearly 100%. Therefore, sepsis screen should be viewed as a panel to *Rule Out* suspicion (rather than Rule In). A repeat sepsis screen 12–24 hours later, especially if the first screen was negative, would clinch the

**Table 2** Clinical features of neonatal sepsis (Young Infant Study)

Symptoms	Signs	
Difficulty in feeding	Temperature ( $> 37.5^{\circ}\text{C}$ or $< 36.5^{\circ}\text{C}$ )	Capillary refill time (CRT) $> 3$ sec
Convulsions	Heart rate ( $> 180/\text{min}$ or $< 100/\text{min}$ )	Lethargy/drowsiness
Movement only when stimulated	Respiratory rate ( $> 60/\text{min}$ )	Cyanosis
Diarrhea (watery stools)	Severe chest in-drawing	Bulging fontanelle
Pus from umbilical stump	Grunting	Abdominal distension
	Apnea	Multiple ( $> 10$ ) skin pustules

decision to start empirical antibiotics: if both tests are negative, sepsis is highly unlikely; if the latter one is positive, it is advisable to treat. The second test is taken as decisive on the basis of kinetics of CRP. It begins to rise only after 6–8 hours of onset of infection and could come negative if tested earlier.

### Lumbar Puncture

Indications of lumbar puncture (LP) include:

- *In EOS: If the infant is symptomatic or if blood culture comes positive.*
- *In LOS: Perform LP in all cases along with sepsis work-up.*

Lumbar puncture may be postponed in critically ill infants until stabilization. The interpretation of cerebrospinal fluid (CSF) findings is different in the newborn period and varies also with gestational age (detailed in chapter 15.3).

### Other Investigations

Culture of other sterile body fluids like urine, peritoneal/pleural/synovial tap should be considered on individualized basis. Of note, maternal cultures including high vaginal swab and blood culture is highly desirable in EOS. Other popular biomarkers of interest have more favorable kinetics; they are procalcitonin and interleukin-6. Former rises within 2 hours and later within minutes (Fig. 1). However, currently, they are not routinely used due to various limitations including the cost. Notably, procalcitonin has been found to be promising in adults and children but convincing evidence in neonates is still lacking.

### Radiology

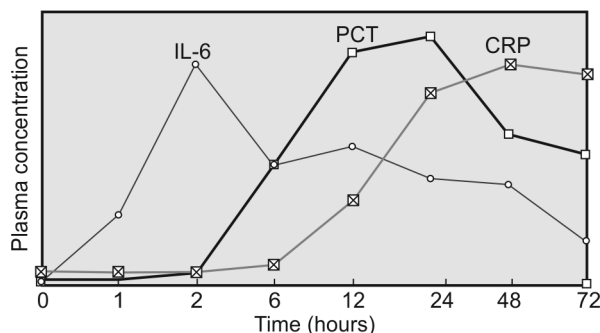
These include chest X-ray (for pneumonia), abdominal X-ray [(for neonatal necrotizing enterocolitis (NEC)] or cranial USG/CT (for meningitis).

## MANAGEMENT

### Supportive Therapy

The spectrum of presentation of neonatal sepsis ranges from mild subtle features to catastrophic presentation. Infants can present with varying level of sickness ranging from mild to grave sickness. Optimal supportive care of the baby is as crucial as timely administration of antibiotics. Therefore, early identification and management of emergency signs should take precedence at presentation. Following points (T\_ABCDEFG\_MN) require to be addressed comprehensively in management of sepsis:

- **Temperature:** The infant should be nursed in the thermo-neutral zone and special attention should be paid to preterm infants where hypothermia is common.



**Figure 1** Kinetics of various markers of the inflammatory host response after endotoxin challenge in human volunteers

Abbreviations: IL-6, interleukin-6; PCT, procalcitonin; CRP, C-reactive protein. Reproduced with permission: Reinhart K, Meisner M, Brunkhorst FM. Markers for sepsis diagnosis: what is useful? Crit Care Clin. Jul;22(3):503-19, ix-x. 2006

- **Airway/Breathing:** Infant's airway should be aligned properly. Oxygen should be supplemented if required targeting normal saturation ranges (90–95%). Ventilatory support may be required in some infants.
- **Circulation:** Maintaining adequate tissue perfusion is important. Unexplained persistent tachycardia (at level higher than 20–30 bpm above baseline) is one of the earliest signs of shock. Initial fluid resuscitation comprises of one or two boluses of 10–20 mL/kg of normal saline over 20 minutes each. If shock persists, inotropic support is provided. Intake/output should be closely monitored.
- **Electrolytes and Fluids:** Maintenance fluid requirements should be carefully adjusted in view of total intake/output avoiding any fluid overload or dehydration. Serum electrolytes should be monitored in a sick infant.
- **Glucose and Metabolic monitoring:** Blood glucose level should be monitored. Metabolic acidosis should be borne in mind during resuscitation if response to inotropes is not up to the expectation. However, there is no role for bicarbonate therapy. Hypocalcemia should be actively looked for too.
- **Bleeding Diathesis:** It may be the underlying cause of shock or may manifest as full blown disseminated intravascular coagulopathy (DIC). While addressing with appropriate blood products including packed cells, platelet concentrates and fresh frozen plasma, vitamin K deficiency should be suspected if bleeding/DIC is not responding to adequate therapy.
- **Nutrition:** Nutritional support is vital. Breastfeeding/breast milk feeding should be permitted in a stable infant. Sick infants may require parenteral nutrition.

### Antimicrobial Therapy

Antibiotics are the cornerstone of management of neonatal sepsis. Typically, the management consists of two steps:

1. Empirical initiation providing a broad-spectrum antibiotics coverage, followed by
2. Subsequent review of therapy at 48–72 hours for one of the two purposes: de-escalating the therapy to narrower spectrum as per the culture report and stopping/continuation of same regimen if no pathogen is isolated (based on clinical scenario).

### Empirical Initiation

Timely administration of first dose of antibiotics is life saving for a septic infant. This implies that precautions should be taken to avoid any inadvertent delay in treatment of an infant due to transport/referral, initial clinical examination or investigations. Antibiotics often started provisionally, pending confirmation by definitive tests are known as empiric therapy. In principle, empiric regimen should provide broadest spectrum cover, essentially implying a combination of antibiotics covering both gram-positive and gram-negative pathogens. The actual choice of antibiotics should vary across the institutions depending on sensitivity profile of prevalent sepsis pathogens. Thus being unit-specific, a single empiric regimen cannot be universal. A simplified stepwise approach to decide on the choices of empiric antibiotics is outlined in **Box 1**.

### Subsequent Review

Because empiric therapy is a stop-gap arrangement, a review of the clinical scenario is warranted at 48–72 hours as two important events would have taken place in the meantime:

1. Report of culture(s) would have been available at bedside. Ascertaining the isolation of a non-contaminant is difficult but vital to management and should be based on review with clinical or microbiology team.
2. More importantly, the clinician would have sufficiently observed the infant for the therapeutic response, having completed a detailed review of history and examination.



**BOX 1 A step-wise approach for framing empiric antibiotics therapy for a unit**

1. Collate frequency table of isolates and their antibiogram of last 6–12 months
2. *First line antibiotics*: Combination of common antibiotic that together cover 60–70% of common isolates
3. *Second line antibiotics*: Other antibiotic combination (besides first line) to cover 80–90% of isolates.

**Note:**

- The antibiotics regimen needs to be reviewed every 6–12 months
- Cephalosporins are generally avoided for empiric regimen since they are known to rapidly induce ESBL (extended spectrum beta-lactamases)/cephalosporinases and are associated with high predilection for fungal colonization
- Reserve drugs as colistin, meropenem, vancomycin or linezolid should not be used empirically.

If the response to antibiotics is satisfactory then antibiotics need to be continued for 5–7 days, if cultures are sterile, and for 10–14 days for a culture positive episode (**Table 3**). De-escalation of the antibiotic options to one with narrowest spectrum out of the antibiogram and as monotherapy is essential. If there was worsening of symptoms or status quo, one may consider starting the second/third line of drugs and duration of therapy suggested is at least 7 days from the day of improvement.

**Important Issues for Antibiotics Therapy**

- Continuation of empirical antibiotic therapy without subsequently reviewing it in light of culture report and clinical response plus the course of illness is not only irrational but also dangerous. Evidence suggests empiric regimen continued for more than 5 days increases the mortality or NEC/LOS risk.
- Choose a combination of antibiotics (based on sensitivity pattern) if pathogens like *Pseudomonas* spp, *S. aureus* or *Enterococcus faecalis* have been isolated. If the pathogen is not reported to be sensitive to any of the tested antibiotics, a combination of two antibiotics with intermediate resistance (in highest doses) should be used. Extended antibiotic susceptibility test with rescue/reserve antibiotics may also be obtained.
- Cephalosporins (except 4th generation) should not be used to treat *Enterobacter* and *Citrobacter* even if they are reported to be susceptible because they produce inducible, chromosomally encoded cephalosporinases.
- In case the infant did not show the expected improvement even after instituting susceptible antibiotic options, antibiotic may be resistant in vivo. In such cases, reserve drugs' antibiotic susceptibility test (AST) should be requested. However, this should only be labeled resistant

after excluding all other known factors that can lead to nonresponse.

- In case infant did improve as expected on empiric antibiotics, but AST report shows resistance, one should suspect in vitro resistance, which should be discussed with microbiology team.
- To treat meningitis, antibiotics with reliable blood brain barrier penetration should be prescribed in highest doses with the goal to rapidly sterilize the CSF. For example, ciprofloxacin lacks good CNS barrier clearance; while vancomycin can reach CSF in adequate concentrations when meninges are inflamed but its doses should be increased as soon as concomitant meningitis is confirmed.
- In cases where culture is negative and laboratory evidence is unsupportive, empiric therapy should never be continued beyond 48–72 hours. However, it may be appropriate to give 7 days therapy for a critically ill infant at presentation where alternative causes do not explain the illness.
- Review the need for continuing antibiotics and adequacy of doses on daily rounds.

**Treatment of Asymptomatic Infants (Flow chart 1)**

Neonates exposed to perinatal risk factors (as described above) are predisposed to EOS. Thus, despite being asymptomatic, these infants require special attention. Empiric antibiotics should be started if the infant is exposed to clear cut chorioamnionitis. For other risk factors, a differential approach is required:

- *Infant of 37 weeks or more*: If adequate monitoring is possible (e.g., adequate nurse: patient ratio), *only close observation for 48 hours* would suffice to decide for discharge. If close monitoring is not possible, perform sepsis screen. If screen is positive, take blood culture. The infant is treated with antibiotics if both the screen and culture are positive; otherwise, wait and watch for 48 hours and discharge if they remained well.
- *Infant of less than 37 weeks*: Perform sepsis screen. If positive, draw blood culture and start empiric therapy. Use blood culture report to review decision of how long to *continue* antibiotics. But, if the sepsis screen is negative, wait for blood culture positivity report even for *initiating* treatment. If blood culture is negative, antibiotics may be deferred altogether.

**Adjunctive Therapy**

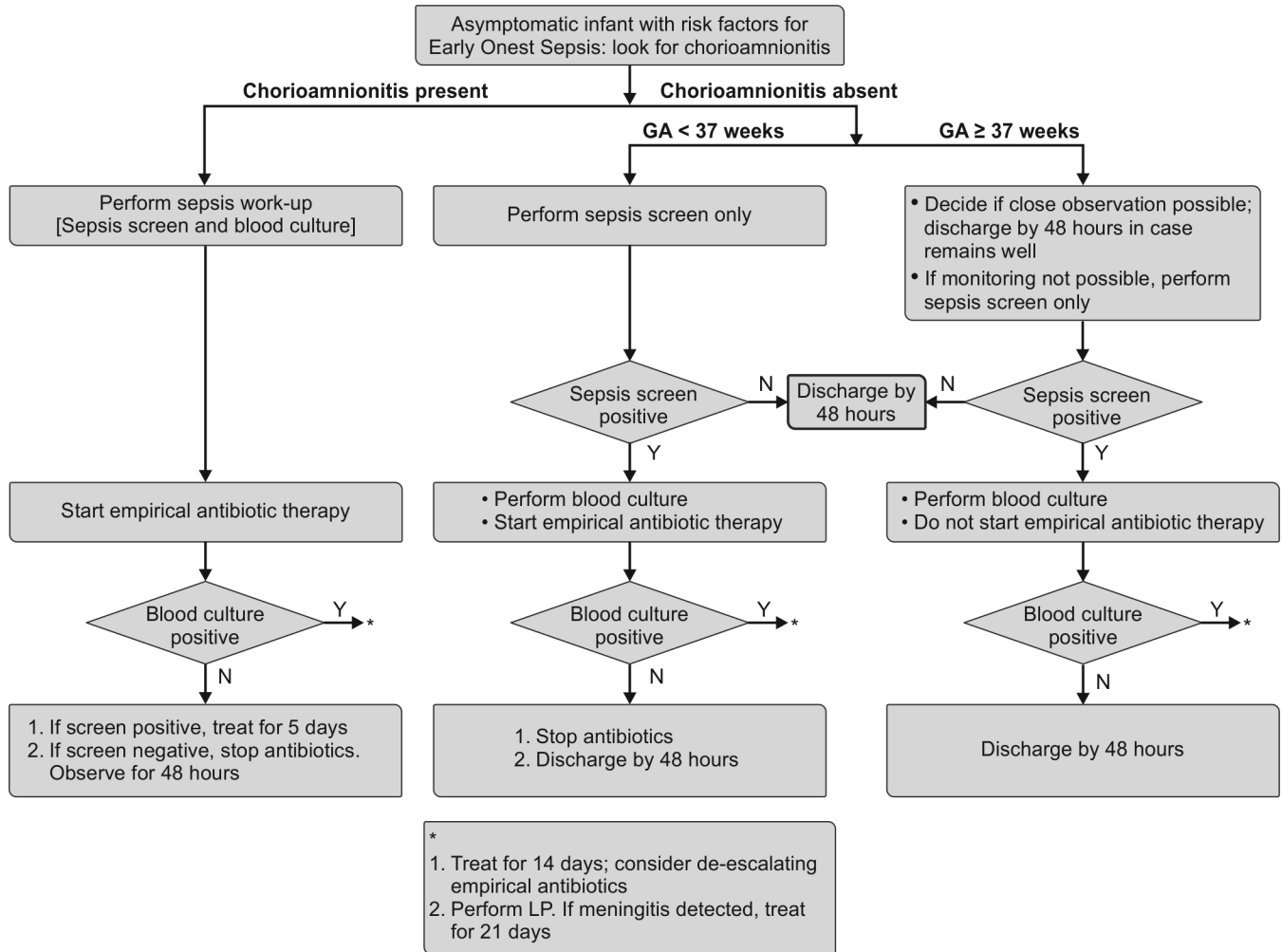
A variety of adjunctive therapies have been tried but none of them have worked well as of today. Therefore, for practical purposes, they have no role.

- *Intravenous immunoglobulins (IVIg)*: Current evidence does not favor the use of polyclonal or IgM-enriched IVIg.
- *Cytokine (Granulocyte colony stimulating factor (G-CSF)/Granulocyte-monocyte (GM-CSF)) infusion*: Similarly, either of these does not impart conclusive benefit in prophylaxis or treatment of sepsis and/or associated neutropenia.

**Table 3** Duration of antibiotic therapy

Condition	Duration	Remarks
Culture negative sepsis	5–7 days	
Culture positive sepsis	14 days	For coagulase negative Staph: when vancomycin therapy is started, duration of 7 days for septicemia and 14 days for meningitis is enough.
Meningitis (culture positive or negative)	21 days	See Chapter 15.3
Urinary tract infection	7–14 days	Once treatment is completed, start the infant on antibiotic prophylaxis (amoxicillin- 10 mg/kg/day or cephalixin 10 mg/kg/day OD) until vesicoureteric reflux is ruled out.



**Flow chart 1** Management of asymptomatic neonates born with risk factors of sepsis

- *Double volume exchange transfusion (DVET)*: Despite evidence of benefit in low quality study, robust evidence is still lacking for its efficacy.
- *Probiotics/prebiotics zinc*: Despite numerous recent studies, robust evidence to support definite benefit is still awaited.
- *Lactoferrin*: Prophylactic oral lactoferrin has been reported to reduce LOS (bacterial and fungal) in VLBW infants and more effective in ELBW infants; however, at present, generated evidence is insufficient to recommend the type, dosage, etc., precluding routine use.

## PREVENTION

Neonatal sepsis is preventable to a great extent by simple common sense approach. Primary prevention measures reduce the incidence of infections by controlling the risk factors (**Table 4**). Hand hygiene is the single most important preventive measure. Hand washing with soap and water is mandatory when visibly dirty or soiled with blood/body fluids. Otherwise, liberal hand rub (preferably alcohol-based) use in between patient contacts or whenever patient surroundings are handled should be adhered to.

**Table 4** Preventive measures

In the postnatal ward	In the nursery
Hand washing before contact by all caregivers	Strict hand hygiene policy
Keep cord dry	Aseptic work culture, no sharing of baby injectables/belonging
Promotion of exclusive breastfeeding	Thorough attention to general hygiene
Educating parents/guardians before discharge	Early enteral feeding
	Minimizing IV fluids or injections, catheters
	Abolishing unnecessary interventions (e.g., stomach wash, routine check for residual before feeding, unnecessary investigations) and promoting useful ones (e.g., Kangaroo mother care)
	IV and central line care ( <a href="http://www.cdc.gov/HAI/pdfs/bsi/checklist-for-CLABSI.pdf">http://www.cdc.gov/HAI/pdfs/bsi/checklist-for-CLABSI.pdf</a> )
	Quality improvement (QI) programs

### IN A NUTSHELL

1. Sepsis is an unusual systemic response to infection and contributes to about 28% of neonatal deaths.
2. Major pathogens causing hospital acquired infections in neonates in developing countries are *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Staphylococcus aureus* with a high rate of antibiotic resistance.
3. NNS presents with nonspecific and subtle features, which often overlap with common noninfectious conditions. Therefore, high index of suspicion is crucial for early identification of NNS.
4. Blood cultures should be taken in every suspected case of neonatal sepsis prior to start of antibiotics.
5. Sepsis screen panel has a low positive predictive value; prefer using a quantitative CRP for the panel rather than qualitative.
6. Even though antibiotics are started empirically, subsequent review after 48–72 hours is a must to de-escalate to narrow range antibiotic or even stop if baby is well and no pathogen is isolated. This will contribute to minimizing spread of antimicrobial resistance.
7. Hand hygiene is the single most important preventive measure for sepsis.

### MORE ON THIS TOPIC

- Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. *Pediatr Clin North Am*. 2013;60:367-89.
- Connell TG1, Rele M, Cowley D, et al. How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. *Pediatrics*. 2007;119:891-6.
- Edmond K, Zaidi A. New approaches to preventing, diagnosing, and treating neonatal sepsis. *PLoS Med*. 2010;7:e1000213.
- Reinhart K, Meisner M, Brunkhorst FM. Markers for sepsis diagnosis: what is useful? *Crit Care Clin*. 2006;22:503-19.
- Sarkar S, Bhagat I, DeCristofaro JD, et al. A study of the role of multiple site blood cultures in the evaluation of neonatal sepsis. *J Perinatol*. 2006;26:18-22.
- Shah BA, Padbury JF. Neonatal sepsis: an old problem with new insights. *Virulence*. 2014;5:170-8.

## Chapter 15.2

# Superficial Infections

Sriparna Basu, Ashok Kumar

Though apparently not life-threatening, superficial infections are a cause of concern for the parents and physicians. If neglected, local infections may spread and lead to systemic infection.

### SKIN INFECTIONS

Newborn's skin begins to colonize by microorganisms at birth. The organisms are almost similar to those found on adult skin. In the normal flora, *Staphylococcus epidermidis*, diphtheroids, streptococci, and coliform bacteria predominate. In preterm and hospitalized neonates, *Staphylococcus aureus* and *Candida albicans* are major organisms to get colonized and produce localized and disseminated diseases.

### Vesiculobullous or Pustular Lesions

Bacterial, viral and fungal infections in neonates may present with vesiculobullous or pustular lesions. The most important bacterial cause of superficial skin infections is *Staphylococcus aureus*. Other etiologic agents include streptococci, *Pseudomonas aeruginosa*, *Haemophilus influenzae* type b and *Listeria monocytogenes*.

### Staphylococcal Pyoderma

Staphylococcal infection leads to the formation of small vesicles, erythematous papules, pustules and large, fragile bullae filled with clear, turbid, or purulent fluid. The lesions develop after a few days of birth. The bullae get ruptured easily with formation of red, weeping, denuded areas with formation of crusts later on. Lesions may develop anywhere but are usually localized in the groin, axillae, periumbilical skin and back. The diagnosis is confirmed by Gram staining of the vesicular fluid showing Gram-positive cocci in clusters along with neutrophils and isolation of *S. aureus* on culture. If lesions are extensive or the infant appears ill, sepsis screen and a blood culture should be obtained prior to starting treatment. Methicillin-resistant *S. aureus* (MRSA) should be ruled out in hospitalized neonates.

**Treatment** If the lesion are small in size and few in number and the infant looks well, aseptic rupture of the pustule with sterile needle and cleaning with povidone-iodine should be done in hospital. Mothers can be instructed for application of topical antibacterial cream such as mupirocin. Maintenance of hygiene, such as daily infant bath or sponging, washing and sun-drying of clothes and bed sheets and hand washing should be emphasized. Application of oil should be avoided till the lesions heal. In multiple and/or large lesions oral antibiotic such as oral amoxicillin or cefadroxil for 7 days can be advised along with topical antibiotics and hygienic measures. Preventive measures are very important in sick hospitalized neonates to prevent disseminated infection and spread of the infection to others.

### Staphylococcal Scalded Skin Syndrome

The staphylococcal scalded skin syndrome (SSSS) is a severe bullous eruption, caused commonly by *S. aureus* (phage type group 2). The organism produces an exotoxin (exfoliatin) which has proteolytic activity on desmoglein-1 (a molecule found in the desmosomes of keratinocytes) which is responsible for the skin changes. SSSS is rarely seen at birth. Most neonates present between days 3 and 7 of life. Clinically, SSSS starts with a bright

erythema resembling a scald. The erythema usually begins on the face and gradually spreads downward with formation of blisters and bullae to involve the whole body, with accentuation in the flexural areas. The bullae are flaccid and rupture easily, progress rapidly into large areas of denudation. In extreme cases, the entire upper epidermis may be shed.

The level of cleavage is superficial. Histologic examination of the skin shows separation at the level of the granular layer with cell death and acantholysis without any inflammatory infiltrate. Crusting may be seen around the mouth and eyes. Conjunctivitis and hyperemia of the mucous membranes are common, but oral ulcerations are rarely seen. The lesions are painful and the infants are febrile and irritable. Gentle pressure applied to the skin leads to separation of the upper epidermis and skin wrinkling (positive Nikolsky's sign). In milder form of the disease, a scarlatiniform eruption is seen with perioral and flexural desquamation but without bullae formation or denudation.

Diagnosis is essentially clinical. Skin biopsy can differentiate SSSS from toxic epidermal necrolysis, where a subepidermal cleavage plane and epidermal necrosis are found. Cultures should be obtained from the nasopharynx, conjunctiva, umbilicus, denuded skin, blood, urine, and any other suspected foci of infection. Intact bullae are sterile.

**Treatment** Infants should be nursed in isolated rooms and all the precautions should be considered to prevent spread of the infection to other neonates. Treatment consists of prompt systemic administration of penicillinase-resistant penicillin, such as cloxacillin, nafcillin or oxacillin for 10–14 days along with strict fluid and electrolyte monitoring and replacement. Maintenance of nutrition by parenteral nutrition or nasogastric/orogastric feeding is vital. Vancomycin should be considered in patients who fail to respond to initial therapy or MRSA is suspected. Supportive skin care should be provided, with the use of skin emollients, such as creams or ointments. Healing occurs by flaky desquamation without any scar formation.

### Streptococcal Skin Infections

Infection with group B streptococci rarely produces skin lesions, though vesicles, bullae, and erosions have been reported occasionally. The lesions may be present at birth or develop later. Group A streptococcal infection occurs primarily as omphalitis or rarely as isolated pustules. The affected neonates should be treated aggressively with parenteral antibiotics (ampicillin and gentamicin for 10 days) as complications, such as, sepsis, cellulitis, meningitis, and pneumonia may occur.

### Listeriosis

*Listeria monocytogenes* infection can present as early or late onset sepsis and meningitis in newborns. Early form often presents with multiple pustules on the skin and mucous membranes.

### Mucocutaneous Fungal Infections

(Also See Chapter 33.3)

Mucocutaneous fungal infections are common in neonatal intensive care units. Increased survival rates of very low birth weight infants in association with an increased number of invasive procedures, widespread use of broad-spectrum antibiotics and simultaneous bloodstream infections often lead to concomitant superficial infections. Most fungal infections are caused by *Candida* spp, though a small number may also be attributed to *Malassezia*, *Zygomycetes*, or *Aspergillus* spp. *Candida albicans* is the most common cause of human candida infections, other pathogenic spp include *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, *C. lusitanae*, and *C. stellatoidea*. Neonatal candidiasis usually develops after the first week of life secondary to the colonization of skin and mucosal

surfaces and commonly affects moist, warm areas, such as groin, or buccal mucous membranes. Common presentations include oral thrush and diaper dermatitis. Cutaneous lesions occasionally may be found over skin folds such as neck and consist of erythematous papules and vesicopustules which get confluent, forming a moist, erosive, scaly dermatitis with formation of satellite pustules. Rarely, paronychia lesions can also occur.

### Oropharyngeal Candidiasis (Oral Thrush)

Oral thrush presents as creamy white plaques in the mouth and may affect the lips, tongue, gums, and palate. The plaques do not scrape off easily. Forceful scraping of the lesions reveals erythema and bleeding at the base. Sometimes in more severe cases, lesions extend to pharynx or esophagus. Infants with thrush may be asymptomatic or may present with refusal to feed. Nipple of the nursing mother should be examined for nipple candidiasis which is usually bilateral. Nipples appear bright red and inflamed. Oropharyngeal candidiasis in the infant can be treated with nystatin oral suspension for 10–14 days or until 48–72 hours after resolution of symptoms. For preterm infants, dose is 0.5 mL (50,000 U) to each side of mouth 6 hourly; for term infants, dose is 1 mL (100,000 U) to each side of the mouth 6 hourly. In presence of candidiasis of the nipple, an antifungal cream should be applied over the nipples after each feeding for 2 weeks. The infant must be treated simultaneously.

### Candida Diaper Dermatitis

Candida diaper dermatitis appears as an erythematous rash in the inguinal region. The rash appears as areas of confluent erythema with multiple tiny pustules or discrete erythematous papules and plaques with superficial scaling. Satellite lesions are typical. In most cases topical application of antifungal cream is adequate, as dissemination is rare.

### Congenital Cutaneous Candidiasis

Congenital cutaneous candidiasis is a rare disorder resulting from a *Candida* spp. infection acquired in utero or during delivery. The manifestations appear at birth or within a few days with formation of pustules, vesicles, skin abscesses, or an erythematous maculopapular rash involving scalp, face, chest, abdomen, perineal area, extremities, or back. These lesions may lead to desquamation. Treatment depends on the extent of involvement. Topical antifungal agents from the imidazole group are the most effective if disease is limited to the skin. Systemic administration of amphotericin B, 5-fluorocytosine, or an imidazole is needed in patients with evidence of disseminated disease. Fluconazole or itraconazole for disseminated candidiasis in the neonate with low birthweight can provide an alternative to systemic amphotericin B and 5-fluorocytosine.

### Subcutaneous Fat Necrosis and Sclerema Neonatorum

*Subcutaneous fat necrosis* appears 1–4 weeks after delivery as well-circumscribed small nodules or large plaques. The lesions are usually localized on the cheeks, buttocks, back, arms, and thighs. The affected area is firm and tense to feel, and the overlying skin is reddish or violaceous. Histologically, a granulomatous reaction in the fat is seen, with formation of spiky crystals and infiltration of foreign body giant cells, lymphocytes, histiocytes and fibroblasts. Common causes of fat necrosis include perinatal asphyxia, hypothermia, shock, trauma, and hypercalcemia. Calcium may be deposited in the lesion, leading to ulceration and sinus formation. Management is the treatment of underlying cause. The lesions usually resolve in several weeks or months without complications. In areas where calcium deposition is seen, careful drainage should be done to lessen subsequent scarring.

*Sclerema neonatorum* is seen in sick neonates and is commonly associated with sepsis, hypothermia and other metabolic abnormalities. It is manifested as diffuse hardening of the subcutaneous tissue, resulting in a tight, smooth skin bound to the underlying structures. The skin is cold and firm to feel. In extensive involvement, whole body becomes stiff, face looks mask-like and joints become immobile. It is associated with high mortality. In case the infant survives, the cutaneous changes resolve by 2 weeks. Treatment with appropriate antibiotics guided by blood culture is essential. In infants who are severely ill, exchange transfusion has been tried, but the efficacy is not proven.

A number of viruses and *Treponema pallidum* (congenital syphilis) can also cause vesiculopustular or bullous lesions in the newborn. Common viruses include herpes simplex virus and varicella-zoster virus, but cytomegalovirus and coxsackie viruses can also cause vesiculobullous lesions.

## OPHTHALMIA NEONATORUM

Ophthalmia neonatorum or neonatal conjunctivitis, is an acute, mucopurulent infection of eyes, occurring in the first 4 weeks of life. The incidence varies from 1.6% to 12% of all livebirths. Previously, ophthalmia neonatorum was an important cause of neonatal blindness, *Neisseria gonorrhoeae* being the most common organism responsible. Availability of improved treatment and introduction of ocular prophylaxis with silver nitrate at birth has resulted in a dramatic reduction in the incidence of ophthalmia neonatorum and improved its prognosis.

### Pathogenesis

Normal conjunctiva contains non-keratinizing, squamous epithelium and thin, highly vascularized substantia propria with lymphoid tissue, plasma cells, mast cells, and macrophages. It also contains accessory lacrimal glands and goblet cells. Neonatal conjunctiva is particularly vulnerable to infection because of their inherent poor immune status and lack of local lymphoid tissue at birth. The inflammation of the conjunctiva results in dilation of blood vessels, chemosis, and increased secretion.

### Etiology

Various bacterial and viral infections may cause ophthalmia neonatorum (**Box 1**). The most common infectious agent is *Chlamydia trachomatis*. Chemical conjunctivitis, seen secondary to silver nitrate prophylaxis, has become less common after the use of erythromycin ointment for prophylaxis.

#### BOX 1 Causes of ophthalmia neonatorum

##### Bacterial

- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Streptococcus pneumoniae*
- *Staphylococcus aureus*
- *Staphylococcus epidermidis*
- *Streptococcus viridans*
- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Haemophilus influenzae*
- *Serratia marcescens*
- *Proteus*
- *Enterobacter*
- Other bacterial infections causing neonatal sepsis

##### Viral

- Adenovirus
- Herpes simplex virus

##### Chemical



### *Chlamydia trachomatis*

*Chlamydia trachomatis* is an obligate intracellular parasite and is the most common cause of infectious conjunctivitis accounting for approximately 40% cases of ophthalmia neonatorum. An infant born vaginally to a mother with chlamydial cervicitis has a 30–50% chance of developing conjunctivitis. The incubation period varies from 5 days to 14 days (typically 1 week after delivery), or earlier if membranes ruptured prematurely. The clinical manifestations vary from mild conjunctival infection with scanty watery discharge to severe mucopurulent conjunctivitis with eyelid edema, chemosis, and pseudomembrane formation. The eyes are usually less inflamed than in gonococcal infection. Most cases of chlamydial infections resolve spontaneously without complications. In untreated cases, superficial corneal vascularization and conjunctival scarring can occur. Loss of vision is rare.

### *Neisseria gonorrhoeae*

*Neisseria gonorrhoeae* is a gram-negative diplococcus and is the most virulent infectious cause of ophthalmia neonatorum. Gonococci can penetrate intact epithelial cells and multiply rapidly. The infection is acquired from the vaginal secretions of the mother at the time of birth. Transmission rate is higher in mothers with concomitant chlamydial infection. Presently, the incidence of gonococcal conjunctivitis has decreased substantially to less than 1%. It develops within 1–5 days of birth, but presentation can be delayed up to 2–3 weeks after delivery. The disease typically presents acutely with copious purulent discharge, profound chemosis, and edema of the eyelids. Eye discharge may also be blood-tinged with superficial conjunctival hemorrhages. If left untreated, gonorrheal conjunctivitis can lead to keratitis, conjunctival and corneal scarring, pannus formation, ulceration, panophthalmitis, permanent visual impairment and perforation of the globe within 24 hours. Affected infants should also be evaluated for disseminated gonococcal infection causing arthritis, sepsis and meningitis.

### Bacterial Conjunctivitis

Other gram-positive and gram-negative organisms, responsible for neonatal sepsis, can also cause ophthalmia neonatorum. *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus viridans*, and *Staphylococcus epidermidis* are responsible for 30–50% of cases. Gram-negative infections are more common in preterm very low birthweight neonates. Infants present with a subacute onset between 4 days to 28 days of life. Common presentations include conjunctival redness with lid edema and varying amount of purulent discharge. Infections may also be acquired postnatally. Ophthalmia neonatorum caused by *Pseudomonas* is rare but infants may present with eyelid edema, redness and purulent discharge which may be severe and progress to corneal perforation, endophthalmitis, blindness, and even death.

### Viral Conjunctivitis

Viral conjunctivitis is characterized by acute onset at 6–14 days after birth and is most commonly caused by adenovirus and herpes simplex virus. Infants with adenovirus conjunctivitis present with petechial or large subconjunctival hemorrhages. Lymphadenopathy is associated in approximately 50% of cases. Infants with herpetic conjunctivitis present with unilateral or bilateral serosanguinous discharge with or without vesicular skin lesions. Lesions on the borders of the eyelids are commonly seen. Other ocular features, such as keratitis, anterior uveitis, cataract, retinitis and rarely optic neuritis may also be present. Infants should be examined for features of systemic infection, such as jaundice, hepatosplenomegaly, pneumonia, meningoencephalitis and disseminated intravascular coagulation.

### Chemical Conjunctivitis

Chemical conjunctivitis presents as a mild, purulent conjunctivitis within the first 24 hours of birth. It is most commonly associated with intraocular silver nitrate prophylaxis. Rarely, it may be seen secondary to prophylaxis with other agents (erythromycin or tetracycline). Chemical conjunctivitis is a self-limiting condition and does not require any diagnostic tests or treatment. The inflammation almost always disappears by 24–48 hours. It is rarely seen in our country since we do not advocate routine antibacterial ocular prophylaxis at birth.

### Investigations

History of genital discharge, genital vesicles, sexually transmitted diseases (STDs) in the parents and results of cervical swabs and cultures from mother during pregnancy or after childbirth should be obtained. If not done earlier, in suspected cases of STD, cervical cultures from the mother should be sent. Other STDs including HIV, hepatitis B and syphilis should be ruled out. Laboratory investigations in neonates have been summarized in **Box 2**.

#### BOX 2 Laboratory investigations in ophthalmia neonatorum

- Conjunctival scraping for Gram, Giemsa, and Papanicolaou stains
- Culture on chocolate agar and/or Thayer-Martin for *N. gonorrhoeae*
- Culture on blood agar for other bacteria
- Culture of corneal epithelial cells for HSV, in cases of corneal involvement
- Conjunctival scraping for polymerase chain reaction assay (PCR) and transcription-mediated amplification (TMA) to detect the infective organism
- Direct fluorescent antibody (DFA) studies
- Sepsis screen and other sepsis work-up to rule out neonatal sepsis and other STDs.

### Treatment

Because of the rapid progression of gonococcal conjunctivitis, treatment should be started promptly in suspected cases without waiting for culture results. Treatment may be altered once laboratory results are available. Eye patching should be avoided. Individual treatment options are summarized in **Table 1**. It should be remembered that blockage of nasolacrimal ducts are common in neonates and may result in thick and copious sticky or crusty discharge. The eye is not red and the infant looks otherwise well. The discharge may be intermittent and responds well to simple cleansing and regular nasolacrimal duct massage.

### Prevention

Several countries advocate the use of preventive ocular prophylaxis within 24 hours after birth. Medications include erythromycin 0.5% ophthalmic ointment, silver nitrate 1.0% solution, tetracycline 1.0% ointment and povidone-iodine 2.5% solution. All are considered equally effective against gonococcal conjunctivitis. There is no effective agent to prevent the transmission of *C. trachomatis*. Universal acceptance of ocular prophylaxis is controversial. Studies have shown that in places where the prevalence of maternal infection is low, routine eye prophylaxis is probably not worthwhile due to the high failure rates of the prophylactic regime.

In India, routine ocular prophylaxis is not advocated. After birth, both eyes should be cleaned with two separate sterile cotton balls soaked with normal saline from medial to lateral direction.

### Prognosis

Ophthalmia neonatorum usually responds to appropriate treatment, and the prognosis generally is good. Timely use of appropriate antibiotics has altered the prognosis of gonococcal

**Table 1** Treatment of ophthalmia neonatorum

Organism	Treatment
<i>Chlamydia trachomatis</i>	<ul style="list-style-type: none"> <li>• Oral erythromycin 40 mg/kg/day QID for 14 days.</li> <li>• Topical treatment alone is not adequate, and is unnecessary when systemic therapy is given.</li> <li>• Erythromycin may have a failure rate of 10–20% and some neonates will require a second or sometimes a third course of erythromycin.</li> <li>• A short course of oral azithromycin (20 mg/kg once daily for 3 days) might be an effective alternative, though, further studies are warranted.</li> <li>• Parents should be treated for <i>Chlamydia</i> infection.</li> </ul>
<i>Neisseria gonorrhoeae</i>	<ul style="list-style-type: none"> <li>• Infants should be hospitalized.</li> <li>• Intravenous or intramuscular single dose administration of ceftriaxone (25–50 mg/kg, to a maximum dose of 125 mg).</li> <li>• Frequent irrigation of the conjunctiva with sterile normal saline is needed.</li> <li>• Parents should be treated for gonorrhea.</li> </ul>
Bacterial conjunctivitis	<ul style="list-style-type: none"> <li>• Systemic antibiotics as used to treat neonatal sepsis along with topical antibacterials (aminoglycosides, polymyxin B sulfate-trimethoprim solution, macrolides, or fluoroquinolones).</li> <li>• In endophthalmitis, subconjunctival injections are occasionally required to salvage the eyes.</li> </ul>
Herpetic conjunctivitis	<ul style="list-style-type: none"> <li>• Systemic acyclovir (60 mg/kg in divided doses 3 times a day) for 14–21 days, with topical antiviral ophthalmic solution (1% trifluridine, 0.1% iododeoxyuridine, or 3% vidarabine).</li> <li>• Topical antibiotics should also be used to prevent secondary bacterial infections.</li> </ul>

conjunctivitis. Morbidity and mortality associated with neonatal conjunctivitis is proportional to the systemic involvement of the infecting agent.

## UMBILICAL CORD INFECTIONS (OMPHALITIS)

Omphalitis is defined as erythema of the umbilical stump with or without induration of the periumbilical area and purulent discharge. The infection may progress to abdominal wall leading to cellulitis, necrotizing fasciitis, myonecrosis, peritonitis, umbilical arteritis or phlebitis, hepatic vein thrombosis, and hepatic abscess. Severe cases are associated with high morbidity and mortality.

Omphalitis is rare in developed countries, where an overall incidence rate of 0.2–0.7% is reported. It is commonly seen in developing countries with incidence rates ranging from 2–54 per 1,000 livebirths in hospitalized neonates. Community-based rates for omphalitis are even higher. One study from Nepal reported an incidence of 105 per 1,000 livebirths. The incidence of case fatality rates following omphalitis ranges from 0 to 15%. Mortality increases significantly after the development of necrotizing fasciitis or myonecrosis. Predisposing factors for high incidence of omphalitis in developing countries are summarized below:

### In Community

- Lack of skilled birth attendants
- Sub-optimal use of infection control practices during and after birth—hand washing, disinfection of delivery surface and instruments, sterile cord cutting and cord tie
- Cultural practices involving application of unsafe substances to the cord
- Delayed health-care seeking behavior.

### In Hospitals

- Very low birthweight and prematurity
- Presence of risk factors for sepsis—chorioamnionitis or maternal infection, premature and prolonged rupture of membranes, poor maintenance of asepsis during delivery
- Umbilical catheterization
- Underlying anatomic abnormality, such as, patent urachus, omphalomesenteric duct, or urachal cyst
- Neonatal alloimmune neutropenia or congenital neutropenia
- Leukocyte adhesion deficiency.

### Pathogenesis

Umbilical cord usually separates between 5 days to 15 days after birth. The freshly cut umbilical stump is rapidly colonized after birth as the macerated tissue provides a good culture medium supporting bacterial growth. The profile of organisms colonizing the cord stump, pathogenic versus nonpathogenic, varies according to the hygienic conditions at the time of birth and immediate postpartum period. Colonized bacteria have the potential to invade the umbilical stump and surrounding tissue, leading to omphalitis. Initial superficial cellulitis may spread to the abdominal wall and infect the fascial planes, muscles and blood vessels, causing necrotizing fasciitis, myonecrosis, thrombophlebitis and disseminated sepsis.

### Causative Organisms

Most of the cases of omphalitis are polymicrobial in origin. Aerobic bacteria are present in approximately 85%. Anaerobes are recovered from one to two-thirds of infants. Common organisms are listed below. Neonatal tetanus caused by *Clostridium tetani* may also be associated with omphalitis.

### Organisms Causing Omphalitis

**Aerobic bacteria** *Staphylococcus aureus*, Group A *Streptococcus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.

**Anerobic bacteria** *Bacteroides fragilis*, *Peptostreptococcus* spp., and *Clostridium perfringens*.

### Clinical Manifestations

In full-term infants, the mean age at onset is 5–9 days. In preterm infants, the mean age at onset is earlier, at 3–5 days. The signs and symptoms of omphalitis depend on the extent of infections.

### Localized Infection

It consists of purulent or malodorous discharge from the umbilical stump, periumbilical erythema, edema and local tenderness. Recently, three case definitions (algorithms) have been standardized to describe the severity of omphalitis based on the extent of periumbilical erythema and absence or presence of pus.

- Algorithm 1: Moderate or severe erythema\*.
- Algorithm 2: Moderate erythema\* with pus, or severe redness (without regard to pus).
- Algorithm 3: Severe erythema\* with pus.

\*For erythema or swelling, severity has been graded as “mild” (limited to the cord stump only), “moderate” (affecting abdominal skin at the base of the stump < 2 cm), or “severe” (erythema spreading outward > 2 cm).

### Extensive Local Disease, with Extension

Necrotizing fasciitis or myonecrosis, initially located in periumbilical location and gradually spreading along the abdominal wall to the flanks, back, and scrotum. Petechiae, ecchymoses,

violaceous discoloration, bullae formation and crepitus may develop in local area.

### Systemic Disease

Hypo/hyperthermia, tachycardia, hypotension or delayed capillary refill, respiratory distress, necrotizing enterocolitis, jaundice, petechiae, or cyanosis, irritability, lethargy, poor feeding, hypo/hypertonia.

### Investigations

Complete sepsis screen including complete blood count with differential, immature-to-total (IT) neutrophil ratio, C-reactive protein, micro-ESR, blood culture for aerobic and anaerobic organisms, and lumbar puncture should be done. Gram stain and culture for aerobic and anaerobic organisms from umbilical discharge need to be taken. In myonecrosis, specimen should be obtained from involved muscle. Investigations necessary for supportive management include blood glucose, electrolytes including calcium, arterial blood gas analysis, renal function tests, coagulation profile, etc. Ultrasonography may show fascial thickening and fluid accumulation between subcutaneous fat and muscle in cases with fascial involvement.

### Treatment

Parenteral antibiotics cover both gram-positive and gram-negative organisms. A combination of antistaphylococcal penicillin, such as cloxacillin (vancomycin in suspected methicillin-resistant organism) and an aminoglycoside antibiotic (gentamicin or amikacin) is recommended. Omphalitis complicated by necrotizing fasciitis or myonecrosis requires coverage of anaerobic organisms also. Surgical debridement of the affected tissue and muscle in necrotizing fasciitis and myonecrosis may be life saving. It also helps to eradicate infection. Metronidazole or clindamycin may be added to provide anaerobic coverage. Antibiotics may be modified once culture reports are available. Duration of antibiotics depends on the severity of the disease; a minimum duration of 7–10 days is advocated.

Patients should be monitored for progression of disease. In uncomplicated cases, erythema of the umbilical stump improves within 12–24 hours after the initiation of antimicrobial therapy. Failure to respond suggests progression of the disease, presence of an anatomic defect, or an immunodeficiency state. Long-term follow-up is indicated as infants developing portal vein thrombosis may develop portal hypertension later.

### Prevention

The delivery should be conducted by skilled birth attendants adhering to clean delivery practices—to follow 5 *cleans* during birth, clean surface, clean hands, clean blade, clean cord tie and clean cord (dry umbilical cord care). Hygienic practices are important during postpartum period including hand washing

with soap and water before touching the baby both in community setting and in hospital. Since 1998, World Health Organization has advocated the use of dry umbilical cord care, i.e., keeping the cord clean without application of anything and leaving it exposed to air.

Recently, large community-based randomized trials have shown that application of 4.0% chlorhexidine (CHX) to the umbilical cord after birth can substantially reduce cord infection and neonatal mortality. Cochrane review demonstrates a reduction in incidence of omphalitis ranging from 27–54% depending on the severity of infection. Cleansing of the umbilical cord with CHX is considered safe and no significant adverse events associated with topical applications have been reported. The most prominent protective effects of CHX are seen during the first week of life.

### IN A NUTSHELL

1. The most important cause of neonatal superficial skin infections is *Staphylococcus aureus*. Other common etiological agents include streptococcal spp, *Pseudomonas aeruginosa*, *Haemophilus influenzae* type b, *Listeria monocytogenes*, Herpes virus, *Treponema pallidum* and *Candida albicans*.
2. Neonatal mucocutaneous candidiasis is common in very low birthweight neonates, usually develops after the first week of life and commonly affects oral mucous membranes and the diaper area.
3. Ophthalmia neonatorum, an acute, mucopurulent infection of eyes, occurs in the first 4 weeks of life and is a potential cause of neonatal blindness. Common organisms responsible are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.
4. Omphalitis, characterized by erythema and/or induration of the periumbilical area with purulent discharge from the umbilical stump, occurs due to poor infection control measures during and after birth.
5. If omphalitis is not diagnosed and treated early, the infection can progress to widespread abdominal wall cellulitis, necrotizing fasciitis, myonecrosis, peritonitis, umbilical arteritis or phlebitis, hepatic vein thrombosis, and hepatic abscess resulting in high morbidity and mortality.

### MORE ON THIS TOPIC

- Hulsmann AR, Oranje AP. Educational paper: neonatal skin lesions. *Eur J Pediatr*. 2014;173:557-66.
- Imdad A, Bautista RM, Senen KA, et al. Umbilical cord antiseptics for preventing sepsis and death among newborns. *Cochrane Database Syst Rev*. 2013;5:CD008635.
- Su J. Common rashes in neonates. *Aust Fam Physician*. 2012;41:280-6.
- Wang SM, Hsu CH, Chang JH. Congenital candidiasis. *Pediatr Neonatol*. 2008;49:94-6.
- Zuppa AA, D'Andrea V, Catenazzi P, et al. Ophthalmia neonatorum: what kind of prophylaxis? *J Matern Fetal Neonatal Med*. 2011;24:769-73.



## Chapter 15.3

# Meningitis in the Newborn

Kumutha Jayaraman, Manigandan Chandrasekaran

Newborn infants are more susceptible to meningitis than any other age group due to their immature immune system, which is deficient in humoral and cellular immune responses (mainly phagocytic and complement functions). There is an increased risk of neurological morbidity during childhood in those who have had neonatal meningitis. It is therefore imperative that meningitis in the newborn is diagnosed and treated early to prevent the adverse outcome.

## EPIDEMIOLOGY

The incidence of neonatal bacterial meningitis varies between 0.22 and 2.66 per 1,000 livebirths globally. The estimated incidence in the developing world is 126,000 cases annually. The highest occurrence is recorded from countries in sub-Saharan Africa and South Asia. The lower incidence in developed countries is mainly due to the widespread use of intrapartum antibiotic prophylaxis to prevent Group B *Streptococcus* (GBS) infection and widely available good supportive care. There are very few population-based surveillance studies on neonatal meningitis in South Asia, especially from India. Meningitis occurs in around 25% of neonatal infants with bacteremia. There are several risk factors associated with the development of bacteremia (**Box 1**).

### BOX 1 Risk factors for neonatal meningitis

#### Maternal risk factors

- Maternal chorioamnionitis (foul smelling liquor, maternal pyrexia and raised inflammatory markers)
- Prolonged pre-labor rupture of fetal membranes (> 24h)
- Maternal colonization with Group B *Streptococcus* (GBS)
- Low socio-economic factors

#### Neonatal risk factors

- Low birthweight
- Preterm birth
- Male gender
- Congenital CNS defects such as open spina bifida
- Invasive procedures like central vascular access, ventilation and presence of a shunt
- Co-existing infections like HIV infection

## ETIOLOGY

The causative organisms for neonatal meningitis are not different from those that cause neonatal sepsis. The age at presentation of meningitis can provide a clue to the probable mode of acquisition and the causative organisms. Early onset meningitis presenting within the first week (especially first 3 days) is most likely due to transmission from mother (vertical transmission). Late onset meningitis, presentation after the first week of life, suggests hospital or community acquisition. In India, the etiological organisms for both early and late onset meningitis are similar. However, in developed countries the etiology is different for the two types of presentation.

*Klebsiella* spp, *Staphylococcus aureus*, and *Escherichia coli* are the predominant causal organisms reported in India. The less common causative agents are *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus agalactiae* (GBS) and *Listeria monocytogenes*. In neonatal infants, who have prolonged duration of hospitalization and invasive treatment,

meningitis may be caused by resistant gram-negative organisms, *Staphylococcus* and fungi. Resistant strains of *Staphylococcus* such as methicillin-resistant *S. aureus* (MRSA) and *S. epidermidis* (CONS) are increasingly being reported at present.

Group B *Streptococcus*, also known as *Streptococcus agalactiae*, is the leading cause for early onset meningitis in western countries, closely followed by *E. coli*. In late onset meningitis, *S. aureus*, CONS and gram-negative bacilli are the predominant causes. The other less common pathogens include *Listeria monocytogenes*, *S. pneumoniae*, *Enterobacter* spp, *H. influenzae*, *Citrobacter* spp, *Pseudomonas* spp and *Serratia* spp.

This difference in etiology can be attributed to a number of factors. India, being a semitropical country, bacteria like *S. aureus* and gram-negative bacilli grow easily while, relatively fragile bacteria like *H. influenzae*, *N. meningitidis* and *S. agalactiae* do not grow that well.

## PATHOGENESIS

The pathogenesis of neonatal meningitis has been studied extensively in animal models, and from observational studies of human cases. Newborn infants have deficiencies in specific and nonspecific immunity. Specific humoral immune deficiencies include lack of mucosal IgA and IgG in preterm infants born before 32 weeks gestation. There is a weakened production of these antibodies because of the immaturity of the antibody producing B cells and plasma cells, and decreased T- helper cells. Deficiencies in nonspecific immunity include impaired leukocyte chemotaxis, phagocytosis and bactericidal activity. Also, they have lower fibronectin concentrations that contribute to diminished opsonization and phagocytosis. These deficiencies are more prominent in preterm infants.

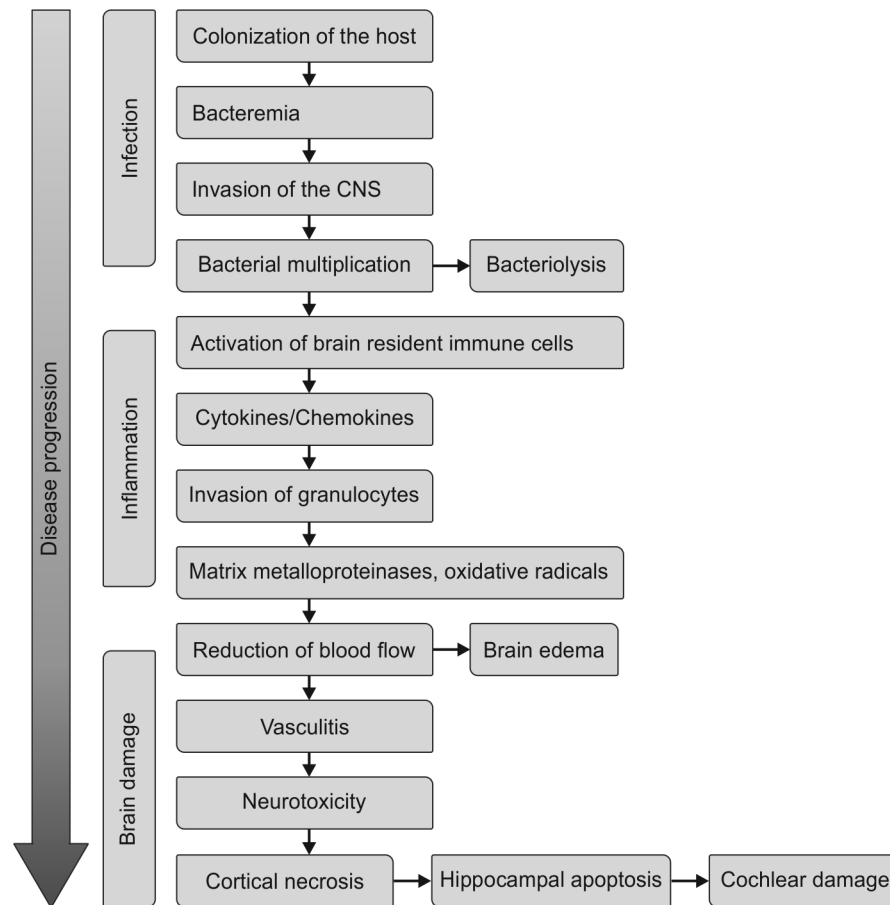
The pathophysiologic process starts with bacterial colonization and its invasion into central nervous system. This leads to multiplication of bacteria in ventricular and subarachnoid spaces, which in turn activates inflammatory cascade. This process, in combination with host factors, results in brain damage (**Fig. 1**).

The routes through which the meninges can be infected are hematogenous spread in generalized sepsis, focal infection with secondary bacteremia and direct inoculation from a congenital defect like open meningocele or dermal sinus. Some bacteria are associated with an increased predilection to cause neonatal meningitis because of their specific characteristics. Those that are closely linked to meningitis are the capsular polysaccharide of GBS type III, K1 antigen of *E. coli*, and *L. monocytogenes* type IVb.

The steps involved from colonization to CNS invasion of the bacteria are described in **Flow chart 1**. Bacterial adhesins are necessary for optimal adhesion of bacteria to the mucosal epithelium and specific endopeptidases (secreted by bacteria) inactivate secretory IgA antibodies. The bacteria enter the mucosal barrier through or between the epithelial cells. Once in the systemic circulation, the polysaccharide capsule of the pathogen aids in the survival in the blood by mediating resistance to complement-mediated lysis and phagocytosis by polymorphonuclear (PMN) leukocytes and macrophages. Finally, the pathogens cross the blood brain barrier transcellularly or paracellularly to reach the CNS.

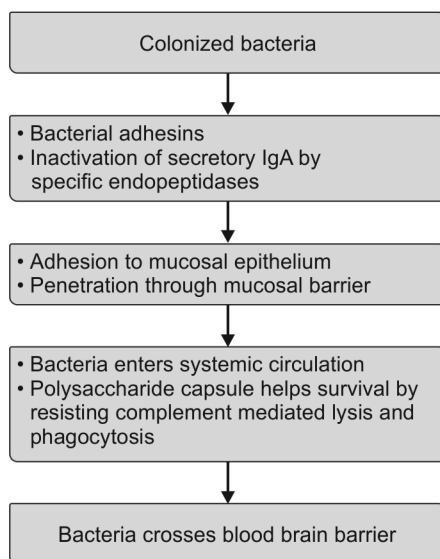
There is rapid multiplication of bacteria in the brain due to the impaired host defense mechanisms at the blood brain barrier. When bacterial growth reaches the stationary phase or when antibiotics start working, bacteriolysis occurs releasing various bacterial components including lipopolysaccharides and peptidoglycans which trigger the inflammatory reaction locally. Immune system in the CNS, including macrophages, dendritic cells and microglia cells, activate brain cells to produce inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6. CSF pleocytosis also happens as a result of this immune recognition. This inflammatory reaction





**Figure 1** Progression of meningitis

**Flow chart 1** Invasion of CNS by the bacteria



and cellular activation result in release of several inflammatory mediators such as matrix-metalloproteinases and reactive oxygen species, both of which play a key role in the development of brain injury. The resultant pathophysiological events include microglial proliferation, cerebral vasospasm, thrombosis and release of excitatory amino acids and free radicals.

The pathological changes observed in infants with meningitis include cerebral edema, subdural effusion, ventriculitis, gliosis, infarction, cortical necrosis, multicystic encephalomalacia, hippocampal apoptosis and cochlear damage.

## CLINICAL FEATURES

Clinical presentation of neonatal meningitis is often subtle, nonspecific, atypical and not different from that of sepsis. The most commonly reported symptoms are fever, lethargy, poor feeding, irritability, seizures and respiratory distress. They can also present with hypothermia, apnea, pallor, respiratory failure and shock. Neurological symptoms and signs, which include stupor, seizures, bulging anterior fontanel, extensor posturing/opisthotonus (**Fig. 2**), nuchal rigidity (very rare) and focal cerebral signs, are less often observed but could be late signs of neonatal meningitis.

The clinical features may be affected by other factors such as gestational age, prior antibiotic treatment and postnatal age. There are no data available currently on timing of onset of these clinical features. Hence, the clinician should have a high index of suspicion of meningitis when evaluating a sick newborn infant.

## DIFFERENTIAL DIAGNOSIS

The clinical features for neonatal meningitis are nonspecific and a variety of other conditions share similar clinical presentation. The clinical picture in neonatal meningitis, in addition to sepsis, may also be due to other noninfectious conditions of the newborn infants. It is important to rule out cardiac and metabolic conditions



**Figure 2** Baby showing opisthotonus posturing

when an infant presents with respiratory distress, lethargy and poor feeding with or without shock. The neurological features of meningitis such as seizures and tone abnormalities could also be due to hypoxic ischemic encephalopathy, hemorrhage, stroke and cerebral edema. Hence, it is important to elicit careful history and perform complete clinical examination in all sick newborn infants.

## APPROACH TO DIAGNOSIS

The definite diagnosis of neonatal meningitis is often difficult as clinical signs are nonspecific and only 30–50% of cases of meningitis have positive blood culture. Lumbar puncture (LP) to examine the cerebrospinal fluid (CSF) is the only way to confirm the diagnosis of meningitis. A comprehensive evaluation of CSF includes gram-stained smear examination, bacterial culture, cell count with WBC differential examination, and quantification of glucose and total protein. Normal values for CSF indices (**Table 1**) are different from that of older children and adults.

Normal polymorphonuclear cells will be around 60% of WBC count in CSF. CSF glucose is usually 70–80% of plasma glucose with the minimum normal value of 50%. Hence, it is important to measure plasma glucose just before performing LP.

Positive CSF culture confirms the diagnosis, while raised WBC count with predominant polymorphonuclear leukocytes, raised protein and low glucose (hypoglycorrhachia) supports the diagnosis of meningitis. These CSF abnormalities are more marked in gram-negative meningitis than those cases caused by GBS or *Listeria monocytogenes*. Treatment is initiated if CSF WBC count is more than  $10/\text{mm}^3$  or glucose less than 25 mg/dL or protein more than 170 mg/dL in preterm infants, and CSF WBC count more than  $8/\text{mm}^3$  or glucose less than 20 mg/dL or protein more than 120 mg/dL in term infants. Clinical judgment will have to be used if results are inconclusive.

The indications for performing CSF examination in newborn infants remain debatable, particularly in infants with no neurological signs or those not severely ill. Many recommendations have suggested that CSF examination should be

done in any newborn infant with suspected sepsis along with blood culture, as around 25% of cases of sepsis were associated with meningitis. However, recent studies have questioned the need for CSF examination in all neonates with suspected sepsis, especially in well infants with risk factors for sepsis who are under 1 week of age. The incidence of meningitis in early onset sepsis is low and the yield from routine CSF analysis in the first week of newborn life is also low. CSF examination should be part of the septic work-up in late onset disease. The contraindications for performing CSF examination are not many; it should be avoided in hemodynamically unstable infants and in those with thrombocytopenia.

Timing of LP is crucial in the interpretation of CSF results. In the presence of meningitis, CSF culture and Gram stain could become negative if LP was performed after administering antibiotics. However, CSF pleocytosis and raised protein may persist for days even after commencing antibiotic course. Hence, it is important to perform LP before antibiotic administration whenever possible, to get correct results. Furthermore, once CSF is collected, it should be analyzed as soon as possible or within 30 min of collection. It has been shown that WBC count and glucose in CSF rapidly fall with time.

The need to repeat LP after 48 hours of antibiotics is controversial. However, many recommend it, as it may have therapeutic and prognostic implications. Delayed clearance of a microorganism, when associated with no or partial clinical improvement, could indicate antibiotic resistance or a complication of meningitis such as brain abscess. Repeat LP is not recommended for those who are making good clinical recovery and the causative organism is susceptible to the given antibiotic treatment. It is recommended for those who have persistent pyrexia and raised acute phase reactants, and clinical deterioration with new neurological findings.

At times, common complication of LP can be traumatic tap. Several calculations and formulae have been proposed and studied, but none of them have provided a consistent result towards diagnosing or excluding meningitis in pediatric population, especially in newborn infants. Hence, once the traumatic LP is obtained, it is important to continue the antibiotic treatment, and then await the culture results. If LP is needed in desperate situations such as strong clinical suspicion, presence of neurological signs and positive blood culture, the procedure can be repeated 24 hours after the traumatic tap.

## OTHER INVESTIGATIONS

Blood culture is usually positive, as neonatal meningitis is commonly associated with or secondary to sepsis. However, it has been shown that around 15% of cases of neonatal meningitis with positive CSF culture may have negative blood cultures.

Nucleic acid amplification tests such as polymerase chain reaction (PCR) assays have been assessed for detecting the presence of bacterial DNA in CSF from infants with bacterial meningitis. Studies suggest a high diagnostic value in detecting microorganisms such as *H. influenzae*, *S. pneumoniae* and *N. meningitidis*. However, data on detection of GBS and *L. monocytogenes* is limited. Before considering implementing this test as a routine part of investigation, more information is needed on the cost effectiveness, prognostic value and usefulness in India.

## Cranial Ultrasound

Ultrasound should be performed initially as a baseline study in cases of neonatal meningitis and should be followed up with repeat scan if any clinical deterioration occurs or rapid increase in head circumference is noted (**Figs 3 and 4**). Complications of meningitis such as ventriculitis, secondary hemorrhage, infarction, hydrocephalus pyocephalus and abscess can all be assessed through ultrasound.

**Table 1** Normal CSF indices for newborn infants (means, range)

Newborn infants	White blood cells ( $\text{mm}^3$ )	Protein (mg/dL)	Glucose (mg/dL)
Preterm	10 (0–30)	100 (50–300)	50 (24–63)
Term (less than 7 days old)	5 (0–20)	60 (30–250)	52 (34–119)
Term (more than 7 days old)	3 (0–10)	50 (20–80)	52 (34–119)

### Computed Tomography Scan

Computed tomography scan is valuable at all stages of neonatal bacterial meningitis. In the acute stage, CT scan may provide information regarding the degree of cerebral edema (small size of ventricles), the occurrence and site of block to CSF flow (dilated ventricles) (**Figs 5A and B**), major infarction (cerebral area of increased or decreased attenuation, depending on the hemorrhagic component to the infarction), the type of associated encephalopathy (e.g., periventricular hypo-attenuation secondary to periventricular leukomalacia), and the presence of abscess or subdural collection. In a study of 45 infants with neonatal gram-negative bacterial meningitis, CT findings were normal in only 30%, demonstrated hydrocephalus in 44%, changes consistent with ischemic lesions in 29%, abscess in 18%, and subdural effusion in 7%.

### Magnetic Resonance Imaging Scan

Magnetic resonance imaging scan is recommended for infants with focal neurological abnormalities, persistent infection or clinical deterioration. It is the imaging method of choice for identifying lesions such as ventriculitis, hydrocephalus, subdural empyema, brain abscess and thrombosis. In addition, diffusion-weighted

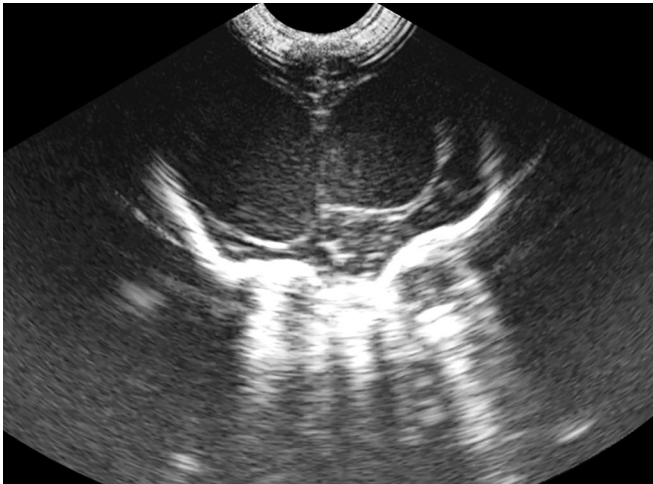
MRI shows ischemic lesions and brain edema more effectively and earlier than CT scan. Identifying these complications early will facilitate in early management and influencing the outcome positively.

### TREATMENT

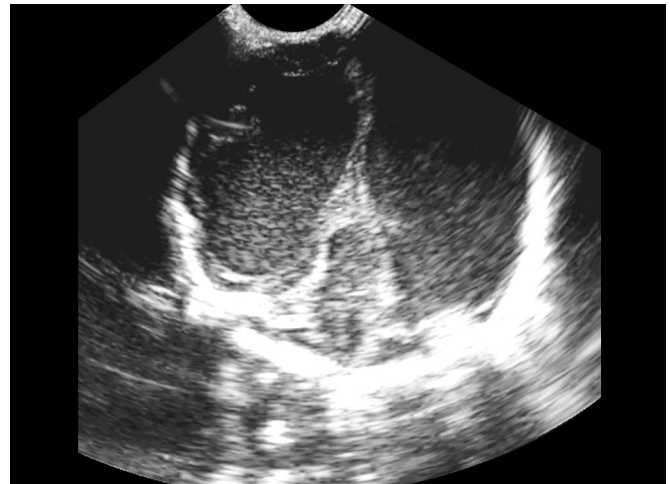
Early diagnosis and prompt treatment is essential in the management of neonatal meningitis in order to prevent adverse outcome. Treatment is divided into three parts, supportive treatment, antibiotic treatment and adjunctive treatment.

### Supportive Treatment

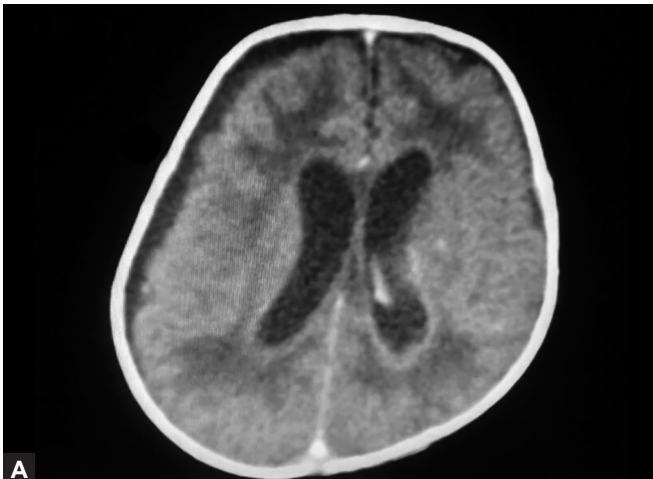
The survival of a sick newborn with meningitis depends upon aggressive supportive care. Care should be taken to avoid hypo or hyperthermia and the infant should be nursed in a thermoneutral environment. Oxygen saturation should be kept in the normal range and assisted ventilation may be needed for respiratory support on some occasions. In cases of septic shock, adequate fluid resuscitation is important in the management for improved survival. Furthermore, inotropes may be required for maintaining normal blood pressure. Septic shock remains one of the risk factors



**Figure 3** USG cranium coronal section at the level of frontal lobe showing ventricular dilatation and turbid CSF, pyocephalus



**Figure 4** USG cranium coronal section at the level of parieto-occipital lobe showing ventricular dilatation and turbid CSF, pyocephalus



**Figures 5A and B** Axial CT with contrast showing ventricular dilatation with marginal contrast enhancement, ventriculitis



for poor outcome in cases of neonatal meningitis. Blood products like platelets and fresh frozen plasma may be needed to correct thrombocytopenia or coagulation abnormalities. The infant should be monitored for hypo or hyperglycemia regularly and need to be treated accordingly. Early recognition and prompt referral to the appropriate healthcare delivery system is vital.

## Antibiotic Treatment

This is the specific treatment for neonatal meningitis. Early use of appropriate antibiotics is vital for a good outcome. The antibiotic treatment should cover likely pathogens and have excellent CSF penetration. The decision on selecting the antibiotic depends on current local prevalence and antibiotic resistance profile of pathogens. The safe combination therapy for suspected meningitis would probably be ampicillin, gentamicin or amikacin and a third generation cephalosporin (such as cefotaxime). This combination is likely to cover the probable pathogens such as gram-negative bacilli, *Staphylococcus*, GBS and *L. monocytogenes*. However, it is best to have one's own unit-specific antibiotic policy based on the profile of locally prevalent pathogens and antibiotic sensitivity. If meningitis is likely to be hospital acquired, cloxacillin or vancomycin should be considered to cover *Staphylococcus* in addition to aminoglycoside and cefotaxime. It is probably prudent to use vancomycin in the combination for suspected hospital-acquired infections as they are usually caused by CONS and MRSA. In late onset meningitis, resistant gram-negative bacilli are common, so, a third generation cephalosporin along with an aminoglycoside would be a better combination to treat than others. Third generation cephalosporins are effective against major pathogens of neonates and it has been used worldwide for the same purpose. They have good CSF penetration. Cefotaxime is often preferred in neonatal infections than ceftriaxone as ceftriaxone can cause jaundice (and kernicterus) by having high affinity for albumin. The suggested empirical antibiotics are listed in **Table 2**. Empirical therapy should be upgraded to second line if clinical improvement fails to occur or new signs appear in 48 hours after starting first line treatment.

**Table 2** Empirical choice of antibiotics for treatment of neonatal meningitis

Clinical scenarios	Antibiotics
First line Early onset/community acquired	Ampicillin, gentamicin or amikacin, and cefotaxime
Second line Hospital acquired or resistant strains likely	Cloxacillin or vancomycin, and gentamicin or amikacin, and cefotaxime

The choice of antibiotics for definitive therapy, once the pathogen is known (positive CSF and/or blood culture), is usually straightforward. Suggested antibiotics for specific microorganisms are mentioned in **Table 3** and the doses in **Table 4**.

The duration of antibiotics in neonatal meningitis has been discussed widely in literature. Currently, there is little evidence to guide the exact duration of antibiotics for neonatal meningitis. However, it is largely recommended that antibiotics should be given for at least 3 weeks for all cases of neonatal meningitis. This duration should be considered as a minimum duration as in some cases, it might need to be extended further. It is important to monitor the following during treatment—head circumference measurement twice weekly, and daily neurological examination to detect any focal neurological deficits. Cranial ultrasound in the first week and at the end of antibiotic therapy should be performed to look for ventricular size, ventricular wall enhancement, midline shift and intraventricular debris. The use of intraventricular antibiotics has been evaluated in several studies. However, Cochrane review recommends avoiding intraventricular antibiotics as a part of treatment in neonatal meningitis.

## Antibiotic Resistance and Newer Antibiotics

Antibiotic resistance is a major problem worldwide with local variations. *Staphylococcus* and *Pneumococcus* resistance to antibiotics has been reported in both developing and developed countries. In India, increasing antibiotic resistance has been reported, particularly for gram-negative organisms to first line antibiotics. This could be ascribed to several factors such as indiscriminate use of antibiotics and lack of surveillance. Newer antibiotic like cefepime, a fourth generation cephalosporin, has greater stability against  $\beta$ -lactamases and better CSF penetration than ceftriaxone. Cefepime has broad-range of activity against most bacteria causing meningitis. Carbapenems such as meropenem and imipenem possess the widest range of activity against gram-positive and gram-negative bacteria. The safety and efficacy of meropenem is similar to that of third generation cephalosporins. Fluoroquinolones (gatifloxacin and moxifloxacin) have good CSF penetration and better in vitro sensitivity against gram-positive bacteria than many antibiotics. Tigecycline, a glycylglycyl antibiotic, is active against many gram-positive and gram-negative bacteria. Aztreonam (for gram-negative organisms) and linezolid (for gram-positive organisms) are emerging antibiotics that have shown promising results in the treatment of meningitis. These antibiotics should be used cautiously, and only in cases of meningitis caused by resistant microorganisms.

**Table 3** Specific antibiotics for bacterial meningitis based on causative microorganism

Microorganisms	Recommended antibiotics	Alternative antibiotics
Enterobacteriaceae ( <i>E. coli</i> and <i>Klebsiella pneumoniae</i> )	Cefotaxime and gentamicin/amikacin	Meropenem, aztreonam, ciprofloxacin
<i>Staphylococcus aureus</i> (methicillin sensitive)	Flucloxacillin	Vancomycin, meropenem
<i>Staphylococcus aureus</i> (methicillin resistant)	Vancomycin	Linezolid
<i>Staphylococcus epidermidis</i> (CONS)	Vancomycin	Meropenem
<i>Streptococcus agalactiae</i> (GBS)	Ampicillin or penicillin G and gentamicin	Cefotaxime, ceftriaxone, vancomycin
<i>Listeria monocytogenes</i>	Amoxicillin/Ampicillin or penicillin G and gentamicin	Trimethoprim-sulfamethoxazole
<i>Streptococcus pneumoniae</i>	Ampicillin or penicillin G	Cefotaxime, cefepime, meropenem
<i>Pseudomonas aeruginosa</i>	Ceftazidime or cefepime	Aztreonam, meropenem
<i>Acinetobacter baumannii</i>	Meropenem	Colistin, polymyxin B



**Table 4** Recommended doses of commonly used antibiotics in neonatal meningitis

Antibiotics	Preterm ( $< 7$ days of age) mg/kg/dose	Preterm ( $> 7$ days of age) mg/kg/dose	Term (0–7 days of age) mg/kg/dose	Term ( $> 7$ days of age) mg/kg/dose
Ampicillin	100 twice daily	100 thrice daily	100 thrice daily	100 four times daily
Amikacin	15 once daily	7.5 thrice daily	10 twice daily	10 thrice daily
Cefotaxime	50 four times daily	50 four times daily	50 four times daily	50 four times daily
Ceftazidime	50 twice daily	50 thrice daily	50 thrice daily	50 thrice daily
Ceftriaxone	50 once daily	50 once daily	50 once daily	75 once daily
Gentamicin	2.5 twice daily	2.5 thrice daily	2.5 twice daily	2.5 thrice daily
Cloxacillin	50 twice daily	50 thrice daily	50 thrice daily	50 four times daily
Penicillin G	1,00,000 U twice daily	1,00,000 U thrice daily	1,00,000 U thrice daily	1,00,000 U thrice daily
Meropenem	40 twice daily	40 thrice daily	40 twice daily	40 thrice daily
Vancomycin	15 twice daily	15 thrice daily	15 twice daily	15 thrice daily

## Adjunctive Treatment

### Steroids

The pathophysiology of brain injury in meningitis involves series of inflammatory reactions and correlates with severity of inflammation in CSF. The use of corticosteroids in meningitis has been studied extensively in animal models as well as in children and adults with meningitis. A recent systematic review, which included 44 studies, concluded that corticosteroids significantly reduced hearing loss and neurological outcome in developed countries, but did not reduce mortality. There are limited information available based on neonatal studies. One RCT from Jordan showed no benefit from the use of corticosteroids. However, a recent study from India, which included 80 newborn infants, showed significant reduction in mortality in the corticosteroid group. But, there are several limitations in the study including methodological issues. Hence, corticosteroids cannot be recommended for neonatal meningitis on the basis of current evidence.

### Glycerol

An osmotic diuretic, has been shown to increase plasma osmolality in children with meningitis, which in turn reduce cerebral edema. A recent study from South America showed that it was effective in preventing severe neurological sequelae in children with bacterial meningitis. However, a randomized clinical trial from Malawi on adults with meningitis showed that glycerol was harmful with increased mortality. Furthermore, there are no studies of its use in neonatal meningitis.

## OUTCOME

The mortality rate is high in neonatal meningitis, but it varies with the nature of the organism, the age of the infant and the quality of care provided. In developed countries, overall mortality rate in neonatal meningitis has fallen over recent decades from 50% in 1970s to less than 10% in recent years. However, in developing countries, mortality remains high in the range between 40–58%. The poor prognostic factors are listed in **Box 2**.

### BOX 2 Poor prognostic factors for mortality in neonatal meningitis

- Male sex
- Prematurity
- Low birthweight
- Meningitis due to gram-negative organism
- Delay in diagnosis and initiation of antibiotic treatment.

The incidence of neurological sequel ranges from 40–55% as reported from various studies in India, while around 20–30% in developed countries. The spectrum of neurological sequel in India is similar to that of developed countries. The adverse outcome following bacterial meningitis is mentioned in **Box 3**. There are several risk factors that can predict later adverse neurological outcome. These factors include young age at presentation, low birthweight, need for inotropes to maintain blood pressure, focal neurological deficits, seizures lasting for several days, under nutrition, delay in starting treatment, abnormal cranial ultrasound findings (like hydrocephalus) and male sex. The incidence of adverse outcome is more in meningitis caused by gram-negative organism than those by gram-positive organisms. Furthermore, adverse outcome depends on the causative organism as well. Hearing loss has been reported commonly in meningitis caused by *H. influenzae* and *S. pneumoniae*. The prognostic value of amplitude integrated EEG in neonatal meningitis has been studied. Low voltage background pattern, less frequent sleep wake cycling and frequent seizures predicted adverse outcome. Brain imaging, specifically MRI scan of the brain, can help us to identify the complications early and guides us to prevent the severity of adverse outcome.

### BOX 3 Possible outcomes following neonatal meningitis

#### Adverse clinical outcomes

- Seizure disorder
- Cerebral palsy
- Hydrocephalus
- Sensorineural hearing loss
- Cognitive and behavioral problems
- Vision impairment
- Speech and language disorders
- Global developmental delay.

## PREVENTION

Preventive strategies include intrapartum antibiotic prophylaxis, better infection control measures and earlier diagnosis and adequate treatment to improve the outcome. Intrapartum antibiotic prophylaxis for GBS-colonized women or those who have clinical risk factors for infection have effected a reduction of early onset GBS infection and therefore, meningitis in developed countries. However, this may or may not prevent early onset infection in India, as the causative organisms are different.

It is essential to prevent transmission using optimal hand-hygiene and better education of healthcare staff. It is also important to avoid catheter-induced infections by removing indwelling catheters such as the long lines and umbilical catheters as soon as possible. In order to prevent adverse outcome following neonatal meningitis, it is vital to diagnose it early and institute appropriate management.

## OTHER CAUSES OF NEONATAL MENINGITIS

### **Candida Meningitis/CNS infection**

The incidence of CNS involvement in candida infection is nearly 25%. *Candida albicans* is the most often observed spp with neonatal infection, but *Candida parapsilosis* is also seen in some NICUs. The increase in incidence of *Candida* in NICUs is attributed to interventions such as prolonged intubation, indwelling vascular devices, steroid therapy, parenteral nutrition, and frequent and prolonged use of broad-spectrum antibiotic therapy. The risk factors associated with fungal infections are mentioned in **Box 4**.

#### **BOX 4 Risk factors for candida infection in newborn infants**

- Preterm infants (less than 32 weeks gestation)
- Intrauterine growth restriction
- Prolonged umbilical or central vascular catheter use
- Total parenteral nutrition use
- Mechanical ventilation
- Prolonged antibiotic use
- Use of corticosteroids.

Candida infection of CNS is essentially the result of blood-stream infection. The clinical signs and symptoms are nonspecific, and similar to bacterial meningitis. Diagnosis of CNS involvement in candida infection is difficult as CSF analysis may be negative with normal CSF cell count and biochemistry. Candida isolation from CSF culture is suggestive of meningitis and never should be dismissed as contaminant. However, CSF culture may be sterile in cases of CNS infection without meningeal involvement. In these situations, diagnosis can be made when *Candida* spp is isolated from another sterile site such as blood and urine, or any organ involvement (like liver or renal abscess). MRI or CT brain may be necessary to diagnose cerebral abscess.

Amphotericin B, 5-flucytosine and fluconazole are the antimicrobials of choice for the treatment of candidiasis in NICU. It is generally recommended to use amphotericin B and 5-flucytosine as combination in candida meningitis. Liposomal preparations of amphotericin B penetrate the blood brain barrier to a greater extent than the conventional preparation. The optimal

duration of the antimicrobials is unknown, but recommended until sterilization of CSF occurs.

### **Viral Meningitis**

Viral meningitis in newborn infants is usually caused by enterovirus, Coxsackie B and echoviruses 4, 6, 9, and 11. In newborn infants, it can be difficult to distinguish clinically from bacterial meningitis as they have common nonspecific signs and symptoms. CSF analysis most often reveals normal levels of protein and glucose with pleocytosis. Enterovirus PCR in CSF has been recently used as a diagnostic tool with reported high sensitivity and specificity. Infants with viral meningitis will need only minimal supportive treatment for short duration. The outcome for viral meningitis is usually good.

### **IN A NUTSHELL**

1. Neonatal meningitis is associated with high case fatality and severe neurological sequelae.
2. Bacterial meningitis is the commonest etiology in newborns and causative organisms are not different for early and late onset disease.
3. Resistant gram-negative organisms and *Staphylococcus* are common causes of meningitis in hospital acquired infections.
4. The clinical features of meningitis are nonspecific and similar to that of sepsis.
5. In strongly suspected cases of sepsis, CSF examination should be done as a part of investigations.
6. Aggressive supportive treatment including temperature stability, ventilation and fluid resuscitation plays a key role in outcome.
7. Appropriate antibiotic treatment should be initiated as soon as possible.

### **MORE ON THIS TOPIC**

- Furyk JS, Swann O, Molyneux E. Systematic review: neonatal meningitis in the developing world. *Trop Med International Health*. 2011;16:672-9.
- Grandgirard D, Leib SL. Meningitis in neonates: bench to bedside. *Clin Perinatol*. 2010;37:655-76.
- National Neonatology Forum. Guidelines. Management of Neonatal Sepsis. From: <http://nnfpublication.org/Articles/Guidelines.aspx?CatId=74>. Accessed May 7, 2014.
- Sankar JM, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. *Indian Pediatr*. 2008;75:261-6.
- Volpe JJ. *Neurology of the Newborn*. 5<sup>th</sup> ed. Philadelphia: Saunders Elsevier; 2008.

## Chapter 15.4

# Deep-seated Infections

Kumutha Jayaraman, Manigandan Chandrasekaran

Deep-seated infections should be considered when an obvious reason or focus of illness could not be identified in a sick newborn infant. They include osteomyelitis, septic arthritis, urinary tract infection (UTI) and deep-seated abscesses. High index of suspicion is necessary for diagnosing these infections as they are not uncommon and there is paucity of signs and symptoms in the early stages.

### SEPTIC ARTHRITIS

Septic arthritis is defined as an inflammation of a synovial membrane with purulent effusion into the joint capsule, usually due to suppurative infectious arthritis. The incidence of septic arthritis is low, around 0.3 per 1,000 livebirths in western countries. The exact incidence in India is not available currently. In a tertiary out-born neonatal unit in South India, the incidence of septic arthritis was 16 per 1,000 neonatal admissions in 2013 (unpublished data). Early involvement of orthopedic team is necessary to avoid crippling sequelae. Septic arthritis can destroy the joint rapidly resulting in bony erosions and fibrous ankylosis. On occasions, the disease progression can extend and result in generalized sepsis.

### Etiology

*Staphylococcus aureus* is the most common causative organism for most cases of septic arthritis in neonatal period. Gram-negative bacilli such as *Klebsiella*, *E. coli*, *Enterobacter*, group B streptococci and *C. albicans* are also responsible for smaller percentage of cases (around 20%). Prematurity and low birthweight infants are particularly vulnerable to septic arthritis. Hip, knee and elbow are the most often affected joints in young infants but any joint can be affected.

### Pathogenesis

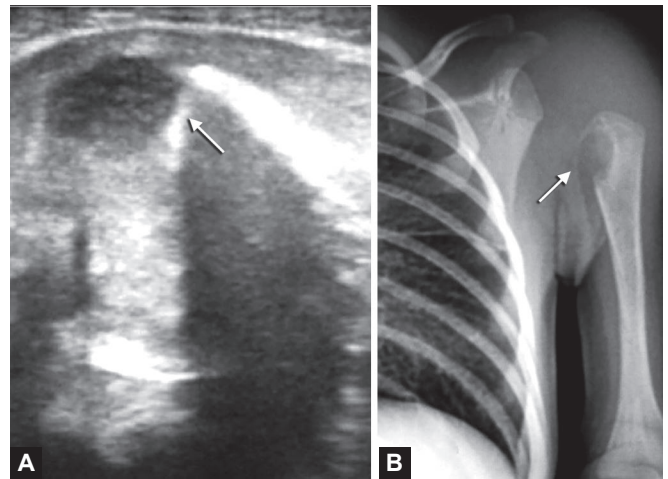
The joint may get infected by hematogenous spread, by direct extension from an adjacent area of osteomyelitis, or by direct inoculation of bacteria. Following bacterial invasion of the joint, there is an acute inflammatory response, which involves migration of polymorphonuclear cells, production of proteolytic enzymes and cytokine secretion by chondrocytes, with subsequent suppuration. The containment of suppuration within the joint, by virtue of thick anatomical barriers, results in increased intra-articular pressure and conditions for destruction of articular cartilage. Degradation of articular cartilage can begin as early as 8 hours of infection. Intracapsular synovial proliferation and an exudate or transudate of fluid, leads to stretching of the joint capsule causing laxity and possible subluxation or dislocation as a consequence.

### Clinical Features

Limitation in use of an extremity progressing to pseudoparalysis is characteristic of septic arthritis, and some infants do show external signs of inflammation (swelling, warmth or erythema), more localized to the affected joint. Evidence of pain with manipulation, such as lifting or diaper changing, is a common sign of bone infection. Newborn infant may show signs of discomfort like crying, on handling the affected joint. The growing preterm infant may present with failure to thrive. In around 20% of cases of septic arthritis, fever may be present.

### Diagnosis

Ultrasound examination of the joint will identify a joint effusion (Figs 1A and B), but the presence of echogenic debris may be more suggestive of infection (Box 1). Plain X-rays in septic arthritis of the hip may be helpful, demonstrating lateral displacement of the hip or dislocation (Figs 1A and B), but may also be entirely normal (Box 2). Abnormal radiological features usually appear late. In septic arthritis, raised white blood cell count, elevated C-reactive protein, and a falling platelet count are often observed. Bone scintigraphy and MR imaging may be needed in those infants suspected of osteomyelitis since normal results at US does not exclude osteomyelitis. Technetium bone scans are helpful when the focus of infection cannot be localized. It is highly sensitive but less specific. MRI scan is highly sensitive and specific for septic arthritis. Delay in diagnosis and treatment results in joint destruction with secondary osteoarthritis or ankylosis, growth plate arrest, dislocation, and avascular necrosis.



**Figures 1A and B** USG (A) and X-ray (B) of shoulder joint with features of septic arthritis. USG shows collection of hyperechoic fluid (as indicated by arrow) in joint space. X-ray reveals joint space widening, soft tissue swelling and lytic lesion in proximal humerus (as indicated by arrow)

#### BOX 1 Ultrasound features of septic arthritis in a newborn infant

- Joint effusion—hyperechoic fluid
- Thickening and elevation of joint capsule
- Synovial hypertrophy
- Adjacent intramuscular collection
- Displacement or dislocation of the joint.

#### BOX 2 X-ray features of septic arthritis

- Soft tissue swelling around the joint
- Widened joint space—because of effusion
- Displacement of adjacent fat pads
- Loss of visualization of white cortical line due to bone destruction marginal erosions
- Features of osteomyelitis including periosteal reaction, bone destruction, sequestrum formation
- Narrow joint space as articular cartilage is destroyed in later stages
- Displacement or dislocation of the joint.

### Treatment

**Antibiotic therapy** This should be started as soon as the diagnosis is suspected. The combination of IV vancomycin and cefotaxime should cover most organisms. Suggested antibiotic therapy is

mentioned in **Table 1**. The recommended duration of antibiotics is 4 weeks (with initial 2 weeks as IV antibiotics), however, it may be increased to 6 weeks depending on coexisting osteomyelitis.

**Surgical management** Removal of pus and inflammatory debris from the joint is an essential component of the management of septic arthritis. Aspiration of the joint is mandatory and should be performed under ultrasound guidance. When conservative treatment fails or in cases of associated osteomyelitis, arthrotomy should be performed. Immobilization of the affected joint is necessary with the splints, as long as the antibiotic therapy is given.

**Table 1** Suggested antibiotics and their dosage in septic arthritis

Gram stain	Antibiotics	Dose
Gram-positive cocci ( <i>Staphylococcus aureus</i> , Group B <i>Streptococcus</i> )	Cloxacillin	25–50 mg/kg 8 hourly
	Vancomycin	15 mg/kg 8 hourly
Gram-negative bacilli ( <i>E. coli</i> , <i>Klebsiella</i> )	Cefotaxime	50 mg/kg 8 hourly after first week of life (12 hourly in the first week of life)
	Amikacin	15 mg/kg 24 hourly
	Meropenem	20 mg/kg 12 hourly
	Piperacillin/tazobactam	90 mg/kg 8 hourly
Gram-negative cocci (meningococci, pneumococci)	Ceftazidime	25 mg/kg 24 hourly in the first week of life (12 hourly after 1 week of age)
	Ceftriaxone	50 mg/kg 24 hourly
	Piperacillin/tazobactam	90 mg/kg 8 hourly

## Prognosis

Untreated hip joint infection can result in vascular compromise and ischemic necrosis of the femoral head (**Box 3**). Early diagnosis and timely treatment can result in good outcome.

### BOX 3 Complications of septic arthritis of the hip joint

- Chondrolysis
- Avascular necrosis femoral head/neck
- Pseudarthrosis of femoral neck
- Premature closure of proximal femoral physis
- Premature closure triradiate cartilage
- Overgrowth of greater trochanter
- Dislocation of the joint.

## OSTEOMYELITIS

Osteomyelitis is relatively uncommon in a newborn infant. Incidence rates have been reported between 0.12 and 0.66 per 1,000 livebirths in western countries.

## Etiology

*Staphylococcus aureus*, *Klebsiella* and *E.coli* are frequent causes of osteomyelitis. Group B *Streptococcus*, coagulase-negative staphylococci, *Enterobacter cloacae*, and *Citrobacter freundii* are infrequent causes, particularly in extremely preterm neonates. Case reports of bone infections caused by *Mycoplasma hominis* and *Ureaplasma urealyticum* have also been reported.

## Pathogenesis

Osteomyelitis is often due to bacteremia; the spread of infection is via hematogenous route. Hence, factors that predispose to bacteremia have been recognized as risk factors for osteomyelitis

(**Box 4**). In preterm infants, umbilical catheterization is associated with a higher incidence of osteomyelitis. Catheterization of other blood vessels, particularly femoral vessels, has also shown to be a risk factor. Septic emboli may form in vascular catheters, acting as a focus for bacteremia and hence, infection.

### BOX 4 Risk factors for neonatal osteomyelitis

- Prematurity
- Birthweight less than 1,500 g
- Total parenteral nutrition
- Invasive procedures like umbilical catheterization.

Long bones are commonly affected in osteomyelitis, particularly femur, tibia and humerus. Most infections are localized to the metaphysis of long bones. This predilection to metaphysis is due to the specific pattern of developing blood vessels near the ends of the bone. The blood flow, near the end of the bone, is sluggish as the arterioles end in venous sinusoids by turning abruptly. Bacteria in the circulating blood get trapped in these areas, accumulate and multiply rapidly which leads to an infection. Furthermore, the lining of the venous sinusoids contains no phagocytic cells. Once infection sets in, inflammatory pathways are triggered, which involves migration of polymorphonuclear cells, production of proteolytic enzymes and cytokine secretion, leading to abscess formation. If not diagnosed and treated at this stage, this infection can spread and eventually lead to periosteal abscess and septic arthritis. In around 70% of cases, the adjacent joint is involved, as the infected metaphysis is intracapsular.

## Clinical Features

In newborn infants, there is often very little systemic response. Hence, many infants remain afebrile and do not appear particularly ill in early stages of infection. Later, the infant begins to develop subtle signs such as nonspecific irritability or poor handling during routine care. Subsequently, established clinical signs such as swelling of the involved limb, local erythema, and more specifically, absence of movement in the affected limb, termed as *pseudoparalysis* are observed (**Box 5**). Sometimes, osteomyelitis in neonates can present as a severe disease similar to a septic newborn and the newborn baby will be sick in those situations. Affected babies may have extreme irritability, lethargy and metabolic acidosis. The babies may have multiple subcutaneous abscesses. They may have cardiovascular and respiratory compromise, presenting in septic shock. In chronic cases of osteomyelitis, bony induration could be felt in the affected area.

### BOX 5 Clinical features of neonatal osteomyelitis

- Irritability
- Persistent crying
- Swelling of the limb
- Subcutaneous swelling due to periosteal abscess
- Local erythema
- Pseudoparalysis—absence of movement of the affected limb.

## Diagnosis

The first abnormality on the plain X-ray is swelling of the soft tissues surround the bony site of infection. This appears in around 3 days after the onset of infection. Signs of bone destruction may be observed in 7 days after the onset of infection. Articular swelling and widening of joint space may be seen in neighboring joint. Bones may evolve to have multiple areas of rarefaction later. As the bone begin to remodel soon, signs including periosteal reaction due to production of thin layer may appear around 2 weeks after



the infection. Ultrasonography may be useful to identify abscess and the site for drainage. Blood cultures are positive in around 50% of infants with osteomyelitis.

### Treatment

The main treatment for osteomyelitis is appropriate parenteral antimicrobial therapy. This should be ideally started after obtaining blood cultures. The combination of cefotaxime and vancomycin is reasonable to start until the specific organism is identified through cultures. When the clinical and/or inflammatory marker response is not observed after starting the initial antibiotics or the clinical condition deteriorates, next line antibiotics should be considered. Carbapenems such as meropenem and imipenem, possess the widest range of activity against gram-positive and gram-negative bacteria. The safety and efficacy of meropenem is similar to that of third generation cephalosporins. Linezolid, tigecycline, and daptomycin should also be considered. Tigecycline, a glycylglycyl antibiotic, is active against many gram-positive and gram-negative bacteria. Aztreonam (for gram-negative organisms) and linezolid (for gram-positive organisms) are emerging antibiotics that have shown positive results in neonatal infections. The total duration of antibiotic therapy should be 6 weeks and the entire course should be administered intravenously. It is also required to immobilize the affected limb in order to help the healing process.

### Long-term Outcome

Neonatal osteomyelitis may affect the growth plate, leading to impaired growth of the affected limb shortening. The final outcome may be apparent only in later life. When neighboring hip joint is involved in osteomyelitis involving femur, it may lead to avascular necrosis of the femoral head. In addition, it may eventually develop degenerative arthritis in the affected joint. Rapid decompression of the infected joint is necessary to have a best outcome in these situations.

## URINARY TRACT INFECTIONS

The incidence of UTI in newborn infants varies from 0.1% to 1%. It is more common in male than female infants in the first 3 months of age. It is also more common in preterm and low birthweight infants; high incidence of up to 20% has been reported in literature. UTI is more commonly associated with late onset sepsis than early onset sepsis. UTI may be asymptomatic in newborn infants, but should be diagnosed and treated promptly as it may result in long-term complications. In around 30–50% of infants with UTI, congenital urinary tract anomalies are concomitant. Hence, it is important to evaluate infants with proven UTI in detailed and appropriate manner.

### Etiology

The commonest pathogen, causing UTI in newborn infants, is *E. coli*. The virulence determinants of uropathogenic *E. coli* have been most studied comprehensively. The most consistent of those factors include adhesins, P fimbriae, cytolysins and hemolysins. Adhesins are specifically important determinants because the initial event in the pathogenesis of UTI is the adherence of *E. coli* to the urogenital mucosa by infecting *E. coli*, an event mediated by adhesins. P fimbriae appear to be especially important in *E. coli* pyelonephritis. Several studies have consistently demonstrated that these adhesins are present in nearly 100% of strains causing pyelonephritis. In addition, Gram-negative enteric bacteria such as *Klebsiella pneumoniae*, *Pseudomonas* spp., *Enterobacter* spp., and some Gram-positive cocci, including coagulase-negative staphylococci, *Staphylococcus aureus* and enterococci, can cause neonatal UTI.

*Candida* spp., has also been shown to be an important causative factor for UTI, particularly in preterm and low birthweight infants who are hospitalized for long duration.

### Pathophysiology

The pathophysiology of UTI characterizes an altered balance between host and pathogen. The abnormal anatomy of the urinary tract aids to aggravate the effects of UTI. Most UTIs start in the bladder and then ascend to produce pyelonephritis. Once bacteria are in the renal parenchyma, focal infection and inflammation develop, and the inflammatory cascade occurs. If this process is not interrupted by treatment, it can produce severe renal injury or scarring. Furthermore, if repeated infectious insults such as these continue without adequate therapy, the long-term result is significant renal scarring. Some infants are more susceptible to bacterial UTIs because their bladder mucosa expresses cell surface proteins that have a high affinity for cell surface antigens on the bacterial cell wall.

### Clinical Features

The symptoms and signs of UTI in newborn are usually generalized rather than specific for UTI. Infants usually present with lethargy, poor feeding, poor weight gain and jaundice. In one study from Iran, UTI was found in around 6% of infants with late onset jaundice. Newborn infants may also present acutely with all the signs of sepsis. Poor weight gain and low grade fever has also been reported with newborn infants with UTI. On clinical examination, signs relevant to the diagnosis of UTI include renal mass due to hydronephrosis or other congenital abnormality, and enlarged bladder suggesting outflow obstruction. Genitalia examination should be done in newborn infants with UTI to rule out urogenital anomalies including phimosis. History should be elicited about the stream of the urine in male infants to rule out posterior urethral valve.

### Diagnosis

High index of suspicion is necessary as the symptoms are nonspecific. In cases of infants with late onset sepsis, or aforementioned symptoms with no focus of infection, collection of urine specimen for analysis and culture must be included in the evaluation. Suprapubic aspiration is the widely recommended method for collecting urine. A urine culture should be repeated in case contamination is suspected, for example, mixed growth of two or more pathogens, or growth of organisms that normally constitute the periurethral flora (enterococci in infants). The culture should also be repeated in situations where UTI is strongly suspected but colony counts are low or equivocal. The number of bacteria required for defining UTI depends on the method of urine collection, as mentioned in **Table 2**.

### Further Investigations

Once a diagnosis of UTI has been proven, it is vital to initiate a radiographic workup [ultrasound study of kidneys and bladder, followed by micturating cystourethrogram (MCU)] to look for any

**Table 2** Criteria for diagnosis of UTI (as recommended by Indian Society of Pediatric Nephrology)

Method of collection	Colony count	Probability of infection
Suprapubic aspiration	Any number of pathogens	99%
Urethral catheterization	$> 5 \times 10^4$ CFU/mL	95%
Clean catch midstream	$> 10^5$ CFU/mL	90–95%

underlying structural anomalies. Around 30–50% of infants with a UTI have aberrant urinary tract anatomy. The most common anatomic abnormality associated with a febrile UTI in a neonate or infant is vesicoureteral reflux (VUR). Typically, a 2- to 4-week period has been recommended between the infection and the MCU. It is more important to ensure that the urine is sterile before performance of the MCU. The infant should be maintained on antimicrobial prophylaxis until imaging rules out any urinary tract pathology.

An important consideration is what happens when UTIs develop in a newborn with an abnormal urinary tract. With the use of prenatal sonography, most of the newborns with an obstructive uropathy are identified at birth, and antibiotic prophylaxis is initiated. However, some newborns may still present with urosepsis and obstructive uropathy gets detected only in the postnatal period. In such cases, the obstructive uropathy might have developed after the initial early normal prenatal ultrasound examination, or the problem went undiscovered because of a lack of access to prenatal care.

### Treatment

All neonatal infants with UTI should be hospitalized and treated with parenteral antibiotics. The choice of antibiotic should be guided by local sensitivity patterns. A guide to antibiotic therapy is provided in **Table 3**. Once the result of antimicrobial sensitivity is available, the treatment may be modified. The duration of antibiotic therapy should be 2 weeks. Intravenous therapy is given for the entire duration of antibiotic therapy. During an episode of UTI, it is important to maintain adequate hydration. Routine alkalization of the urine is not necessary. Paracetamol is used to relieve fever; therapy with nonsteroidal anti-inflammatory agents should be avoided. A repeat urine culture is not necessary, unless there is persistence of fever and toxicity despite 72 hours of adequate antibiotic therapy.

Sometimes, an obstructed system may be noticed during the investigations. The management may be different in these cases as the use of surgical drainage by either ureterostomy or percutaneous nephrostomy. During treatment if the newborn infant does not defervesce within 72 hours or clinical condition worsens underlying obstruction must be suspected. Under these circumstances, an ultrasound examination to rule out obstruction is warranted.

**Table 3** A guide to antibiotic therapy in newborn infants with UTI

First line	Ampicillin	50 mg/kg 8 hourly (75 mg/kg 6 hourly in infants more than 7 days old)
	Gentamicin	4 mg/kg 24 hourly
	Amikacin	15 mg/kg 24 hourly
Second line (In infants older than 7 days of age)	Cefotaxime	100 mg/kg 12 hourly (8 hourly in infants more than 7 days old)
Second line (In cases of hospital onset infections)	Vancomycin	15 mg/kg 12 hourly (8 hourly in infants more than 7 days old)
Third line	Meropenem	20 mg/kg 12 hourly (8 hourly in infants more than 7 days old)

### Long-term, Low Dose, Antibacterial Prophylaxis

It is used to prevent recurrent UTI. The antibiotic used should be effective, non-toxic with few side effects and should not alter the growth of commensals or induce bacterial resistance. The recommended antibiotic for prophylaxis in newborn infants and in first 3 months of age is co-trimoxazole [sulfamethoxazole and trimethoprim (2 mg/kg)] once a day. Some prefer amoxicillin (15–20 mg/kg once a day) as a first choice. Cephalexin (10 mg/kg/day) and cefadroxil (5 mg/kg/day) may be used as alternatives.

The indications and duration of prophylaxis depend on patient age and presence or absence of VUR. Antibiotic prophylaxis is recommended for patients with (i) UTI below 1-year of age, while awaiting imaging studies, (ii) presence of VUR, (iii) frequent febrile UTI (three or more episodes in a year) even if the urinary tract is normal. For grades 1 and 2 of VUR, antibiotic prophylaxis should be given until 1 year of age. For grades 3, 4 and 5, it should be given until 5 years of age, and also surgery should be considered in these grades if breakthrough febrile UTI occurs.

Breakthrough UTI results either from poor compliance or associated voiding dysfunction. The UTI should be treated with appropriate antibiotics. A change of the medication being used for prophylaxis is usually not necessary.

### Long-term Outcome

Infants with a renal scar (reflux nephropathy) should be counseled regarding the importance of early diagnosis and treatment of UTI and regular follow-up. Physical growth and blood pressure should be monitored every 6–12 months, through adolescence. Investigations include urinalysis for proteinuria and estimation of blood levels of creatinine. Annual ultrasound examinations are done to monitor renal growth.

### IN A NUTSHELL

1. Septic arthritis is a medical emergency that requires rapid diagnosis and treatment to avoid morbidity and mortality.
2. *S. aureus* is the most frequent causative pathogen for septic arthritis and osteomyelitis.
3. Hip is the common site for septic arthritis, while long bones are commonly affected in osteomyelitis.
4. Urinary tract infections in newborn infants should be preferably confirmed by suprapubic bladder puncture.
5. Parenteral antibiotics should be given in suspected pyelonephritis for total duration of 2 weeks.
6. Infants with UTI should be evaluated for the presence of complications, underlying anomalies or voiding dysfunction.
7. Renal ultrasound as first-line imaging in neonatal UTI, together with clinical criteria and laboratory parameters (raised inflammatory markers) determine further risk-oriented diagnostic imaging strategies (i.e., MCU).
8. Long-term antibacterial prophylaxis should be initiated in infants with urethral valves, high-grade vesicoureteral reflux, and obstructive megaureter.

### MORE ON THIS TOPIC

- Beetz R. Evaluation and management of urinary tract infections in the neonate. *Curr Opin Pediatr.* 2012;24:205–11.
- Deshpande SS, Taral N, Modi N, Singrakha M. Changing epidemiology of neonatal septic arthritis. *J Orthop Surg (Hong Kong).* 2004;12:10–13.
- Fisher RG. Neonatal osteomyelitis. *Neoreviews.* 2011;12:e374–e380.
- Samayam P, Ravi Chander B. Study of urinary tract infection and bacteriuria in neonatal sepsis. *Indian J Pediatr.* 2012;79:1033–6.
- Shariff KA, Richards EP, Townes JM. Clinical management of septic arthritis. *Curr Rheumatol Rep.* 2013;15:332.

## Chapter 15.5

# Neonatal Tetanus

Mala Kumar, Shalini Tripathi

Neonatal tetanus (NT) is an acute neurological illness occurring in the first 28 days of life. It is the second most important cause of infant mortality among the six vaccine preventable infections in developing countries. It has been largely eliminated from developed countries as a result of maternal immunization during pregnancy. However, it is still rampant in developing countries especially in Asia and Africa. In 1989, the World Health Assembly community had pledged to eliminate (incidence of less than one case per 1,000 livebirths) NT by 1995 but could not do so. In 1999, a new target date for elimination of NT was set by 2005. However, in December 2013, only 34 of 59 countries in the world had achieved maternal and NT elimination leaving 25 countries that still had not eliminated the disease.

Neonatal tetanus has been eliminated in 15 states of India in 2008. According to World Health Organization in 2011, 734 cases of NT were reported in India. Maximum numbers of cases were from West Bengal, Assam and Odisha. However, the disease is under reported. True NT burden is likely to be substantially higher than the reported numbers as many of the neonates are born at home and die there. NT has marked seasonal incidence in India. More than 50% of the total annual cases occur in the months of July, August and September.

## ETIOLOGY AND PATHOGENESIS

The causative organism for NT is *Clostridium tetani*, which is a Gram-positive obligate noninvasive anaerobic bacillus. It looks like a racquet and bears spores. These spores are very robust and are resistant to disinfectants and to boiling. They can be destroyed by autoclaving at 120°C for 20 minutes or prolonged exposure to iodine, formalin or glutaraldehyde or by gamma irradiation. The spores are abundant in the soil and animal and human feces.

They germinate in sites with a low oxidation reduction potential like in necrotic tissue. The vegetative form is destroyed by disinfectants, boiling and antibiotics. The vegetative form produces a very potent inactive neuron-specific toxin (tetanospasmin). Tetanus toxin is very potent toxin second to only botulism toxin. Its minimum lethal dose is 2.5 ng/kg in humans. The genes for the neurotoxin and its transcriptional regulator, ToxR are located in an intracellular plasmid. At autolysis, after the death of the bacterium, the toxin is released and transformed by proteases into its active form: a 100 kDa heavy chain and 50 kDa light chain. After release tetanus toxin diffuses into the adjacent muscle tissue and binds to specific glycoproteins of the plasma membrane of the alpha motor neurons and is absorbed by endocytosis. The toxin then travels by a retrograde axonal transport system and at the spinal cord and brain-stem level diffuses across synaptic spaces to enter glycinergic and gabaergic inhibitory interneurons. It then crosses the synapse to enter the presynaptic neuron and inhibits the release of inhibitory transmitters: glycine and gamma-aminobutyric acid (GABA) from vesicles. The action of the inhibitory neurons is impeded leaving alpha motor neuron excitation unopposed. This causes uninhibited firing of the motor neurons causing rigidity. There is simultaneous contraction of agonists and antagonists causing painful spasms. In addition, the toxin can have a profound effect on the autonomic nervous system causing a hyperadrenergic state. The effect of the toxin persists for weeks.

## CLINICAL FEATURES

The clinical picture of a neonate with tetanus is remarkable. The neonate is born to an unimmunized or partially immunized mother and the cord has been cut unhygienically. The incubation period, i.e., the period between the introduction of spores of tetanus and the first symptoms of disease is 3–21 days. Most neonates have the first symptom after day 2 of life but within the first 2 weeks in the form of failure to suck. This is accompanied by excessive crying, irritability and fever. This is followed by appearance of the pathognomonic signs of *trismus* (lockjaw) and *risus sardonicus* (facial rigidity). In severe cases, generalized muscular spasms which are typically stimulated by touch, noise or bright light follow. The spasms are painful and the neonate remains fully conscious throughout the illness. The neonate may assume the posture of opisthotonus and may develop respiratory arrest. As a rule, NT follows a descending pattern of nerve involvement. The first sign is trismus followed by difficulty in swallowing, stiffness of neck and rigidity of abdominal muscles especially on touch. The period between the first symptom and the first spasm is known as the period of onset. The shorter this period, the more severe is the disease. Autonomic dysfunction may be evident with the development of hypertension, hypotension, diaphoresis and arrhythmias. Recovery begins after 3 weeks and occurs over a period of about 4 weeks. In half of the neonates with tetanus omphalitis is not evident.

## Complications

The complications of NT include laryngospasm, hyperactivity of autonomic nervous system, fracture of long bones and spine, aspiration pneumonia (a common late complication), coma, and death—mostly occurs in the first week of disease.

## DIAGNOSIS

Diagnosis is essentially clinical. The typical setting is a neonate born to an unimmunized mother at home with unhygienic cord care with typical symptomatology. Cultures from the umbilical stump usually grow no organisms and are of no use in making a diagnosis. A confirmed case of NT is defined as a child with history of all three of the following:

1. Normal feeding and crying during the first 2 days of life
2. Onset of illness between day 3 and 28 of life
3. Inability to suckle (trismus) followed by stiffness (generalized muscle rigidity) and or convulsions (muscle spasms).

## DIFFERENTIAL DIAGNOSIS

### Meningitis

This may be associated with bulging fontanel along with other features of neonatal sepsis like refusal to feed, hypothermia but trismus is not present.

### Hypocalcemia

It presents in either first 2–3 days (early onset) or end of the first week-beginning of the second week (late onset). There is no trismus; infant appears normal between episodes of seizures and there are no spasms on touch. Serum calcium is low.

## MANAGEMENT

### Supportive Care

The neonate should be nursed in a dark, quiet room with minimal stimuli and facility for mechanical ventilation. The patient should be kept nil oral initially and given IV fluids. Endotracheal



intubation should be done to prevent aspiration of secretions before laryngospasm develops. Since endotracheal intubation may provoke spasms and seizures, early tracheostomy may be required.

### Neutralization of Unbound Tetanus Toxin

As soon as the diagnosis of tetanus is made and neonate is adequately sedated, single dose of human tetanus immunoglobulin [tetanus immune globulin (TIG) produced by Serum Institute of Pune] should be given intramuscularly. The dose of TIG is still undetermined. Single dose of 500 units usually suffices but dose as high as 3,000–6,000 units may be given. Infiltration of TIG into the wound and intrathecal administration to neutralize toxin in the spinal cord, is not recommended. If human TIG is not available equine antitoxin (1,500–3,000 unit) can be given intravenously or intramuscularly after sensitivity testing (0.1 mL intradermal injection in a 1:10 dilution). Pooled intravenous immunoglobulin also contains 4–90 U/mL of TIG, but the dose of IVIG for treating NT is not known.

### Antimicrobial Therapy

Conventionally Penicillin G in a dose of 100,000 units/kg/day IV divided every 4–6 hourly for 10–14 days is the antibiotic of choice. Metronidazole (30 mg/kg/day) divided 6 hourly is equal or better than Penicillin G as Penicillin G is a GABA antagonist just like tetanus toxin.

### Treatment of Muscle Spasms

First priority in NT should be to decrease muscle spasm. Benzodiazepines with or without neuromuscular blocking agents are the mainstay of symptomatic therapy for NT. Benzodiazepines are GABA agonists and thereby antagonize the effects of the toxin. Diazepam is proved to be effective in decreasing spasms without depression of cortical centers. It is started at a dose of 0.1–0.2 mg/kg/dose every 3–6 hourly. If spasms are not controlled, then can be increased to 0.4–0.6 mg/kg/dose. High dose diazepam can also be given in a dose of 10–40 mg/kg/day as IV infusion. The presence of a ventilator as a backup is a must while using high doses of diazepam. The propylene glycol present in the injectable preparation of diazepam may cause lactic acidosis, which should be monitored. Diazepam is continued over 2–6 weeks with gradual withdrawal as sudden withdrawal may cause withdrawal reaction. Gradual withdrawal is done by decreasing 10% of its dose every third day. Midazolam is given in a dose of 0.05–0.15 mg/kg/dose slowly IV over more than 15 minutes (with a final infusion concentration of 0.5 mg/mL of normal saline or dextrose); it can be repeated after 2–4 hours or be given as a continuous infusion in a dose of 0.1–0.2 µg/kg/minute. Lorazepam can also be given in a dose of 0.05–0.1 mg/kg/dose IV over more than 5 minutes. It can be repeated after 10–15 minutes if necessary. Midazolam has the advantage of not having propylene glycol, thus avoiding lactic acidosis.

If the muscle spasms are not adequately controlled by benzodiazepines or threaten ventilation due to laryngospasm or respiratory muscle spasm, neuromuscular blocking agents like vecuronium/pancuronium can be used along with mechanical ventilation. Patient should be monitored meticulously while on these drugs and the drugs must be stopped once a day to assess the patient's condition. Vecuronium (0.1 mg/kg/dose, range 0.03–0.15 mg/kg/dose; IV push; q 1–2 hour as needed), has less cardiovascular side effects than pancuronium (0.1 mg/kg/dose, range 0.05–0.15 mg/kg/dose, slow IV push; q 1–2 hour as needed). Pancuronium can increase the autonomic instability by inhibiting catecholamine reuptake and causes tachycardia.

Other agents which can be used to control muscle spasm are meprobamate, phenobarbitone, chlorpromazine, dantrolene

and baclofen. Intrathecal baclofen has been proved promising in children but there are no data available in neonates. Pyridoxine (100 mg/day) in addition to the conventional treatment has been found to decrease mortality and spasm in neonatal studies but large studies are not available.

For autonomic dysfunction alpha and beta blocker—labetalol or magnesium sulfate can be used. Magnesium sulfate acts by blocking peripheral neuromuscular transmission and by decreasing the release of acetylcholine at motor end plate by motor nerve impulse. It also reduces catecholamine release from adrenal medulla and receptor responsiveness to released catecholamines. It is given by IV loading 75 mg/kg then continuous infusion at a rate of 20–50 mg/kg/hour. Magnesium levels need to be monitored as it can cause muscle paralysis by antagonizing calcium metabolism. Labetalol is given as a continuous infusion in a dose of 0.4–1 mg/kg/hour not exceeding 3 mg/kg/hour. Hypotension if present, is treated by fluid administration, dopamine and norepinephrine infusion.

### PROGNOSIS

Onset of symptoms within the first week of life, a short period of onset, high fever, tachycardia and severe spasms resulting in apnea are predictors of a poor prognosis. The most important factor affecting outcome is the kind of supportive care given. Mortality is 75% without treatment and less than 10% with wholehearted management. The cause of death is aspiration pneumonia or anoxia due to spasms. About 10–30% of survivors demonstrate neurological sequel in the form of mental retardation and spastic motor deficits due to hypoxic ischemic injury due to severe muscle spasms and respiratory compromise.

### PREVENTION

Recovery from tetanus does not result in toxoid neutralizing antibodies, so patient has to be actively immunized after recovery. Infants born to immune mothers acquire temporary immunity for about 5 months. However, if an infant is born less than 15 days after the mother's second dose of TT, the infant will not be protected. A significant level of immunity in mothers can be achieved by two doses of TT at least four weeks apart. In addition, ensuring hygiene during delivery and in cord care can be effective in preventing NT.

#### IN A NUTSHELL

1. Neonatal tetanus is a vaccine-preventable disease that can be eliminated by maternal immunization.
2. Trismus is a pathognomonic feature of NT.
3. Antimicrobial treatment, tetanus immunoglobulin, diazepam and respiratory support can reduce mortality.
4. Early intubation/tracheostomy reduces mortality.
5. Superadded bacterial pneumonia may contribute to mortality.
6. Clinical disease does not confer long lasting immunity on the infant and, therefore, active immunization with diphtheria starting at 6 weeks is a must.

### MORE ON THIS TOPIC

- Godel JC. Trial of pyridoxine therapy for tetanus neonatorum. *J Infect Dis.* 1982;145:547–49.
- Roper MH, Vandelaer JH, Gasse FL. Maternal and neonatal tetanus. *The Lancet.* 2007;370:1947–59.
- Singhi S, Jain V, Subramanian C. Post-neonatal tetanus: issues in intensive care management, *Indian J Pediatr.* 2001;68:267–72.
- UNICEF. Elimination of Maternal and Neonatal Tetanus. From: [http://www.unicef.org/health/index\\_43509.html](http://www.unicef.org/health/index_43509.html). Accessed April 15, 2014.



## Chapter 15.6

# Intrauterine Infections

Sriparna Basu, Ashok Kumar

Congenital infections are defined as those infections which are acquired through transplacental entry of organisms from maternal bloodstream into the fetus, or transmitted during passage through the birth canal. Maternal illness is usually mild and sometimes even unnoticed; however, the impact on the developing fetus may be severe enough to cause fetal loss or congenital malformation. Chronic postnatal infection with development of sequelae in later life may also be seen in some cases. Severity of manifestation depends on the gestational age of the fetus at the time of infection, virulence of the organism, extent of damage to the placenta, and the nature of maternal infection (primary versus reinfection).

## NOMENCLATURE

The first documented congenital infection is Rubella embryopathy. It was discovered by the Australian ophthalmologist Sir Norman Gregg in 1941. The acronym *TORCH* was proposed by Andres Nahmias in 1971 to include four congenital infections (*T*Oxoplasmosis, *R*ubella, *C*ytomegalovirus and *H*erpes simplex) which were at times difficult to differentiate. In 1975 Harold Fuerst proposed a new acronym *STORCH* which included Syphilis, *T*oxoplasmosis, *O*ther (Varicella zoster, Parvovirus) *R*ubella, *C*ytomegalovirus and *H*erpes simplex. Later on, to expand the list, even a bigger acronym *CHEAP TORCHES* was suggested. It included Chicken pox, Hepatitis, Enterovirus, HIV and Parvovirus. The list of Other infections continues to grow even today with identification of new etiologies and resurgence of several others. A complete list of infections is given in **Box 1**. Important congenital infections are discussed below.

### BOX 1 Intrauterine infections that can affect fetus or infant

#### Viruses

- Cytomegalovirus
- Rubella
- Herpes simplex virus
- Varicella zoster virus
- Hepatitis B and C
- Human immunodeficiency virus
- Parvovirus B19
- Measles virus
- Mumps virus
- West Nile virus
- Adenovirus
- Influenza virus
- Enteroviruses—coxsackie, echo
- Lymphocytic choriomeningitis virus
- Papilloma virus

#### Bacteria

- *Treponema pallidum*
- Group B *Streptococcus*
- *E. coli* and other gram-negative bacteria
- *Mycobacterium tuberculosis*
- *Listeria monocytogenes*
- *Salmonella*
- *Campylobacter*
- *Borrelia burgdorferi*

#### Parasites

- *Toxoplasma gondii*
- *Plasmodium* spp
- *Trypanosoma cruzi*

#### Fungi

- *Candida albicans*

## CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is the largest and most complex member of the herpes virus family infecting humans. It is the most common congenital infection, the leading cause of mental retardation from viral etiology and the most frequent nonhereditary cause of sensorineural hearing loss (SNHL) worldwide. The prevalence of congenital CMV infection varies from 0.2% to 2% (average 0.65%) in developed countries. In developing countries, the reported prevalence varies substantially, both within and among different countries. Several authors have reported prevalence as high as 6–14%.

## Transmission

Cytomegalovirus is a ubiquitous infection and spreads by close contact through saliva, blood, genital secretions, urine or breastmilk. Neonatal infection commonly occurs by three routes of transmission—intrauterine or transplacental, intrapartum, and postnatal (through breastmilk). It is estimated that 1–4% of CMV seronegative mothers become infected during pregnancy, and 30–40% of them transmit virus to the fetus. Most CMV infections during pregnancy are asymptomatic even during the acute stage of the disease. It has been reported that less than 5% of pregnant women with primary infection are symptomatic, and even a smaller percentage suffers from mononucleosis syndrome. The likelihood of fetal transmission and symptomatic disease is much higher during primary maternal infection (5–15%). Most children born to mothers with secondary CMV infection are asymptomatic at birth, and less than 10% of them develop postnatal sequelae.

Breastfeeding infants of CMV-seropositive mothers have an estimated rate of infection between 39% and 59%. The risk is higher at maternal viral load more than  $7 \times 10^3$  genome equivalents/mL. Excretion of the virus in breastmilk is maximum between 2 weeks and 2 months postpartum.

## Pathogenesis

Acute CMV infection leads to lytic virus replication, enlargement of cells with intranuclear inclusions, end-organ damage and ultimately virus-mediated cell death. Characteristic changes are seen in brain, liver, placenta and most of the other infected organs. Host inflammatory response targeting virus-infected cells may also lead to cellular damage. Factors contributing to fetal damage include gestational age of the fetus at the time of infection, immune status of the mother, extent of placental injury, viral load in the amniotic fluid, genotype of the infecting CMV strain along with fetal and placental genetic induction in response to infection and the effects of these induced genes.

## Clinical Manifestations

Symptoms and long-term neurodevelopmental sequelae are seen in 11–12.7% of congenital CMV infection. Clinical features seen in symptomatic CMV infection have been summarized in **Box 2**. SNHL is most commonly seen when CMV infection occurs in the first or second trimester. It is usually progressive, unilateral or bilateral, may even be absent at birth manifesting later in life. Incidence of CMV-induced hearing loss at birth has been recorded as 21% and 25% at 4 years of age. High incidence of mortality (about 30%) has been documented in severely affected infants. Most often deaths are secondary to hepatic dysfunction, bleeding, disseminated intravascular coagulation or superadded bacterial infections.

The important laboratory changes that may be seen include elevated alanine aminotransferase, thrombocytopenia, conjugated hyperbilirubinemia, evidence of hemolysis and elevated cerebrospinal fluid (CSF) protein.

**BOX 2 Clinical features of congenital cytomegalovirus infection**

- **Central nervous system:** Microcephaly, lethargy/hypotonia, lissencephaly with thinning of cortex, migrational abnormalities, polymicrogyria, schizencephaly, cerebellar hypoplasia, ventriculomegaly, periventricular calcification, delayed myelination, dysmyelination and white matter disease, periventricular cysts, seizure disorders, including infantile spasm
- **Ears:** Sensorineural hearing loss
- **Eyes:** Chorioretinitis, optic atrophy, cortical visual impairment, strabismus
- **Skin:** Petechiae, purpura, blueberry-muffin rash
- Prematurity/small for gestational age
- Jaundice, hepatitis
- Hepatosplenomegaly
- Pneumonia
- Hydrops
- Hypoplasia and hypocalcification of tooth enamel

**Diagnosis****Antibody Titers**

They are not reliable markers of fetal infection as maternal CMV IgG may cross the placenta, and only 20–70% of infected infants mount a weak IgM response.

**Viral Detection**

Viral detection in neonatal body fluids, such as urine, blood and saliva, by polymerase chain reaction (PCR), culture or antigen testing (pp65 antigen) within first 3 weeks of life may be done, which differentiates congenital infection from postnatal transmission. Saliva and urine samples are preferred as high levels of viruses are present in these fluids.

**Neurodiagnostic Imaging**

Cranial ultrasound is a good screening test in neonatal period though MRI of brain may be more definitive for symptomatic/affected infants.

**Other Investigations**

Ophthalmological evaluation for chorioretinitis and audiological evaluation by auditory evoked response to provide supportive evidence in symptomatic newborns.

**Treatment**

Currently, four drugs (ganciclovir, valganciclovir, cidofovir and foscarnet) have been licensed for the treatment of symptomatic congenital CMV disease involving central nervous system (CNS). Fomivirsen is also licensed for intravitreal administration to treat CMV-induced retinitis in patients with acquired immunodeficiency syndrome (AIDS). Of these drugs, only ganciclovir has been approved for treatment of neonates. Ganciclovir is administered in a dose of 12 mg/kg/day, by intravenous infusion in two divided doses for 6 weeks. All infected children should be closely monitored and followed-up at 1, 3, 6 and 12 months and then annually until school age. Monitoring includes physical, neurological and neurodevelopmental evaluation.

**RUBELLA**

Rubella is a single-stranded RNA virus, a member of the family *Togavirus*, and the genus, *Rubivirus*. In unimmunized populations, 10–20% women of reproductive age group are susceptible to rubella infection. Each year worldwide, an estimated 238,000 children are born with congenital rubella syndrome (CRS); most of these births take place in developing countries. Incidence of congenital infection in association with maternal reinfection is rare.

**Transmission**

During pregnancy, rubella virus can directly infect and replicate in the placenta. Though fetal infection can occur at any stage of pregnancy, outcome is dependent on the timing of maternal infection with respect to gestational age of the fetus. During first trimester, infection rates are highest (81% overall, but 100% infection rate is observed in first 10 weeks), decline to 25% at the end of the second trimester, and again increase to 100% during the last month of gestation. However, infection of a fetus does not result in malformation always. The risk of malformation is inversely proportional to the gestational age. Malformation occurs in 90% of infections during first 2–10 weeks, 34% of infections during 11–18 weeks, and 0–10% for those infected after 18 weeks.

**Pathogenesis**

The mechanisms of fetal damage by rubella virus are poorly understood, though it is known that the structural damage occurs secondary to defective organogenesis. It has been postulated that during maternal viremia, rubella virus reaches the fetus via the chorion. Virus-infected desquamated epithelial and endothelial cells are transported to the fetal circulation and reaching almost every fetal organ, inducing retardation in cell division, cellular apoptosis, interference with the cell cycle and tissue necrosis. Rubella virus is noncytolytic, allows cell survival at the cost of persistent infection, decreased growth rate and shortened survival time. Virus particles may also be retained in secluded tissues like lens, and virus antigens may persist in various target organs with recurrent phases of increased virus production and replication. Noninflammatory response is seen, which is the hallmark of rubella embryopathy. Rubella virus can be isolated postnatally from urine, stool, nasopharyngeal secretions and CSF with CRS. In severely affected infants, virus may persist for up to 1 year of age.

**Clinical Manifestations**

**Box 3** lists the clinical manifestations seen in congenital rubella. The classic triad of CRS consists of sensorineural hearing loss (SNHL), cataracts and heart defects. Half (~50%) of infants with CRS may appear normal at birth, but CNS abnormalities develop with time. Among the clinical manifestations, SNHL is the most common (~58%) abnormality seen in CRS. Deafness may be the only abnormality if infection occurs after 12 weeks' gestation. The retinopathy is usually benign and nonprogressive. World Health Organization (WHO) has provided the following case definitions of CRS:

- **Suspected case:** Any infant younger than 1 year in whom a health worker suspects CRS for presenting with heart disease and/or suspicion of deafness and/or one or more of the following eye signs: cataract, diminished vision, nystagmus, squint, microphthalmus, or congenital glaucoma; or when an infant's mother has a history of suspected or confirmed rubella infection during pregnancy, even when the infant shows no signs of CRS.
- **Clinically confirmed CRS case:** An infant in whom a qualified physician detects two of the complications listed below in section A or one from section A and one from section B:
  - A. Cataracts, congenital glaucoma, congenital heart disease, hearing impairment, pigmentary retinopathy
  - B. Purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease, jaundice with onset within 24 hours after birth.
- **Laboratory-confirmed CRS case:** An infant with rubella IgM antibody who has clinically confirmed CRS.
- **Congenital rubella infection:** An infant with rubella IgM antibody who does not have clinically confirmed CRS.

**BOX 3 Clinical manifestations of congenital rubella syndrome**

- **General:** Intrauterine growth retardation, prematurity, stillbirth, abortion
- **Cardiovascular:** Patent ductus arteriosus, pulmonary artery stenosis, coarctation of the aorta, myocarditis, ventricular septal defect, atrial septal defect
- **Ocular (unilateral or bilateral):** Cataract, salt-and-pepper pigmentary retinopathy, cloudy cornea, glaucoma, microphthalmia, subretinal neovascularization
- **Aural:** Hearing loss (usually bilateral, mostly sensorineural)
- **Central nervous system:** Meningoencephalitis, microcephaly, mental retardation, behavioral disorders, autism, intracranial calcifications, chronic progressive panencephalitis, hypotonia, speech defects, encephalographic abnormalities
- **Skin:** Blueberry muffin rash indicating dermal erythropoiesis, chronic rubelliform rash, dermatoglyphic abnormalities
- **Pulmonary:** Interstitial pneumonia
- **Gastrointestinal:** Hepatosplenomegaly, jaundice, hepatitis, splenic fibrosis
- **Hematological:** Thrombocytopenia (usually transient and does not respond to steroid therapy), hemolytic anemia, altered blood group expression
- **Immunological:** Hypogammaglobulinemia, lymphadenopathy, thymic hypoplasia
- **Skeletal:** Radiolucencies of long bones (most commonly seen in metaphyses of distal femur and proximal tibia), large anterior fontanel, micrognathia
- **Endocrine:** Growth hormone deficiency, thyroid disease (hypothyroidism, hyperthyroidism, and thyroiditis), diabetes mellitus (becomes apparent later in second or third decade of life)
- **Genitourinary:** Cryptorchidism, polycystic kidney, inguinal hernia, hypospadias, nephrosclerosis, nephrocalcinosis
- Dental defects

**Diagnosis**

Diagnosis can be confirmed in serum by detecting rubella-specific IgM before 3 months of age, or by detection of rubella IgG between 6 months and 12 months of age. Isolation of rubella virus from pharyngeal secretions, urine, stool, eye discharge, blood and CSF up to 1 year of age confirms the diagnosis.

**Treatment**

No specific treatment is available, only supportive management can be provided. Since neonates with CRS are likely to excrete high concentrations of rubella virus, they should be nursed in isolation to avoid the spread of infection. A multidisciplinary team is required to manage the child. The outcome depends on the severity of organ damage. Heart defects and cataract can be corrected surgically, but damage to CNS is permanent. Long-term follow-up is important, as some abnormalities may develop even beyond the first decade of life.

Effective vaccination program is already available and should be strongly encouraged to eliminate rubella and CRS.

**TOXOPLASMOSIS**

*Toxoplasma gondii* (*T. gondii*) is an obligate intracellular protozoan parasite. Three different strains, type I, II and III with variable virulence have been identified, of which type I and II are found to be associated with congenital toxoplasmosis in humans. Oocyst, excreted in cat feces, is the source of infection to humans. Oocyst may remain viable and infective in warm, moist soil, and raw meat, for up to 1 year and contaminate drinking water. Worldwide, prevalence of congenital toxoplasmosis is 1–10 per 10,000 livebirths, with an overall transmission rate of 33%. High burden of the disease is seen in South America and in some Middle-eastern and low-income countries.

**Transmission**

Vertical transmission can occur in utero or during vaginal delivery. Only primary infection during pregnancy results in congenital toxoplasmosis with an incidence of 40%. However, in women with coexisting AIDS, latent toxoplasmosis may get reactivated resulting in congenital transmission.

Majority of pregnant women with acute infection do not have any obvious symptoms. The risk of infection to the fetus and its severity depends on the gestational age at the time of maternal infection. Fetal transmission rate is 25% in first trimester, 75% in third trimester, and increases to 90% during last few weeks of pregnancy. The severity of the fetal organ damage is inversely proportional to gestational age, earlier infections being the most severe ones. HIV-positive infants with congenital toxoplasmosis have a rapid and progressive course of the disease.

**Pathogenesis**

*Toxoplasma gondii* is highly mobile and travels actively through blood and lymph and across biological barriers including placenta. Congenital toxoplasmosis is caused by the transplacental passage of tachyzoites from mother to fetus. Clinical symptoms and course of infection depend on the bulk of inoculation, virulence of the organism, gestational age at the time of infection, gender, genetic factors and immune status of the mother.

**Clinical Manifestations**

Clinical features of congenital toxoplasmosis vary widely and can manifest at different times before and after birth. Most infected newborns (70–90%) are asymptomatic at birth but up to 80% of them develop learning or visual disabilities later in life. The classic triad consists of chorioretinitis, intracranial calcifications and hydrocephalus and is found in less than 10% of infected infants. The clinical features are summarized in **Box 4**.

**BOX 4 Clinical features of congenital toxoplasmosis**

- Intrauterine growth restriction
- Fever
- Vomiting
- Maculopapular rash
- Anemia
- Generalized lymphadenopathy
- Jaundice
- Hepatosplenomegaly
- Eosinophilia
- Thrombocytopenia
- Abnormal bleeding
- **Ocular manifestations:** Chorioretinitis, chorioretinal scars, strabismus, nystagmus, optic atrophy, microcornea, microphthalmos, cataract, retinal detachment, vitritis, phthisis
- **CNS manifestations:** Meningoencephalitis, intracranial calcifications (mostly diffuse), abnormal cerebrospinal fluid (xanthochromia and pleocytosis), hydrocephalus, microcephaly, seizure disorder, bulging fontanel, abnormal muscle tone, deafness, delayed developmental milestones

**Diagnosis**

A positive toxoplasma IgG in an infant of 12 months of age is considered diagnostic of congenital toxoplasmosis, and is considered the *gold standard* for ultimate and definite laboratory diagnosis. Serological diagnosis can also be made in newborns with positive toxoplasma IgM or IgA antibody titers, 5 or 10 days after birth, respectively (in order to exclude maternal blood contamination). The immunosorbent agglutination assay (ISAGA) method for IgM and the enzyme-linked immunosorbent assay (ELISA) method for IgA have been found to have superior performance for the diagnosis of congenital toxoplasmosis in the



infant. However, it appears that the IgM ISAGA is a more sensitive method than the IgM ELISA for the diagnosis of congenital disease.

Analysis of CSF can be helpful in infants suspected of being infected with *T. gondii* and who have clinical signs and imaging studies suggestive of CNS involvement. A positive *T. gondii*-specific IgM in fluid CSF is diagnostic of congenital disease, whereas positive toxoplasma IgG titers probably reflect passive transfer of serum toxoplasma IgG. A positive *T. gondii* PCR in the CSF, peripheral blood and urine of the newborn is considered diagnostic of congenital toxoplasmosis. Congenital toxoplasmosis is one of the rare entities that can produce CSF eosinophilia or extremely high levels of protein (up to 1,000 g/dL).

## Treatment

Currently, WHO and the Centers for Disease Control and Prevention (CDC) have recommended a combination therapy with pyrimethamine, sulfadiazine and leucovorin as the standard treatment for neonates with congenital toxoplasmosis. Sulfadiazine is used at a dose of 100 mg/kg/day in two divided doses for up to 1 year; pyrimethamine is used at a dose of 1 mg/kg/day for first 6 months, then 1 mg/kg/day three times per week in second 6 months. Both these drugs are used along with folinic acid (leucovorin) at a dose of 5–10 mg three times per week. In resistant cases, trimethoprim-sulfamethoxazole, clindamycin and azithromycin may be tried in consultation with infectious disease specialist. Duration of therapy is based on severity of symptoms, age of the patient at the time of diagnosis and response to therapy. Prolonged therapy, often up to 1 year, is recommended.

## HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV) 1 and 2 are uncommon, but important causes of neonatal morbidity, occurring in 1 of 3,200 livebirths, though the prevalence of genital HSV infection varies from country to country and among different ethnic backgrounds. HSV 2 is mainly associated with genital infection and commonly results in neonatal infection. However, cases occurring after HSV-1 have also been reported. In most cases of neonatal infection, mothers do not have an active genital lesion at the time of delivery.

## Transmission

Majority of the neonatal infections are acquired intrapartum (about 85%). Infants born to mothers with primary genital herpes infections at the time of delivery have 50% risk of developing infection compared with 25% risk when mothers already are seropositive against HSV-1 (nonprimary first episode) and less than 2% risk when mothers are seropositive against HSV-2 and having recurrence of infection.

## Clinical Manifestations

The classical triad of neonatal HSV infection consists of cutaneous manifestations, ophthalmologic findings and neurologic involvement. The clinical features are listed in **Box 5**. Neonatal HSV typically presents within first 1–3 weeks after birth but presentation may be delayed up to 4–6 weeks of age. Neonates with disseminated and skin, eyes, and/or mouth (SEM) HSV disease present earlier, at 10–12 days of age, whereas infants with CNS disease present later, at 17–19 days of age. Approximately, 50% of infants with neonatal HSV disease have CNS involvement, and approximately 70% have characteristic vesicular skin lesions. At least 50% of patients suffer from long-term sequelae. Hemorrhagic pneumonitis, severe coagulopathy, liver failure, seizures and meningoencephalitis are associated with poor prognosis.

## BOX 5 Clinical features of congenital herpes simplex infection

### In utero infection

- *Skin*: Scarring, active vesicular lesions, hypo/hyperpigmentation, aplasia cutis, erythematous macular exanthem
- *Eyes*: Microphthalmia, retinal dysplasia, optic atrophy, chorioretinitis
- *Central nervous system*: Microcephaly, encephalomalacia, hydranencephaly, intracranial calcification

### Intrapartum or postpartum infection

- *Disseminated disease*: It involves multiple organs, including lung, liver, adrenals, skin, eye and brain. Common manifestations include poor feeding, lethargy, fever, apnea, convulsion, respiratory distress, hepatomegaly, jaundice and disseminated intravascular coagulation
- *CNS disease with or without skin lesions*: Common manifestations include seizures, lethargy/irritability, tremors, temperature instability, bulging fontanel
- *Disease limited to the skin, eyes and/or mouth disease*: Common manifestations include vesicles or zoster-like eruptions on skin, eyes and mouth.

## Diagnosis

Since most of the affected newborns are born to mothers who do not have current active genital HSV lesions, a high level of suspicion is necessary to diagnose HSV infection in acutely sick infants. Viral cultures should be collected from various sites, including mouth, nasopharynx, conjunctivae, rectum, skin vesicles, urine, stool, blood and CSF after 48 hours of age. For diagnosing HSV encephalitis, HSV-PCR testing should be done from CSF, though it should be remembered that one negative HSV-PCR test result does not completely rule out HSV infection and these neonates must be monitored closely up to 4–6 weeks of age. Electroencephalography and brain imaging are useful in infants where CNS infection is suspected clinically despite negative HSV-PCR results.

## Treatment

In the presence of active genital HSV lesions or prodromal symptoms at the time of delivery, cesarean section should be performed to reduce the risk of neonatal HSV transmission. Breastfeeding is not a contraindication unless there are active lesions over the breasts. Mother should wash hands before touching the baby.

All infants with suspected or diagnosed HSV infection must be treated with intravenous acyclovir at a dose of 60 mg/kg/day in 3 divided doses. The treatment should be started promptly, especially in case of disseminated infections as the starting time is crucial for prognosis. HSV infections localized to skin, eyes and mucous membranes need treatment for 14 days, whereas CNS or disseminated infections require therapy for 21 days.

## CONGENITAL VARICELLA

The incidence of varicella during pregnancy is 1–5 cases per 10,000 pregnancies. Transplacental transfer of varicella-zoster virus causes spontaneous abortion, fetal demise, and congenital anomalies. Fetal infection in first 20 weeks of gestation can result in a constellation of anomalies known as congenital varicella syndrome (CVS). The incidence of CVS is approximately 1–2%, risk increases if the infection occurs during 13–20 weeks. About 30% of symptomatic infants die in the first postnatal months. Varicella can also be life-threatening in neonates who acquire infection during delivery. Perinatal acquisition of the disease occurs in the newborn within first 10 days after birth if the mother is infected from 5 days before to 2 days after delivery. Clinical manifestations and management issues of both congenital varicella and perinatal varicella are discussed in Section 31 (Chapter 31.6).



## CONGENITAL SYPHILIS

Syphilis is a systemic sexually transmitted disease caused by the spirochete, *Treponema pallidum*. In spite of availability of accurate diagnostic tests and effective treatment, about 11 million people acquire new infections annually even today. Nearly 1.5 million pregnant women are infected with syphilis each year, and approximately half of them remain untreated and face adverse fetal outcome. As per WHO estimation, in 2009, congenital syphilis led to 2.6 million stillbirths and an additional 3.1 million neonatal deaths. In developing countries, mother-to-child transmission of syphilis contributes to one-fourth of all stillbirths and 11% of neonatal deaths. In India, seroprevalence among pregnant women is approximately 1%.

### Transmission

Intrauterine transmission of infection usually takes place between the 16th and 28th weeks of gestation, though it may occur as early as 9 weeks. The risk of transmission is directly proportional to the stage of maternal syphilis during pregnancy and gestational age of the fetus when maternal infection is acquired. In early maternal syphilis, the risk of fetal transmission can be as high as 80%, whereas infectivity decreases in late syphilis. Highest level of spirochetemia is observed during the first 2 years after infection and decreases slowly thereafter because of the development of acquired immunity. After an infection with syphilis, it takes 10–45 days for blood tests to become positive; therefore, an initial negative test does not rule out infection. High-risk pregnant women negative in the first test should be tested again later in the pregnancy or at the time of delivery.

### Clinical Manifestations

Congenital syphilis is divided classically into early and late disease. Early congenital syphilis manifests during the first 2 postnatal years (**Box 6**) and late after 2 years. Approximately, 30–40% of fetuses with congenital syphilis are stillborn, and approximately 75% of liveborn infants remain asymptomatic at birth. Most of the affected children develop varied symptoms between 3 weeks and 14 weeks after birth. Late congenital syphilis is characterized by Hutchinson's triad—interstitial keratitis, Hutchinson's teeth and SNHL.

### Diagnosis

Confirmation of the diagnosis requires demonstration of *T. pallidum* in fetal or neonatal tissues or in the placenta in dark field microscopy. Desquamated or ulcerative skin lesions or snuffles should be examined for spirochetes by dark field microscopy or fluorescent antibody techniques. Treponemal and nontreponemal serological tests can be done to diagnose infected neonates. Treponemal tests include fluorescent treponemal antibody absorption (FTA-ABS) and the particle agglutination (TP-PA) tests. Nontreponemal tests are the Venereal Disease Research Laboratory (VDRL) slide test and the rapid plasma reagin (RPR) test. Any positive nontreponemal test in the infant must be confirmed with a treponemal test. If the neonatal antibody titers are more than four times that of the mother, it indicates fetal infection. Moreover, transplacentally acquired nontreponemal (VDRL or RPR) antibody disappears in uninfected infants by 6 months of age. Passively acquired treponemal antibody [FTA-ABS and/or microhemagglutination assay (MHA-TP)] disappears by 15–18 months.

### Treatment

Infants with presumptive or confirmed congenital syphilis should be treated with aqueous penicillin G, 50,000 U/kg intravenously

#### BOX 6 Clinical manifestations of early congenital syphilis

- **Reticuloendothelial:** Generalized, nontender lymphadenopathy, anemia (hemolytic or nonhemolytic), leukopenia or leukocytosis, thrombocytopenia, hepatosplenomegaly, extramedullary hematopoiesis.
- **Mucocutaneous:** Snuffles, i.e., thick or bloody nasal discharge, laryngitis, coppery-brown maculopapular rash involving palms and soles followed by desquamation, blistering and crusting, mucous patches on palate and perineum, perioral and perianal condyloma lata. Skin lesions are highly infectious
- **Skeletal:** Symmetrical long bone lesions, more commonly seen in lower extremities, metaphyseal osteochondritis with mild to severe destructive lesions, developing within 5 weeks of infection, Wimberger sign, i.e., demineralization and destruction of the proximal tibial metaphyses, diaphyseal periostitis with periosteal new bone formation, developing after 16 weeks of infection, osteitis producing alternate linear bands of translucency and radiodensity in long bones giving a *celery stick* appearance and dactylitis with involvement of metacarpals, metatarsals and proximal phalanges.
- **Neurological:** Features of acute meningitis with cerebrospinal fluid shows pleocytosis, elevated protein low glucose and reactive Venereal Disease Research Laboratory test, untreated chronic meningovascular syphilis may lead to hydrocephalus, cerebral infarctions and cranial nerve palsies
- **Ocular:** Salt and pepper chorioretinitis, glaucoma, uveitis
- **Renal:** Immune complex mediated nephrotic syndrome seen after 2–3 months of infection
- **Pulmonary:** Pneumonia alba or obliterative fibrosis
- **Heart:** Myocarditis
- **Gastrointestinal system:** Pancreatitis, gastrointestinal inflammation and fibrosis

every 12 hours (1 week of age or younger) and every 8 hours (older than 1 week) for a total of 10 days as outlined by American Academy of Pediatrics.

### Follow-up

Infants with congenital syphilis should have serial nontreponemal tests done at 1, 2, 4, 6 and 12 months. When children are treated appropriately, the nontreponemal titer becomes nonreactive by 12 months of age. A second course of treatment should be considered in children with persistently positive titers, even at a low level. After treatment, infants with initial abnormal CSF (increased cell count or protein and positive VDRL in CSF) should have a repeat CSF examination done at 6 months of age. A positive CSF VDRL 6 months after initial treatment necessitates for a second course.

## HEPATITIS VIRUS

Acute viral hepatitis is the most common cause of jaundice in pregnancy, although the course of most of the viral infections is not affected by pregnancy itself. The incidence of vertical transmission of hepatitis A virus (HAV) infection during pregnancy or postpartum period is rare.

Hepatitis B virus (HBV) does not cross the placenta because of its large size, and cannot infect the fetus unless the maternal-fetal barrier is broken by some procedure, such as amniocentesis. Infected women transmit HBV infection to the infant during delivery. Without adequate active and passive prophylaxis, the newborn remains at high risk (70–90%) to develop a chronic HBV infection, and its long-term complications. Breastfeeding by a surface antigen of the HBV (HBsAg) positive mother does not increase the risk for acquisition of HBV infection in the infant. Perinatal acquired hepatitis B infection in a neonate born to HBsAg positive mother can be prevented by hepatitis B

vaccine and hepatitis B immunoglobulin (0.5 mL intramuscular) administered 12–24 hours within birth. This has shown to be 85–95% effective.

The prevalence of HCV among pregnant women is approximately 1%, and the rate of vertical transmission is 4–7% per pregnancy in women with detectable viremia. Mother-to-infant transmission of HCV infection can occur in utero, intrapartum or during perinatal period. The average rate of infection is approximately 4/100 infants. In utero transmission rate is about 33–50%. Transmission rate increases with HCV-RNA positivity at the time of delivery, high viral load more than  $10^6$  IU/mL, rupture of membrane more than 6 hours before delivery and fetal scalp electrode monitoring, female gender and coinfection with HIV. Infants infected through vertical transmission are otherwise asymptomatic, except elevated transaminase levels. However, cirrhosis, and rarely, hepatocellular carcinoma have been reported during childhood.

Perinatal transmission with hepatitis D virus is rare. Hepatitis E and G virus infection does not have any known effects on the fetus. However, premature delivery with high infant mortality of up to 33% has been observed.

## CONGENITAL TUBERCULOSIS

Tuberculosis remains a major global health problem and one of the leading infectious causes of death. The incidence of tuberculosis in women of child-bearing age is 2% in countries where the disease is endemic. Congenital tuberculosis is relatively rare because genital tuberculosis and tuberculous endometritis are associated with infertility. Till date, approximately 340 cases have been reported in literature.

### Transmission

Congenital tuberculosis is caused by *Mycobacterium tuberculosis* and the disease occurs when maternal tuberculosis involves the genital tract or the placenta. Congenital tuberculosis is acquired through various routes and, therefore, the clinical manifestations in the newborn can vary.

#### Transplacental

Transmission occurs by hematogenous spread of the maternal disease at any time of pregnancy. Miliary lesions are seen in placenta and the predominant organ involved in fetus is the liver.

#### Perinatal

Inhalation or aspiration of infected materials from maternal genitourinary tuberculosis during passage through the birth canal results in pulmonary or gastrointestinal tuberculosis in the neonate. The disease manifests approximately 3 weeks after birth.

#### Postnatal

Transmission from open maternal pulmonary tuberculosis or other close contacts can result in pulmonary tuberculosis in neonates.

### Clinical Manifestations

Signs of congenital tuberculosis are usually evident during the second or third week after birth and simulate neonatal sepsis of other bacterial/viral origin or any other intrauterine infections, such as syphilis or CMV infection. Common clinical manifestations include low birthweight, hepatosplenomegaly, respiratory distress,

fever, lymphadenopathy, poor feeding, lethargy or irritability, abdominal distension, ear discharge and papular skin lesions. Uncommon findings include vomiting, seizures, apnea, cyanosis, jaundice, meningitis, petechiae, progressively deteriorating liver function or sudden death.

### Diagnosis

Diagnosis is difficult because more than 50% of mothers remain asymptomatic and often are diagnosed only after congenital tuberculosis is diagnosed in their neonates. Congenital tuberculosis should be suspected in newborns who have nonresolving pneumonia, not responding to antibiotic therapy, persistent fever and hepatosplenomegaly, high CSF lymphocyte count in absence of any bacterial pathogen isolated on culture. Neonates born to mothers with known tuberculosis, especially in human immunodeficiency virus positive cases, should be thoroughly investigated to rule out congenital tuberculosis.

Diagnostic work-up includes chest X-ray, gastric aspirate examination for acid-fast bacilli (AFB), lumbar puncture and culture of body fluids. Chest X-ray may show scattered infiltrates, bronchopneumonia or consolidation. Tuberculin skin tests are usually negative in newborns with congenital or perinatally acquired infection. Hepatic granulomas may be seen in liver biopsy. Fluorescent staining of early morning gastric aspirate is relatively more sensitive, but the overall yield is less than 50%. AFB cultures have their own limitations. A minimum of 1–6 weeks is required for *Mycobacterium tuberculosis* to grow even in liquid media and the organism is isolated in less than 75% cases with other clinical evidence of pulmonary tuberculosis. PCR and other nucleic acid amplification tests can be done. Histopathological examination of placenta for granulomatous lesions and demonstration of AFB should be done in addition to routine work-up for tuberculosis in the mother.

### Treatment

Treatment should be started with a combination of isoniazid, rifampin, pyrazinamide and an aminoglycoside, such as amikacin. Total duration of therapy depends on the clinical course of the disease. Most of the studies recommend 1 year therapy (4-drug treatment for 2–3 months followed by isoniazid, rifampin for 9–10 months). All the antitubercular drugs are rapidly absorbed and well tolerated in neonates. To avoid neurotoxicity, pyridoxine (vitamin B<sub>6</sub>) should be added in exclusively breastfed infants. Corticosteroids are indicated in neonates with meningitis and pericardial or pleural involvement. In the absence of prompt treatment, prognosis may be poor, almost 50% of the neonates with congenital tuberculosis may die.

Asymptomatic infants born to mothers with active tuberculosis should receive isoniazid prophylaxis in most cases for 3 months, after which time a tuberculin skin test should be done to determine infection and need for further evaluation and treatment.

## LESS COMMON ORGANISMS

Effect of congenital infections caused by less common organisms, such as parvovirus, listeria, coxsackievirus, echovirus, measles, mumps, poliovirus, lymphocytic choriomeningitis virus (LCMV), West Nile virus and influenza virus is discussed in **Table 1**. The overall risk of symptomatic infection by these organisms is relatively low and often overlooked.

### IN A NUTSHELL

1. The acronym *CHEAP TORCHES* captures the expanded list of organisms that cause congenital infections in the newborn.
2. Cytomegalovirus, rubella and toxoplasmosis are the most common causes of chronic intrauterine infection in the fetus and newborn.
3. Herpes simplex infection is characterized by the triad of cutaneous, ophthalmic and neurologic involvement.
4. Congenital tuberculosis should be suspected in newborns who have nonresolving pneumonia, persistent fever and hepatosplenomegaly, in the absence of any bacterial pathogen isolated on culture.

### MORE ON THIS TOPIC

- de Jong EP, Vossen AC, Walther FJ, Lopriore E. How to use neonatal TORCH testing. *Arch Dis Child Educ Pract Ed.* 2013;98:93-8.
- Gomez GB, Kamb ML, Newman LM, et al. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *Bull World Health Organ.* 2013;91:217-26.
- Lamont RF, Sobel JD, Carrington D, et al. Varicella-zoster virus (chicken-pox) infection in pregnancy. *BJOG.* 2011;118:1155-62.
- Oz HS. Maternal and congenital toxoplasmosis, currently available and novel therapies in horizon. *Front Microbiol.* 2014;5:385.
- Surveillance Guidelines for Measles, Rubella and Congenital Rubella Syndrome in the WHO European Region. Geneva: World Health Organization; 2012.
- Swanson EC, Schleiss MR. Congenital cytomegalovirus infection: new prospects for prevention and therapy. *Pediatr Clin North Am.* 2013;60:335-49.

**Table 1** Clinical manifestations of less common congenital infections

Infective agent	Effects on fetus
<i>Plasmodium</i> spp	<p>Malaria infection during pregnancy may lead to abortion, low birthweight and intrauterine growth restriction, premature delivery, congenital infection or perinatal death</p> <p>Congenital malaria is defined as the presence of malarial parasites (ring forms) in the peripheral smear of the newborn within first 7 days of life</p> <p>Malarial infection may be acquired by the fetus in utero or during delivery</p> <p>Clinical manifestations in newborns are indistinguishable from neonatal sepsis and include fever, irritability, refusal to feed, anemia, jaundice and hepatosplenomegaly</p> <p>Diagnosis is made by examination of peripheral blood smears, although these can be negative in low parasitemia (&lt;50 parasites/<math>\mu</math>L blood). Malaria can also be detected by polymerase chain reaction from cord blood</p>
Parvovirus B19	Abortion, fetal anemia, hydrops fetalis, myocarditis, intrauterine fetal demise
<i>Listeria monocytogenes</i>	<p>Infection in early pregnancy may lead to abortion. Later infection may cause stillbirth or preterm labor associated with meconium-stained or greenish amniotic fluid and neonatal infection. Presents with first 2–3 days after birth with features of neonatal sepsis, congenital pneumonia or disseminated granulomatous lesions called granulomatosis infantisepticum. Microabscesses and granulomas containing the organism can be demonstrated in different organs, particularly the lungs, liver and spleen</p> <p>Ampicillin plus an aminoglycoside is the treatment of choice in infected neonates</p>
Coxsackie virus	<p>Complications are more common with group B infection than group A</p> <p>Intrauterine exposure to coxsackie B virus (CBV) may be associated with development of insulin-dependent diabetes mellitus (IDDM) in later life</p> <p>Infection early in pregnancy can cause miscarriage, congenital cardiac anomalies, birth defects and orofacial clefts</p> <p>Transplacental passage of CBV toward the end of gestation may produce severe maculopapular rash, pneumonia, myocarditis and meningoencephalitis, which may be fatal</p>
Echovirus	Congenital anomalies, hepatitis, peritonitis, coagulopathy, fetal death and IDDM in offspring in later life have been reported
Measles virus	Measles during pregnancy increases the rate of maternal complications and mortality. Fetal infection increases the chances of abortions, early fetal death and premature delivery
Mumps virus	<p>Increased risk of spontaneous abortions and fetal death</p> <p>A possible association between maternal mumps during pregnancy and fetal cardiomyopathy, especially endocardial fibroelastosis has been reported</p> <p>Perinatal mumps infection following vertical transmission is rare, may lead to respiratory distress and pulmonary hypertension. Prognosis is good</p>
Poliovirus	<p>Perinatal transmission is seen when maternal infection occurs later in pregnancy. Associated with increased rate of spontaneous abortions and stillbirths and with paralysis of the newborn infants (congenital polio)</p> <p>A possible association of intrauterine polio infection with schizophrenia has been documented</p>
Lymphocytic choriomeningitis virus	Chorioretinitis, hydrocephalus, mental retardation, visual impairment, intrauterine fetal death
West Nile virus	Infants born to mothers with symptomatic West Nile virus infection within 3 weeks prior to delivery may develop symptomatic disease shortly after birth
Influenza virus	Risk of fetal infection and congenital abnormalities is unclear

# Section 16 NEUROLOGICAL PROBLEMS OF THE NEWBORN INFANT

**Section Editor** Siddarth Ramji

## Chapter 16.1

### Seizures in the Neonates

Amit Upadhyay, Pranjali Saxena

Neonatal seizures are the frequent and distinctive clinical manifestation of neurological dysfunction in the newborn infant. These are to be actually recognized and managed for broadly three reasons. Firstly, they are significant cause of neonatal morbidity and mortality. Secondly, they may interfere with treatment measures, such as nutrition and ventilation for associated disorders. Thirdly, the seizures have been shown to be detrimental to developing brain and may cause cognitive/neurological impairment and epileptic disorders in later life.

#### DEFINITION

A seizure is defined clinically as a paroxysmal alteration in neurologic function, i.e., motor, behavior and/or autonomic function. The seizures can be:

- **Epileptic seizures** Clinical phenomena associated with corresponding electroencephalography (EEG) seizure activity, e.g., clonic seizures.
- **Nonepileptic seizures** Clinical seizures without corresponding EEG correlate, e.g., subtle and generalized tonic seizures.
- **EEG seizures** Abnormal EEG activity with no clinical correlation.

#### INCIDENCE

The National Neonatal Perinatal Database (NNPD 2002–03) data from 18 tertiary care units across India, has reported its incidence of 10.3 per 1,000 livebirths. The incidence was found to increase with decreasing gestation and birthweight—with preterm infants reporting almost twice the incidence as compared to term neonates (20.8 and 8.4 per 1,000 live-births respectively). In developed countries, the incidence in babies under 1,500 g has been reported to be as high as 57.5 per 1,000 in very low birthweight (VLBW) infants as compared to only 2.8 per 1,000 for infants with birthweights of 2,500–3,999 g in population based studies.

#### ETIOLOGY

The common causes of seizures as per NNPD from India are hypoxic ischemic encephalopathy, metabolic disturbances (hypoglycemia and hypocalcemia), and meningitis. Common causes of neonatal seizures are discussed below.

#### Birth Asphyxia

It is the most common cause of neonatal seizures in both full-term and premature infants. Multiple factors like hypoglycemia, hypocalcemia, polycythemia, intracranial bleed, etc., may contribute in isolation or in combination, to seizures in babies

with perinatal asphyxia. Seizures usually occur within the first 24 hours of birth. Seizures occurring within 4–6 hours of birth suggest intrauterine insult. Subtle, multifocal, clonic or tonic seizures can occur. It will be associated with low Apgar scores, delayed cry (for >3 min), low pH and high base deficit in arterial blood gas (ABG) analysis.

#### Intracranial Hemorrhage

Seizures due to subarachnoid, intraparenchymal or subdural hemorrhage occur mainly in term neonates, while seizures secondary to intraventricular hemorrhage (IVH) occur in preterm infants. Most seizures due to intracranial hemorrhage (ICH) occur between 2 days to 7 days of age. Subarachnoid hemorrhage often present as seizures in a *well-baby* on 2nd–3rd day of life.

#### Intracranial Infection

Seizures due to bacterial infections like meningitis occur only in or after latter half of the first week. Seizures associated with herpes simplex encephalitis also tend to occur in late neonatal period. Nonbacterial infections like neonatal encephalitis due to toxoplasma, rubella, and cytomegalovirus infection can cause seizure episodes with in the first 3 days of life.

#### Developmental Defects

Aberrations of brain development can result in seizures, which begin at any time during the neonatal period. Most aberrations are of cerebral cortical dysgenesis and neuronal migration disorders (lissencephaly, pachygyria, and polymicrogyria). They can be best diagnosed by magnetic resonance imaging (MRI) of brain.

#### Metabolic Disturbances

Hypoglycemia is most frequent in high-risk babies like preterm, small or large for gestation. The onset is usually in first 2 days. It is diagnosed by screening with glucostix and confirmed by standard laboratory values. Early onset hypocalcemia occurs in first 3 days of life most often in preterm, infants of diabetic mothers and babies with perinatal asphyxia. Late onset hypoglycemia occurs in full-term infants who avidly consume cow milk with a suboptimal ratio of calcium or magnesium to phosphorus. Hypomagnesemia is a frequent accompaniment.

#### Other Metabolic Disturbances

These are uncommon causes of seizures and include hyponatremia, hypernatremia, hyperammonemia, amino acid and organic acid abnormalities, mitochondrial disturbances, peroxisomal disorders, pyridoxine dependency, folinic acid responsive seizures, glucose transporter deficiency among other rare ones.

#### Local Anesthetic Intoxication

It occurs as a result of neonatal intoxication with local anesthetics. They can be inadvertently injected into the infant's scalp, during placement of paracervical, pudendal, or epidural block or local anesthesia for episiotomy. Two distinguishing features of local



anesthetic intoxication are: (1) pupils fixed to light and often dilated; and (2) eye movements fixed to the oculocephalic (doll's eyes) reflex. These infants improve over the first 24–48 hours (if properly supported) and anticonvulsant drugs are of questionable value.

### Drug Withdrawal

A rare cause but not an infrequent cause in developing countries. The drugs particularly involved are narcotic-analgesics (e.g., methadone), sedative-hypnotics (e.g., shorter-acting barbiturates), tricyclic antidepressants, cocaine, alcohol, etc.

### Syndromes

Epileptic syndromes are benign familial neonatal seizures, benign idiopathic neonatal seizures (5th-day fits), early myoclonic encephalopathy, early infantile epileptic encephalopathy (Ohtahara syndrome) and malignant migrating partial seizures. Nonepileptic syndromes are benign neonatal sleep myoclonus and hyperekplexia.

### PATHOPHYSIOLOGY

Seizure activity results from an excessive synchronous electrical discharge (i.e., depolarization) of neurons within the central nervous system. Depolarization is produced by the influx of sodium ( $\text{Na}^+$ ), and repolarization is produced by the efflux of potassium ( $\text{K}^+$ ). A potential across the membrane is maintained by energy dependent Na-K-ATPase pump, which extrudes  $\text{Na}^+$  and takes in  $\text{K}^+$ . Excessive neuronal depolarization may result from following reasons:

- Disturbance in energy production (e.g., hypoxemia-ischemia and hypoglycemia) can result in a failure of the ATP-dependent  $\text{Na}^+$ - $\text{K}^+$  pump.
- Relative excess of excitatory versus inhibitory neurotransmitters can result in an excessive rate of depolarization as in hypoxia-ischemia and hypoglycemia causes increase in extracellular levels of glutamate (the principal excitatory neurotransmitter in cortex) because of excessive synaptic release and diminished reuptake by energy-dependent transport in both presynaptic nerve endings and glia.
- A relative deficiency of inhibitory compared to excitatory neurotransmitters also results in an excessive rate of depolarization. The brain concentration of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter, is decreased when the activity of its synthetic enzyme, glutamic acid decarboxylase, is depressed. Calcium and magnesium normally inhibits  $\text{Na}^+$  influx by interacting with the neuronal membrane; thus, hypocalcemia or hypomagnesemia would be expected to cause an increase in  $\text{Na}^+$  influx and depolarization.

### EVOLVING CONCEPTS IN SEIZURE GENERATION

Seizures in newborns differ from those observed in older infants and children as they rarely have organized generalized tonic-clonic activity. Even seizure activity in premature infants differs from those in full-term infants. The reasons for these variation relate to developmental differences in neuroanatomy and neurophysiology.

### Neuroanatomical Features

Neuroanatomical developmental processes that occur in the perinatal period are an organization of events. These events include the attainment of proper orientation, alignment, layering (i.e., lamination) of cortical neurons, elaboration of axonal and dendritic ramifications, and establishment of synaptic connections. Only lamination is well developed in the human newborn while neuritic

outgrowth and synaptogenesis are less developed. So, the cortical connectivity to propagate and sustain a generalized seizure cannot occur in developing neonatal human brain.

### Neurophysiological Features

Factors implicated in seizures in human newborn are as follows:

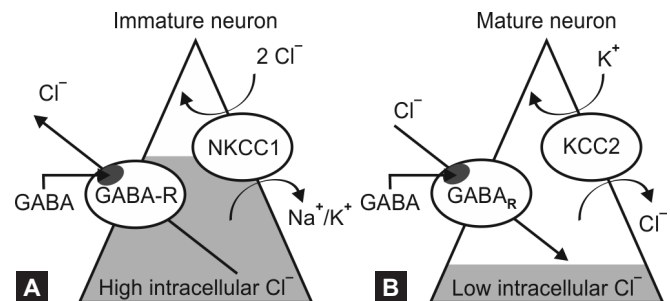
- In limbic and neocortical regions, development of excitatory mechanisms such as N-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are over expressed, and exhibit multiple properties that enhance excitation.
- GABA receptors have excitatory rather than inhibitory activity in perinatal neurons because of elevated intraneuronal  $\text{Cl}^-$  concentration. This is a result of increased expression of NKCC1 receptors (sodium-potassium-chloride cotransporter) which mediates chloride influx, with relatively decreased expression of KCC2 receptors (potassium-chloride-cotransporter), which mediates  $\text{Cl}^-$  efflux (**Figs 1A and B**).
- Deficient development of substantia nigra system which mediates inhibition of seizures.
- *Impaired propagation of electrical seizures from core of brain to surface*: Studies on rat models demonstrated that certain epileptic phenomena can occur without any surface-recorded EEG discharges, and such phenomena can be generated at subcortical (i.e., deep limbic, diencephalic, brain stem) regions. Likewise, neurons of the inferior colliculus of human midbrain are particularly sensitive to injury by hypoxic-ischemic insults, manifesting as subtle seizures. Thus they may not exhibit simultaneous electrographic discharge and account for the inconsistent electroclinical correlation in subtle seizures in newborns.

### Physiological Changes during Seizures

During seizure the metabolic demand of brain increases. The blood glucose may remain normal or increases but brain glucose falls markedly with a rise in lactate levels. Systemic blood pressure rises to increase the cerebral blood flow, so as to meet the metabolic demand of brain. These short-term changes are followed by the changes in cell structure and synaptic linkages leading to long-term neurological abnormalities. Thus, recurrent seizures are detrimental to developing neonatal brain.

### CLASSIFICATION

Four essential clinical seizure types have been recognized: subtle, clonic, tonic, and myoclonic. Clinical seizure associated with electrical activity is true form of seizures. However, electroclinical dissociation (ECD) is not uncommon. ECD can be



**Figures 1A and B:** (A)  $\text{Cl}^-$  influx and hyperpolarization (inhibition); (B)  $\text{Cl}^-$  efflux and depolarization (excitation)

**Abbreviations:** GABA, gamma-aminobutyric acid; NKCC1, sodium-potassium-chloride cotransporter; KCC2, potassium-chloride-cotransporter.

**Table 1** Electrical activity in different types of clinical seizures

Clinical seizure	Electroencephalographic seizure	
	Common	Uncommon
Subtle	+	
Clonic		
• Focal	+	
• Multifocal	++	
Tonic		
• Focal	+	
• Generalized		+
Myoclonic		
• Focal, multifocal		+
• Generalized	+	

either ways. Some clinical seizures may not be associated with electrical correlation and vice versa. Subtle, multifocal clonic and generalized myoclonic seizures are more likely to be associated with electrical activity rather than generalized tonic seizures (Table 1).

### Subtle Seizures

It is called subtle because the clinical manifestations are mild and frequently missed. They are probably the most common type. They constitute about 50% of neonatal seizures. Subtle seizure include ocular-tonic horizontal deviation of eyes or sustained eye opening with ocular fixation or cycled fluttering; oral-facial-lingual movements—chewing, tongue-thrusting, lip-smacking, etc.; limb movements—cycling, paddling, boxing-jabs, etc.; autonomic phenomena—tachycardia or bradycardia, apnea may be a rare manifestation of seizures. Apnea due to seizure activity has an accelerated or a normal heart rate when evaluated 20 seconds after onset. EEG correlation is variable.

### Clonic Seizures

It represents the seizure type associated most consistently with time-synchronized EEG seizure activity. They constitute about 25–30% of neonatal seizures. It has rhythmic and usually rather slow (approximately one to three jerks per second at the onset, with the rate progressively declining with the seizure). Clonic seizures are categorized as *focal* or *multifocal*. EEG correlation is common with focal-clonic type of seizure. Multifocal refers to clinical activity that involves more than one site, asynchronous, migratory and usually crossing midline, whereas generalized refers to clinical activity that is diffusely bilateral, synchronous, and nonmigratory.

### Tonic Seizures

It is sustained flexion or extension of axial or appendicular muscle groups. They constitute about 5% of neonatal seizures. These seizures may be focal or generalized and may resemble decerebrate (tonic extension of all limbs) or decorticate posturing (flexion of upper limbs and extension of lower limbs). They are most common seen in perinatal asphyxia. So incidence is more in studies where asphyxia is predominant cause of seizure. Usually they are not associated with EEG changes.

### Myoclonic Seizures

It is single or multiple lightning fast jerks of the upper or lower limbs and are usually distinguished from clonic movements because of more rapid speed of myoclonic jerks, absence of slow return and predilection for flexor muscle groups. They constitute

about 15–20% of neonatal seizures. Common changes seen on the EEG include focal sharp waves and hypsarrhythmia.

## SEIZURE MIMICS

### Jitteriness or Tremors

These are most common condition mimicking seizures in neonates. These are known as rhythmic segmental myoclonus. They are commonly seen in hypoglycemia, hypocalcemia and in some normal neonates. These are characterized by rhythmic fast movements (4–6/s) which are provoked by stimulus like gently pulling the leg or hand or with elicitation of startle or Moro reflex. These are not associated with gaze abnormality or other autonomic and EEG changes.

### Benign Neonatal Sleep Myoclonus

The nonepileptiform myoclonus is of unclear mechanism but may be related to a transient dysmaturity of the brainstem reticular activating system. It usually presents in the first week of life. It occurs only during sleep, and is rapidly abolished by arousal; it can also be precipitated by gentle rhythmic rocking or tactile stimuli. EEG is normal in this condition. It resolves spontaneously over weeks to months. Long-term outcome is good and epilepsy does not develop later. Early diagnosis is important as use of barbiturates worsen this condition.

## APPROACH TO NEONATAL SEIZURES

### Seizure History

Complete seizure description with history of associated eye movements, restraint of episode by gentle hold or passive flexion of the affected limb, change in color of skin (mottling or cyanosis) and whether the infant was conscious or sleeping at the time of seizure should be elicited. The day of life on which the seizures occurred may provide an important clue to its diagnosis. While seizures occurring on day 0–3 might be related to perinatal asphyxia, ICH, and metabolic causes, those occurring on 4–7 day or beyond may be due to sepsis, meningitis, metabolic causes and developmental defects.

### Others

Obtain information suggesting perinatal asphyxia, intrauterine infections or diabetes in mother. A history of sudden increase in fetal movements may be suggestive of intrauterine convulsions. Information of place of delivery is important as babies born at home may not have received Vitamin K and hemorrhagic disease of newborn can lead to ICH. Features like lethargy, poor activity, drowsiness, and vomiting after initiation of breastfeeding may be suggestive of inborn errors of metabolism. Late onset hypocalcemia consequent to hyperphosphatemia, should be considered in the presence of cow's milk feeding.

### Family History

History of consanguinity in parents, history of seizures or mental retardation in family and early fetal/neonatal deaths could be suggestive of inborn errors of metabolism. History of seizures in either parent or sib(s) in the neonatal period may suggest benign familial neonatal convulsions (BFNC).

### Examination

The neonate should also be examined for the presence of any obvious malformations or dysmorphic features. Presence of hepatosplenomegaly or an abnormal urine odor may be suggestive of inborn error of metabolism (IEM). The skin should be examined

for the presence of any neurocutaneous markers. Presence of sepsis, hypoglycemia, jaundice, hepatomegaly in a baby may point towards galactosemia. Neurological state like lethargy/shrill cry and presence of a bulging anterior fontanel may be suggestive of meningitis or ICH. Sequential neurological examination at 8–12 hourly intervals may be more important and revealing than a single one time examination.

## INVESTIGATIONS

Investigations should be individualized with an emphasis on early identification of correctable cause. It should proceed in parallel with stabilization of vitals. *Essential investigations* which need to be done in all babies include blood sugar, serum electrolytes (Na, Ca, Mg), ABG, cerebrospinal fluid (CSF) examination, cranial ultrasound (US), and EEG. An ABG should be done to look for evidence of hypoxia and IEM. CSF study may be withheld if severe cardiorespiratory compromise is present or even omitted in infants with severe birth asphyxia (documented abnormal cord pH/base excess and onset of seizures within 12–24 hours). *Additional investigations* may be considered in neonates who do not respond to anticonvulsant drugs or earlier in neonates with specific features or in unexplained clinical scenario. These include neuroimaging [computed tomography (CT), MRI], detailed screen for congenital infections (TORCH) and work-up for IEM.

## MANAGEMENT

### Initial Management

The first step in successful management of seizures is to admit and nurse the baby in thermoneutral environment and to ensure warmth, airway, breathing, and circulation (TABC). Oxygen should be started, IV access should be secured, and blood should be collected for glucose and other investigations. A brief relevant history be obtained and quick clinical examination should be performed. All this should be done within 2–5 minutes.

### Correction of Hypoglycemia and Hypocalcemia

If glucose estimation reveals hypoglycemia or if there is no facility to test blood sugar immediately, 2 mL/kg of 10% dextrose should be given as a bolus injection followed by a continuous infusion of dextrose at 6–8 mg/kg/min. If hypoglycemia has been treated or excluded as a cause of convulsions, the neonate should be screened for hypocalcemia (iCa is seen in most ABG). If however, it cannot be tested immediately, 2 mL/kg of 10% calcium gluconate IV diluted in distilled water over 10 minutes under strict cardiac monitoring, should be given. If ionized calcium levels are suggestive of hypocalcemia, the newborn should receive calcium gluconate at 8 mL/kg/day for 3 days. If seizures continue despite initial correction of hypocalcemia, serum magnesium should be tested. If hypomagnesemia is documented (serum Mg <1.6 mg/dL), 0.25 mL/kg of 50% magnesium sulfate should be given intramuscularly (IM) every 12 hourly for 3 doses.

### Antiepileptic Drug Therapy

Antiepileptic drug (AED) therapy should be given if seizures occur after correction of hypoglycemia or hypocalcemia. Antiepileptic drugs should be considered in the presence of even a single clinical seizure since clinical observations tend to grossly underestimate electrical seizures (diagnosed by EEG) and facilities for continuous EEG monitoring are not universally available. Phenobarbitone is the drug of choice in neonatal seizures. The issues related to AED are discussed briefly below.

#### Clinical versus Electrical Seizures

As per World Health Organization (WHO) recommendations, all clinically apparent seizures lasting for more than 3 minutes or brief

serial seizures are to be treated. If continuous EEG monitoring is available, all electrical seizures should be treated even in absence of clinically apparent seizures, especially if babies are paralyzed.

### Preferred First-Line AED for Neonatal Seizures

Commonly used first-line AEDs for treatment of neonatal seizures are phenobarbitone and phenytoin. Phenobarbitone has been used as first-line drug for neonatal seizures in loading dose of 20 mg/kg/dose. Though it is very commonly used, various trials have shown its limitation in control of seizures in neonatal period (efficacy has been reported from 44% to 72%).

### Preferred Second-Line Drug for a Newborn not Responding to First Dose of Phenobarbitone

Till more data is available phenobarbitone is the most preferred drug (further loading dose of 10 mg/kg/dose till cumulative dose 30 mg/kg is achieved). For children not responding to maximum tolerated doses of phenobarbitone, as per WHO, either phenytoin or benzodiazepine or lidocaine may be used as second-line AED. Role of levetiracetam needs to be aggressively evaluated, considering its wide therapeutic index. A recent pilot study from our institute demonstrated reasonable efficacy of levetiracetam as second-line drug.

- The Cochrane review found only one randomized controlled trial (RCT) that showed comparable seizure control rate with phenobarbital and phenytoin [relative risk (RR) 1.03, 95% confidence interval (CI) 0.96–1.62], controlling seizures in only half of cases.
- Based on the available evidence, the WHO guideline on neonatal seizures recommends phenobarbitone as the first-line agent for management of neonatal in doses of 20 mg/kg/dose IV dissolved in 1:10 dilution with normal saline slowly over 20 minutes (not faster than 1 mg/kg/min).
- The Cochrane review found one study that randomized infants who failed to respond to phenobarbital to receive either lidocaine or midazolam as second-line agents. There was a trend for lidocaine to be more effective in reducing seizure burden (RR 0.40 95% CI 0.14–1.17) but both groups had similarly poor long-term outcomes assessed at 1 year.
- Based on the available evidence, the WHO guidelines on neonatal seizures recommend either midazolam or lidocaine as the second-line AED in neonatal seizures.
- However, given the lack of robust evidence and constraints involved in providing respiratory support and/or cardiac monitoring in most neonatal units in India, it seems appropriate to use phenytoin or levetiracetam as the second-line agent in neonates with seizures.

**Table 2** provides a summary of AEDs and their dosages recommended for neonatal seizures. **Flow chart 1** provides an algorithm for management of neonatal seizures.

### End Point of Treatment

If facility for continuous EEG monitoring is not available, abolition of all clinical seizures should be the target till three drugs are used. One has to weigh the benefits of controlling all electrical or clinical seizures against risks with multiple antiepileptic drugs (AEDs). After use of three AEDs, not all twitch/movement should be treated. Further AED should be given only if seizures are associated with abnormality in heart rate or blood pressure. Even when continuous EEG monitoring is available, it may not be impossible to control all electrical seizures with currently available drugs.

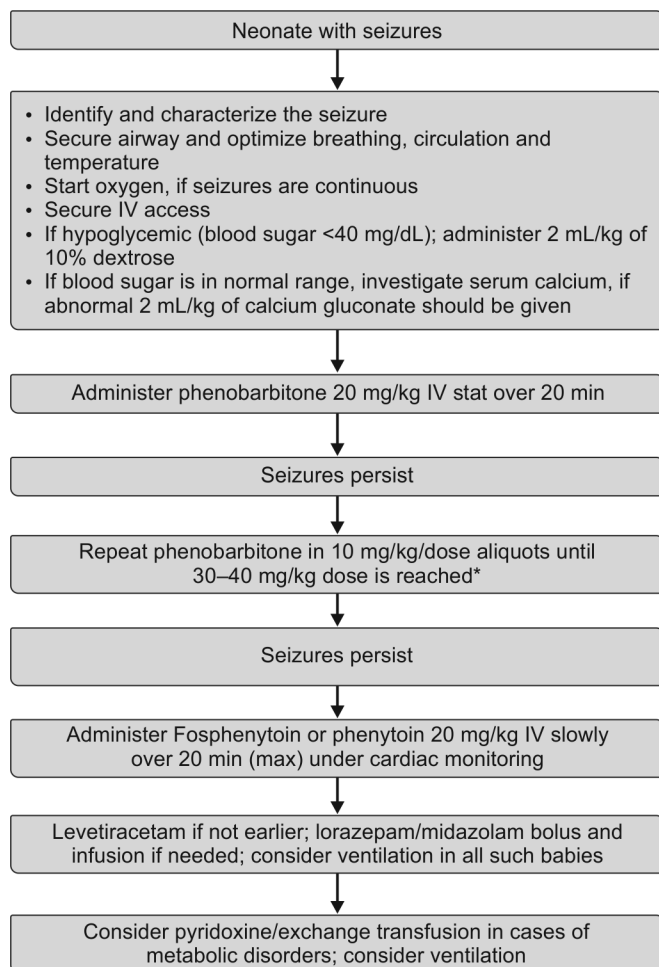
### Maintenance Dose of Antiepileptic Drugs

Traditionally, loading dose of AED has been followed by maintenance dose of AED to maintain the desired serum

**Table 2** Anticonvulsants used in neonatal period

Drugs	Doses	Possible adverse effects
Phenobarbitone	Loading at the rate of 20 mg/kg/dose followed by 10 mg/kg/dose IV till maximum 40 mg/kg/dose Maintenance dose: 3–5 mg/kg/day q 12–24 hourly IV/IM/PO	Hypertension, hypotension, respiratory depression and create brain death like state. Long-term effect on attention, memory and cognition has been postulated
Phenytoin	20 mg/kg, IV (0.5–1.0 mg/kg/min) IV Maintenance dose: 3–4 mg/kg/day q 12 hourly IV	Respiratory depression, hypotension or bradycardia or other cardiac abnormalities, avoid oral route due to poor bioavailability
Levetiracetam	Loading 30–60 mg/kg IV at the rate of 5 mg/kg/min. Maintenance dose: 10 mg/kg/dose q 8–12 hourly IV/PO	Safe drug, wide therapeutic index. Drug level monitoring not required
Lorazepam	0.05–0.10 mg/kg, IV over 5 min	Respiratory depression, apnea, and bradycardia
Midazolam	0.2 mg/kg, IV bolus; then, 0.1–0.4 mg/kg/hour	Advantage of less respiratory depression and sedation than lorazepam
Sodium valproate	20–25 mg/kg/dose IV followed by 5–10 mg/kg q 12 hourly IV/Oral	Hepatotoxicity, elevated blood ammonia levels
Lidocaine	4 mg/kg IV followed by infusion of 2 mg/kg/hour	Arrhythmia, hypotension and seizures
Paraldehyde	0.1–0.2 mL/kg/dose IM or 0.3 mL/kg/dose with coconut oil in 3:1 per rectal	Respiratory disturbance (pulmonary hemorrhage, pulmonary edema, hypotension), secondary to pulmonary excretion of paraldehyde
Pyridoxine	1 mL IM in both sides either in gluteal region or in anterolateral aspect of thigh	Hypotension, apnea
Topiramate	Initial dose and maintenance dose of approximately 3 mg/kg	Anorexia, weight loss, vomiting, diarrhea, acidosis
Bumetanide	Inhibits NKCC1 receptors (under trial)	

Abbreviation: NKCC1, sodium-potassium-chloride cotransporter.

**Flow chart 1** Algorithm for management of neonatal seizures

\* 30 mg/kg in perinatal asphyxia especially if no facility to monitor serum levels.

level and prevent recurrence of seizures for the duration. After the pathophysiology which caused seizures has been corrected or reverted, the AED can be gradually tapered and stopped. Duration of maintenance dose therapy has been under considerable scientific attention recently. Its duration has been significantly curtailed from months to weeks and now to a few days only. A recent trial from our institute on about 150 babies indicated that withholding maintenance altogether after control of seizures with only a single loading dose of phenobarbitone does not result in higher incidence of breakthrough seizures.

As per WHO guidelines, in neonates with normal neurological examination and/or normal EEG, consider stopping AED if baby is seizure free for more than 72 hours. The drugs can be reinstituted in case seizure recurs.

### Stopping Antiepileptic Drugs

No clear guidelines are available for weaning of AEDs after acute or chronic use. In acute stage, one can start weaning AED once no seizures are observed for at least 3–5 days. General consensus is to discontinue all medications at discharge if clinical examination is normal, irrespective of etiology and EEG. In patients on multiple AEDs, after a seizure free period of 48–72 hours, one should stop that drug first which is added last and stop the phenobarbitone in last. The seizure recurrence depends on three factors: (1) neurological examination, (2) cause of neonatal seizure and (3) EEG pattern. Protocol of stopping AED takes into account these three factors.

### Management of Neonatal Seizures in Primary Care Settings

Newborn presenting to a primary health center (PHC) or first referral unit (FRU) with seizures needs to be stabilized hemodynamically before referring to higher center. Temperature of the baby should be maintained by placing under radiant warmer (if available), intranasal oxygen should be started, the airway cleaned by suction and baby's neck be kept in slight extension. Initial steps are same as described earlier.



Check blood sugar if facility is available, else give 10% dextrose empirically at 2 mL/kg body weight (approximately 5 mL in term and 3 mL in preterm neonates). If seizure persists, intravenous (IV, if accessible) or intramuscular (IM) phenobarbitone is to be given at loading dose of 20 mg/kg body weight. If IM injection cannot be given for any reason, same dose can be given through nasogastric tube. First dose of antibiotic should be given before transport. After this, patient should be transported to higher center. During transportation, one should assure that TABC (temperature, airway, breathing and circulation) is maintained properly. The family needs to be counseled appropriately. Before transporting one should communicate with referral team for condition at referral availability of bed and medical personal at the receiving center. Transport should ideally be in transport ambulance vehicle with facilities of oxygen, IV fluids and resuscitation kit and a medical personal should accompany the baby.

## PROGNOSIS

Appropriate management and regular neurological assessment can prevent major neurodevelopmental sequelae such as motor deficits and mental retardation after neonatal seizures. Recurrent seizures may lead to specific learning difficulties or poor social adjustment, in late teenage years.

Good prognosis is associated with subarachnoid hemorrhage (SAH) and late onset hypocalcemia. Risk of subsequent epilepsy after neonatal seizures due to perinatal asphyxia is approximately 30–50%, and after seizures secondary to cortical dysgenesis, it is almost 100%. Major background disturbances such as burst suppression are highly predictive of poor outcome, particularly if they persist into the second week of life. Ictal patterns alone may not be as accurate for predicting outcome, unless they occur in high numbers, long durations, and multifocal distribution.

## PREVENTION

### Antenatal Strategies

Proper antenatal care including electronic fetal monitoring (EFM) during labor has shown to reduce incidence of neonatal seizures. Antenatal steroid given to mothers with threatened preterm deliveries has been shown to reduce intraventricular hemorrhage by almost 50%. Similarly, antenatal magnesium sulfate therapy in eclampsia mothers decreases risk of seizures in newborns (MAGPIE trial).

### Perinatal Strategies

Good neonatal resuscitation in first golden minute of birth in babies of birth asphyxia with or without meconium by reducing the duration of hypoxia and hypercapnea can be helpful in preventing seizures. One can minimize free radical neuronal

injury in asphyxiated babies by preventing hyperoxia and setting oxygen saturation target to 88–92%.

## Postnatal Strategies

Promotion of exclusive breastfeeding as it reduces incidence of sepsis and meningitis. Late onset hypocalcemia seizures can be reduced by exclusive breastfeeding rather than cow's milk. Screening for blood sugar levels and hematocrit in high-risk babies like premature, intrauterine growth retarded and infant of diabetic mothers can lead to early diagnosis of hypoglycemia and polycythemia, preventing neurological sequelae. Newborn screening for metabolic diseases may lead to early diagnosis and treatment of conditions like galactosemia.

### IN A NUTSHELL

1. Neonatal seizures are one of the major causes of neonatal mortality and morbidity, hence it has to be critically recognized, evaluated and treated.
2. All electrical seizures are to be treated and in absence of electrical seizure monitoring all clinical seizures should be treated.
3. Phenobarbitone is the first drug of choice in treatment of neonatal seizures.
4. Levetiracetam has upcoming role as second-line drug with good safety and efficacy profile.
5. Early stopping (48–72 hours) of AEDs is now advised as to prevent long-term side effects of these drugs.
6. Long-term prognosis of babies with neonatal seizures strongly depends on gestation age, etiology and interictal EEG pattern.
7. Parental counseling and regular neurodevelopmental screening has to be done in babies with neonatal seizures till the age of 2 years to prevent long-term abnormal neurological outcome.

### MORE ON THIS TOPIC

- Booth D, Evans DJ. Anticonvulsants for neonates with seizures. *Cochrane Database Syst Rev*. 2004;4:CD004218.
- Cherubini E, Gaiarsa JL, Ben-Ari Y. GABA: an excitatory transmitter in early postnatal life. *Trends Neurosci*. 1991;14:515-9.
- Mizrahi EM, Kellaway P. *Diagnosis and management of neonatal seizures*. Philadelphia: Lippincott-Raven; 1998.
- Scher M. Seizures in neonates. In: Richard J, Avroy A, Fanaroff MB, Michele C. Fanaroff and Martin's Neonatal-Perinatal Medicine: diseases of the Fetus and Infant. 9<sup>th</sup> ed. United States: Elsevier; 2010.
- Volpe JJ. *Neurology of the newborn, neonatal seizures*. 5th ed. Philadelphia: WB Saunders Elsevier; 2008,pp.203-37.
- World Health Organization. *Guidelines on neonatal seizures*. Geneva: World Health Organization; 2012. From: [www.newbornwhocc.org](http://www.newbornwhocc.org). Accessed October 27, 2014.

## Chapter 16.2

# Hypoxic Ischemic Encephalopathy

B Vishnu Bhat, B Adhisivam

According to the WHO, perinatal asphyxia is defined as a *failure to initiate and sustain breathing at birth*. According to the American Academy of Pediatrics and ACOG, significant perinatal asphyxia is present when all of the following criteria are present: (1) profound metabolic or mixed acidemia (pH < 7) in umbilical cord blood, (2) persistence of low Apgar scores less than 3 for more than 5 minutes, (3) signs of neonatal neurologic dysfunction (e.g., seizures, encephalopathy, tone abnormalities), and (4) evidence of multiple organ involvement (such as that of kidneys, lungs, liver, heart and intestine). The associated dysfunction of the central nervous system (CNS) is referred to as hypoxic ischemic encephalopathy (HIE).

Every year, around 4 million babies die in the neonatal period (first 28 days of life) globally and asphyxia is one of the important direct causes accounting for 23% of these neonatal deaths. Among the survivors of asphyxia, cerebral palsy is a sequel which results in loss of an individual's productive capacity and may be a lifelong burden for the family and social institutions.

## EPIDEMIOLOGY

There is an estimated 0.7–1.2 million neonatal deaths annually across the world attributable to asphyxia. Nearly 99% of these deaths occur in developing countries and only 1% in developed countries. HIE occurs in 1.5 per 1,000 live full-term births. About 15–20% of affected newborns die in the postnatal period, and in addition 25% will continue to have childhood disabilities. Moreover HIE is a major problem for the individual, family, and society accounting for 15–28% of children with cerebral palsy and 25% of all cases of developmental delay. The prevalence of cerebral palsy among term deliveries has remained the same, approximating 2 per 1,000 livebirths despite significant advances in perinatal care. Long-term outcome is found to depend on the severity of neonatal encephalopathy (NE). According to National Neonatal Perinatal Database (2003), Apgar score less than 7 at 1 minute (including moderate and severe asphyxia) was documented in 9% of all intramural deliveries and 2.5% babies had Apgar scores less than 7 at 5 minutes of age. Twenty percent of all neonatal deaths were due to perinatal asphyxia. Manifestations of HIE were seen in approximately 1.5% of all babies. Perinatal asphyxia was also the most common cause for stillbirths accounting for one-third of all such cases.

## ETIOLOGY

It is practically impossible to ascertain the exact time of the hypoxic insult sustained by a newborn unless some convincing evidence is available. Some of the common causes for HIE are listed in **Table 1**. Clinical presentation of NE of varying etiologies can overlap and therefore its clinical presentation alone makes it difficult to identify the etiology. It is important to exclude other causes of NE in the absence of risk factors for perinatal asphyxia.

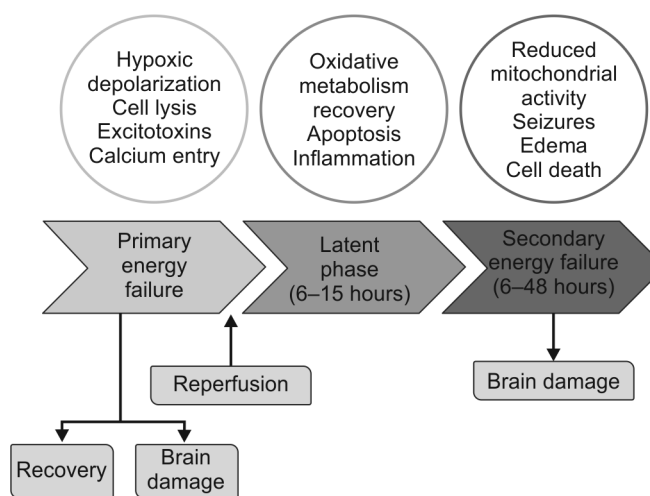
## PATHOPHYSIOLOGY

Hypoxic ischemic encephalopathy is not a single *event* but is rather a continuum starting from the time of insult. Two distinct episodes of neuronal impairment are known to occur during this time. The

immediate (primary) hypoxic insult is followed by a latent period of recovery which lasts for almost 6 hours. Subsequently there is a longer and profound period of secondary neuronal damage due to the release of chemical mediators. Neural tissue may die initially during the actual ischemic or asphyxial event. Several neurons however recover at least partially from the primary insult in a *latent* phase but die hours or even days later (secondary or delayed cell death) (**Fig. 1**).

**Table 1** Etiology of hypoxic ischemic encephalopathy

Maternal	Uteroplacental	Fetal
Cardiac arrest	Placental abruption	Fetomaternal hemorrhage
Asphyxiation	Cord prolapse	Twin to twin transfusion
Severe anaphylaxis	Uterine rupture	Severe isoimmune hemolytic disease
Status epilepticus	Hyperstimulation with oxytocic agents	Cardiac arrhythmia
Hypovolemic shock		



**Figure 1** Pathophysiology of hypoxic ischemic encephalopathy

The pathophysiology of HIE includes two phases—(1) *primary* and (2) *secondary* energy failure based on the cerebral energy state. Cerebral blood flow and oxygen substrates are decreased in primary energy failure. Reduction in adenosine triphosphate (ATP) and other phosphorylated compounds like phosphocreatine and significant tissue acidosis are important features during this phase. An *excitotoxic-oxidative cascade* characterized by excessive stimulation of neurotransmitter receptors and membrane depolarization causing an increase in intracellular calcium and osmotic dysregulation is also observed. Intracellular calcium activates neuronal nitric oxide synthase, leading to the release of the oxygen-free radical nitric oxide, which in turn affects mitochondrial respiration (**Flow chart 1**). These signals from damaged mitochondria lead to apoptosis or programmed cell death till energy supplies are available. However, cessation of these energy supplies results in cell necrosis. Activation of caspase enzyme system can also trigger apoptosis. Resolution of hypoxia can reverse the decrease in ATP and intracellular pH and enhances recycling of neurotransmitters. In case of prolonged and severe insult, the initial cascade of events will cause a second interval of energy failure in the mitochondria.

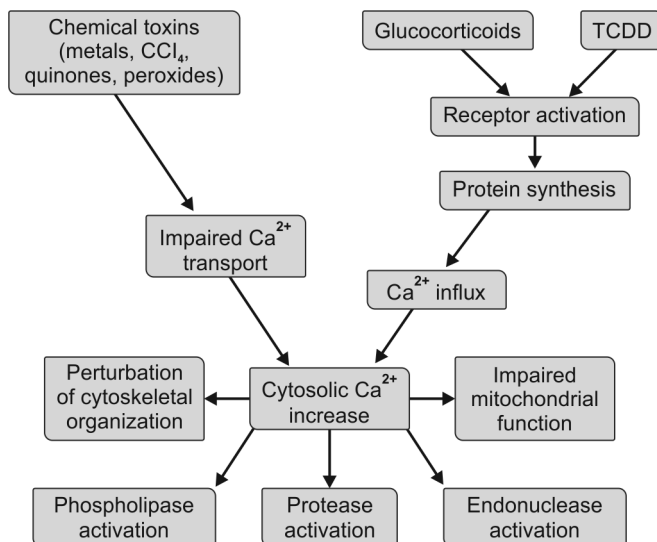
during which time the brain is depleted of ATP. This secondary energy failure differs from the primary in that the decline in the levels of phosphorylated compounds is not accompanied by brain acidosis. The secondary energy failure is characterized by continuing excitotoxic-oxidation cascade, apoptosis, inflammation and altered growth factor levels and protein synthesis (**Table 2**). The interval between primary and secondary energy failure represents a latent phase that corresponds to a therapeutic window (approximately 6 hours). Research has shown that cell death in the brain exposed to hypoxic insult is delayed over several days to weeks and apoptosis and necrosis continue depending on the region and severity of the injury. Gestational age has a role in the susceptibility of the brain to hypoxic damage. In term neonates, the gray matter is primarily affected (selective neuronal necrosis), while in the preterm it is the white matter leading to periventricular leukomalacia. The other factors which contribute to the degree of damage include cellular susceptibility, watershed areas, regional metabolic rates and degree of asphyxia.

### Oxidative Stress and DNA Damage in Asphyxia

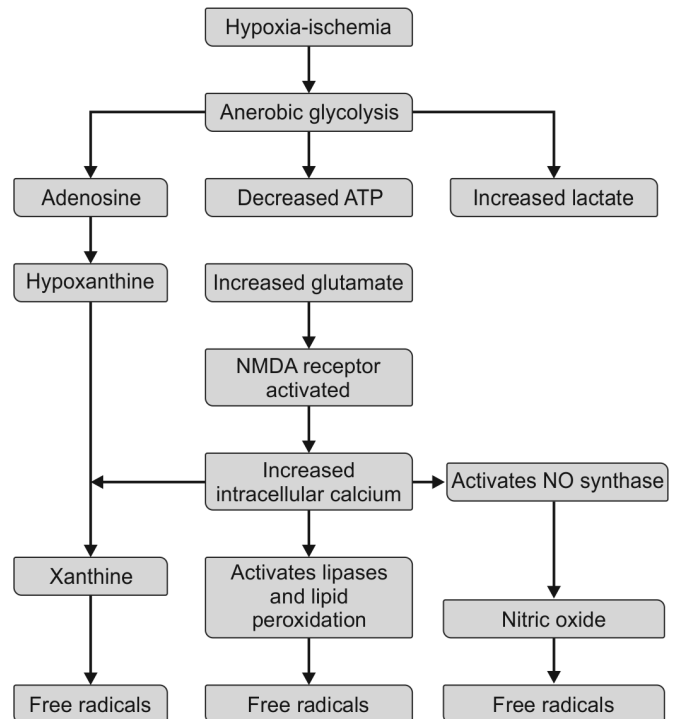
There are three important pathways that lead to free radical production. First one is *Fenton reaction*. During hypoxic ischemia, protein-bound iron is liberated from its binding proteins in the neuronal and microglial cells. Non-protein bound iron (NPBI) or free iron will accumulate during hypoxic ischemia. Upon

reperfusion and reoxygenation, NPBI will react with hydrogen peroxide to form the toxic hydroxyl-free radical. NPBI has been related to excessive brain damage in the immediate posthypoxic ischemia period. Second, the activation of neuronal and inducible nitric oxide synthase (nNOS and iNOS respectively) leads to the generation of the nitric oxide radical (NO•), which reacts with superoxide to form the toxic peroxynitrite (ONOO•). Peroxynitrite and reactive oxygen species cause DNA damage and cell death. Finally, hypoxanthine, accumulated during the hypoxic ischemic episode as a degradation product of ATP, is metabolized to uric acid by xanthine oxidase (XO). This reaction gives rise to further formation of superoxide radicals (**Flow chart 2**). These toxic-free radicals contribute substantially to reperfusion injury of the brain after severe hypoxia-ischemia. Neonatal brain is more susceptible to oxidative stress because of low concentrations of antioxidants, a high consumption of oxygen when transitioning from fetal to neonatal life and presence of high concentrations of unsaturated fatty acids that break down to form more oxygen-free radicals.

**Flow chart 1** Pathophysiology of hypoxic ischemic encephalopathy—key events



**Flow chart 2** Free radicals production in hypoxic ischemic encephalopathy



**Table 2** Characteristics of energy failures related to hypoxic ischemic encephalopathy

Primary energy failure	Secondary energy failure
Decrease in cerebral blood flow, oxygen substrates and ATP	Continuing of excitotoxic-oxidative cascade
Excitotoxic-oxidative cascade	Activation of microglia— inflammatory response
Loss of ionic homeostasis across membranes	Activation of caspase proteins
Entry of intracellular calcium	Reduction in levels of growth factors, protein synthesis
Mitochondrial disruption	Continuing apoptosis and necrosis
Brain acidosis	
Apoptosis and necrosis	

## CLINICAL FEATURES

The important CNS clinical features of HIE include altered level of sensorium, seizures and tone abnormalities. Their appearance is variable depending on the progression of energy failure and severity of insult and the usual time frame of these clinical features are depicted in **Figure 2**. For quantifying the severity of HIE, Sarnat and Sarnat classification is commonly used while Levene's classification is also helpful (**Tables 3 and 4**). Though the CNS features are sine qua non of HIE, all other organ systems including the kidney and heart are also affected in variable proportions depending on the disease severity and quality of care (**Table 5**). All organs in the body are at risk of cell injury and death when subjected to hypoxia. Certain organs are more susceptible to injury than others, and distinct physiological reflexes attempt to protect the vital organs from damage (i.e., diving reflex).

Acute kidney injury (AKI) is a common occurrence in infants with NE, with a reported incidence of 50–72%. Most of these studies are small and employ varying definitions for AKI based on elevation of serum creatinine, oliguria, decreased glomerular filtration rate and presence of hematuria and proteinuria. Nevertheless, these studies emphasize the frequency of AKI complicating NE and underline the uncertainty surrounding the precise and early diagnosis of AKI in critically ill neonates. The majority of AKI following perinatal hypoxia-ischemia is prerenal in origin and often nonoliguric.

Cardiovascular dysfunction forms part of the clinical spectrum of multiorgan dysfunction, which is very common when a term newborn sustains a hypoxic ischemic insult. The reported incidence of cardiovascular dysfunction ranges from 29% to 78%. Oxygen deprivation secondary to a hypoxic ischemic event is thought to cause myocardial damage with subsequent development of a low cardiac output, decreased myocardial contractility, systemic hypotension and pulmonary hypertension.

## DIFFERENTIAL DIAGNOSES

History of prolonged and difficult labor coupled with need for significant resuscitation, low apgar scores, altered sensorium and early onset seizures will usually point toward HIE. However, other differential diagnoses, like inborn errors of metabolism, neuromuscular disorders, developmental defects of brain and sepsis, should be kept in mind as their clinical features may overlap with HIE. It is not uncommon to find meconium aspiration syndrome and sepsis associated with HIE in term and preterm babies respectively.

## APPROACH TO DIAGNOSIS

A detailed history regarding the pregnancy and intrapartum period reflecting events leading to compromised blood or oxygen supply to the fetus should be obtained. These events include placental abruption, amniotic fluid embolism, tight nuchal cord, cord prolapse/avulsion, maternal hemorrhage (placental abruption/accreta), trauma or cardiorespiratory arrest, uterine rupture, and acute severe and sustained fetal decelerations. A history of maternal elevation of temperature increases the risk of NE. A careful neurologic examination needs to be performed to diagnose encephalopathy.

## INVESTIGATIONS

Apart from the standard investigations for supportive care, the following may be helpful in the management and prognosis of HIE.

## Electroencephalography

Electroencephalography (EEG) is not indicated routinely in all asphyxiated babies. However, it helps in the diagnosis and management of seizures and prognosticating the babies for long-term outcomes. The prognosis is likely to be poor if the EEG shows long periods of inactivity (> 10 sec); brief period of bursts (< 6 sec) with small amplitude bursts; interhemispheric asymmetry and asynchrony; or isoelectric and low voltage (< 5 mV).

## Amplitude-integrated Electroencephalography

Amplitude-integrated electroencephalography (aEEG) can be performed on continuous basis in neonatal intensive-care unit (NICU) and the following abnormalities would indicate poor prognosis: wide fluctuations in the amplitude with the baseline voltages dropping to near zero; peak amplitudes under 5 mV; and seizure spikes. While a normal aEEG may not necessarily mean that the brain is normal, a severe or moderately severe aEEG abnormality may indicate brain injury and poor outcome.

## Cranial Ultrasound

Cranial ultrasound (US) is not good for detecting changes of HIE in the term babies. However, hypoechoic areas can be seen in very severe cases (having large areas of infraction). In preterm babies, US can pick up periventricular leukomalacia and intraventricular-periventricular hemorrhage by serial cranial US during the first week of life.

## Computed Tomography

Computed tomography (CT) is more useful after a traumatic delivery and suspected of having an extra-axial hemorrhage.

## Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is preferred over CT as it has a greater interobserver agreement and no radiation exposure. Abnormalities of thalami and basal ganglia in term infants and that of white and gray matter at term equivalent age in preterm infants and an altered signal at the level of the posterior limb of the internal capsule are strong predictors of subsequent risk of poor neurodevelopmental outcome. The second most common pattern of injury is injury to the watershed regions. Diffusion weighted MRI can pick up abnormalities within days after birth, though more pronounced in later during the first week.

## MANAGEMENT

The management of neonates with HIE was limited to supportive intensive care, including resuscitation in the delivery room followed by stabilization of hemodynamic and pulmonary disturbances (hypotension, metabolic acidosis, and hypoventilation), correction of metabolic disturbances (glucose, calcium, magnesium, and electrolytes), treatment of seizures, and monitoring for multiorgan dysfunction. These general guidelines for supportive care are outlined in **Table 6**. Newer approaches are discussed below:

## Therapeutic Hypothermia

Therapeutic hypothermia (TH) has been proven to be effective in reducing morbidity associated with HIE and has become the standard of care for HIE in developed countries. However, in underdeveloped and transitional countries where the problem is more common, therapeutic cooling is still in the nascent phase. There are several reasons for this problem in resource restricted settings including the cost of devices needed for providing TH. Two recent systematic reviews on the efficacy and safety of TH in low- and-middle-income resource settings have been unable to



Birth–12 hours	Depressed level of alertness, periodic breathing or respiratory failure, intact pupillary and oculomotor responses, hypotonia, seizures
12–24 hours	Change in level of alertness, seizures, apneic spells, jitteriness, weakness in proximal limbs, upper > lower (term), lower > upper (preterm)
24–72 hours	Stupor or coma, respiratory arrest, brain stem pupillary and oculomotor disturbances, catastrophic deterioration with severe intraventricular hemorrhage and periventricular hemorrhagic infarction (premature)
> 72 hours	Persistent yet diminishing stupor, disturbed sucking, swallowing, gag and tongue movements, hypotonia > hypertonia, limb weakness

**Figure 2** Hypoxic ischemic encephalopathy—clinical features**Table 3** Sarnat and Sarnat classification of hypoxic ischemic encephalopathy

	<i>Stage 1</i>	<i>Stage 2</i>	<i>Stage 3</i>
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculo-vestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems decreased
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Spars	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)
Electroencephalogram findings	Normal (awake)	Early low-voltage continuous delta and theta Later, periodic pattern (awake) Seizures: Focal 1–1.5 Hz spike and wave	<i>Early:</i> Periodic pattern with isopotential phases <i>Later:</i> Totally isopotential
Duration	Less than 24 hours	2–14 days	Hours to weeks

**Table 4** Levene's classification of hypoxic ischemic encephalopathy

<i>Feature</i>	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
Consciousness	Irritable	Lethargy	Comatose
Tone	Hypotonia	Marked hypotonia	Severe hypotonia
Seizures	No	Yes	Prolonged
Sucking/respiration	Poor suck	Unable to suck	Unable to sustain spontaneous respiration

generate unequivocal evidence of its benefits in low- and middle-income countries.

Therapeutic hypothermia is neuroprotective by inhibiting many steps in the excitotoxic-oxidative cascade, including

**Table 5** Organ system dysfunction in perinatal asphyxia

CNS	Hypoxic ischemic encephalopathy, intracranial hemorrhage, seizures, long-term neurological sequelae
Cardiac	Myocardial dysfunction, valvular dysfunction, rhythm abnormalities, congestive cardiac failure
Renal	Hematuria, acute tubular necrosis, renal vein thrombosis
Pulmonary	Delayed adaptation, respiratory failure, meconium aspiration, surfactant depletion, primary pulmonary hypertension
GI tract	Necrotizing enterocolitis, hepatic dysfunction
Hematological	Thrombocytopenia, coagulation abnormalities
Metabolic	Acidosis, hypoglycemia, hypocalcemia, hyponatremia

**Table 6** Guidelines for management of hypoxic ischemic encephalopathy

<ul style="list-style-type: none"> <li>Follow neonatal resuscitation program (NRP) guidelines</li> </ul>
<ul style="list-style-type: none"> <li>Establish adequate ventilation/oxygenation and circulation</li> </ul>
<ul style="list-style-type: none"> <li>Oxygen—For babies born at term, it is best to begin resuscitation with room air rather than 100% oxygen. If despite effective ventilation there is no increase in heart rate or if oxygenation remains unacceptable, use of higher concentration of oxygen should be considered</li> </ul>
<ul style="list-style-type: none"> <li>Ventilation—Avoid hypocapnia or hypercapnia</li> </ul>
<ul style="list-style-type: none"> <li>Maintain normal temperature—Avoid hyperthermia</li> </ul>
<ul style="list-style-type: none"> <li>Maintain normal tissue perfusion</li> </ul>
<ul style="list-style-type: none"> <li>Glucose—Correct hypoglycemia</li> </ul>
<ul style="list-style-type: none"> <li>Treat seizures if present</li> </ul>
<ul style="list-style-type: none"> <li>Maintain normal hematocrit and correct metabolic acidosis</li> </ul>
<ul style="list-style-type: none"> <li>Therapeutic hypothermia if indicated</li> </ul>

inhibiting the increase in brain lactic acid, glutamate, and nitric oxide concentrations and epileptic activity (**Flow chart 3**). Moreover, TH inhibits protease activation, mitochondrial failure, free radical damage, lipid peroxidation and inflammation. TH has been shown to decrease brain energy use, prolong the latent phase, reduce infarct size, decrease neuronal cell loss, retain sensory motor function, and preserve hippocampal structures. Prolonging TH from 24 hours to 72 hours after hypoxia-ischemia attenuates brain damage and improves behavioral performance. The sooner hypothermia can be initiated; the more likely it is to be successful. Hypothermia is most effective when administered during the latent phase of the injury, before the onset of the secondary phase of energy failure (6 hours). The degree of neuroprotection progressively declines if cooling is initiated more than a few hours after insult. Moderate hypothermia at brain temperatures of 32–34°C initiated immediately or within a few hours after reperfusion and continued for 24–72 hours has been shown to favorably affect outcome in newborn and adult animals.

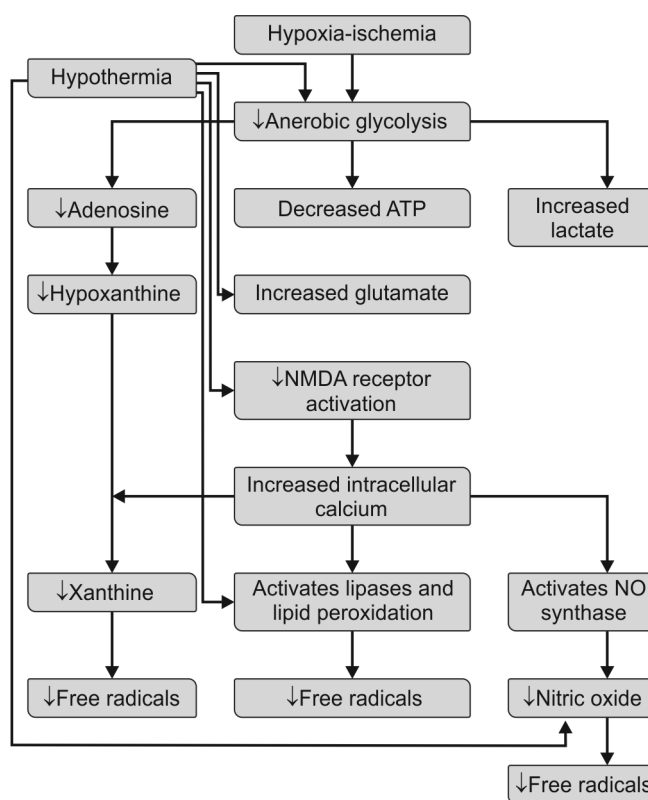
There are several modes of achieving TH. *Selective head cooling* is attractive, because it can provide adequate neuroprotection with minimal risk of systemic adverse effects, but it is associated with differential gradients within the brain and does not correlate well with the core body temperature. In contrast, *total body cooling* is more likely to be associated with adverse effects but causes fewer gradients within the brain and it correlates well with the core body temperature. Manually controlled cooling systems are associated with greater variability in temperature compared with servo-controlled systems. A manual mattress often causes initial overcooling. It is unknown whether large variation in temperature adversely affects the neuroprotection of TH.

### Prerequisites for Initiating Therapeutic Hypothermia

Strict guidelines and adequate supervision are essential for implementing TH for HIE. Monitoring facilities of the NICU, trained personnel and a backup system to manage complications should be in place. Inadvertent or accidental excessive hypothermia should be a *never event* in the NICU, especially in low-birthweight infants. The minimum prerequisites (4Ps) for an optimum TH implementation are described in **Table 7**.

### Problems in Instituting Therapeutic Hypothermia in India

In a review on ethical and practical issues relating to the global use of TH for perinatal encephalopathy, Wilkinson et al. have summarized the following points which are pertinent to Indian scenario. In resource restricted settings, brain damage due to perinatal asphyxia may be more established owing to maternal malnutrition, intrauterine growth restriction, obstructed labor and suboptimal obstetric/neonatal care. More than two-thirds of the deliveries in India happen outside

**Flow chart 3** Therapeutic hypothermia—possible mechanisms**Table 7** Prerequisites for an optimum therapeutic hypothermia implementation

Place	Personnel	Infrastructure	Protocols
Level III NICU	Trained neonatologist and nursing staff with round the clock monitoring	<ul style="list-style-type: none"> <li>Radiant warmer</li> <li>Cooling device</li> <li>Rectal and surface probes for temperature monitoring</li> <li>Multiparametric monitors (temperature, NIBP, SPO<sub>2</sub>, heart rate, respiratory rate)</li> <li>ABG machine</li> <li>Mechanical ventilator</li> <li>Glucometer</li> <li>aEEG (desirable)</li> <li>MRI (desirable)</li> </ul>	<ul style="list-style-type: none"> <li>Timely identification of HIE</li> <li>Ensuring TH for eligible infants within 6 hours of birth</li> <li>Evidence-based standard protocol for providing and monitoring TH</li> <li>Standardized neurodevelopmental follow-up</li> <li>Continuing staff education</li> </ul>

the hospital. The usefulness of cooling may be reduced if there is a high incidence of pre-existing brain damage or if the therapeutic window has elapsed. By the time the neonates are admitted in the neonatal unit, the secondary surge of neuronal death related to secondary energy failure may have already happened.

In several areas, HIV infection and puerperal sepsis are relatively common among mothers. Perinatal asphyxia may also coexist with neonatal sepsis, and it may be challenging to differentiate both the conditions at birth. Exclusion of infected infants is unlikely to be realistic and core temperature reduction may result in neutrophil compromise, which can worsen sepsis and pneumonia. This may partially explain the relationship between hypothermia and neonatal death in developing countries. Accidental hypothermia is witnessed in many asphyxiated infants in developing countries due to a number of factors including home birth, lack of basic neonatal care and overhead radiant warmers. Accidental hypothermia must be differentiated from TH and may dilute the benefit of TH in the standard care group in clinical research. Excessive cooling or *overcooling* is commonly associated with *inadequately controlled* cooling which usually happens during transport of very ill asphyxiated infants. In low-resource settings, the mandatory measuring of core body temperature may not always be practical when practicing TH. The adverse effects associated with TH are summarized in **Table 8**.

### Newer Therapies

The understanding of the differential responses to hypoxia-ischemia as an initial insult leading to cellular degeneration in brain has opened the way to develop new pharmacologic and therapeutic approaches. Due to the complex pathophysiology, therapies can target early pathways such as oxidative stress, inflammation and apoptosis or delayed pathways such as the deprivation of growth factors and cell death. Pharmacological interventions should start at different points of time according to their mechanisms of action (**Table 9**). The association of moderate hypothermia with neuroprotective drugs may decrease cell injury and optimize endogenous repair.

### Biomarkers

Biomarkers of neonatal HIE with good potential clinical applications include neuron-specific enolase, glial fibrillary acidic protein, brain-derived neurotrophic factor, and S100 $\beta$ . Serum and

urinary neutrophil gelatinase-associated lipocalin (NGAL) and urinary cystatin C (CysC) are early predictors of AKI secondary to HIE. Troponin-T and troponin-I are sensitive markers of myocardial injury following a perinatal hypoxic ischemic insult and may help predict severity of neonatal hypoxic ischemia and mortality. These findings are promising and open up the possibility of biomarkers playing a significant role in the early diagnosis and treatment of HIE and its complications.

### OUTCOME/PROGNOSTIC FACTORS

Prognosis of HIE can be made using the duration of the abnormal neurological symptoms and aEEG/conventional EEG changes. Infants who do not progress to Sarnat stage 3 and who have clinical signs of moderate encephalopathy for less than 5 days generally have a normal outcome. Persistence of Sarnat stage 2 symptoms for more than 7 days or abnormal cerebral background activity on aEEG/conventional EEG is frequently associated with later neurologic impairments. According to Murray et al., normal or mildly abnormal video EEG results within 6 hours after birth were associated with normal neurodevelopmental outcomes at 24 months of age. In contrast, clinical factors, such as more severe grade of encephalopathy, a higher number of neonatal seizures, requirement of more than one anticonvulsant medication, diffuse abnormalities on radiologic imaging, and abnormal findings on neurologic examination at discharge, are significantly associated with poor neurologic outcome by 2 years of age in infants with HIE. A recent systematic review from Netherlands revealed that aEEG, EEG, visual evoked potentials, diffusion weighted and conventional MRI had good prognostic value in HIE.

### PREVENTION

The best way to prevent HIE is to eliminate asphyxia during pregnancy and delivery. Awareness of HIE risk factors can help parents and medical personnel prevent this condition. HIE can be prevented by a multipronged approach involving all stake holders. Identifying high-risk cases and eliminating risk factors (treating maternal anemia, infections and malnutrition), early referral of high-risk patients to specialized birth centers, improving antenatal care, training health personnel in assessing and resuscitating newborn babies and developing appropriate transport systems for pregnant women and sick newborn babies are likely to decrease the incidence of HIE. Optimal antenatal, intrapartum, and postnatal care will save millions of newborn lives and also prevent HIE.

**Table 8** Complications of therapeutic hypothermia

• Skin erythema
• Sclerema and subcutaneous fat necrosis
• Pulmonary hemorrhage
• Pulmonary vasoconstriction
• Increased risk of infections
• Disseminated intravascular coagulation
• Increased blood viscosity—hemoconcentration
• Hypoglycemia
• Acid-base and electrolyte disturbances
• Hypotension—marked decrease in myocardial contractility and cardiac output in experimental animal models
• Bradycardia and other cardiac arrhythmia, sudden cardiac arrest

**Table 9** Newer therapies for hypoxic ischemic encephalopathy

Target pathway/area	Agent/therapy
Oxidative stress/excitotoxic damage	Melatonin, allopurinol, statins
Reperfusion	Magnesium, xenon, argon, deferoxamine, melatonin, cannabinoids
Inflammation/apoptosis	N-acetyl cysteine, melatonin, erythropoietin, iminobiotin
Downregulation of trophic factors	Erythropoietin
Cell death	Stem cells

### IN A NUTSHELL

1. Hypoxic ischemic encephalopathy is a complex process evolving over hours to days providing a unique window of opportunity for neuroprotective treatment interventions.
2. Advances in neuroimaging, brain monitoring techniques, and tissue biomarkers have improved the ability to diagnose, monitor, and care for newborn with HIE as well as predict their outcome.
3. Therapeutic hypothermia is the most promising neuroprotective intervention to date for infants with moderate to severe HIE.
4. Challenges remain in early identification of infants at risk for HIE, determination of timing and extent of hypoxic ischemic brain injury, as well as optimal management and treatment duration.

### MORE ON THIS TOPIC

Aggarwal R, Deorari AK, Paul VK. Post-resuscitation management of asphyxiated neonates. *Indian J Pediatr.* 2001;68:1149-53.

AIIMS protocol 2014—Post-resuscitation management of asphyxiated neonate. Available from URL: [http://www.newbornwhocc.org/clinical\\_proto.html](http://www.newbornwhocc.org/clinical_proto.html). Accessed May 6, 2014.

Bharadwaj SK, Bhat BV. Therapeutic hypothermia using gel packs for term neonates with hypoxic ischemic encephalopathy in resource-limited settings: a randomized controlled trial. *J Trop Pediatr.* 2012;58:382-8.

Bhat BV, Adhisivam B. Therapeutic cooling for perinatal asphyxia—Indian experience. *Indian J Pediatr.* 2014;81(6):585-91.

Galvao TF, Silva MT, Marques MC, et al. Hypothermia for perinatal brain hypoxia-ischemia in different resource settings: a systematic review. *J Trop Pediatr.* 2013;59:453-9.

Joy R, Pournami F, Bethou A, et al. Effect of therapeutic hypothermia on oxidative stress and outcome in term neonates with perinatal asphyxia: a randomized controlled trial. *J Trop Pediatr.* 2013;59:17-22.

Perrone S, Stazzoni G, Tataranno ML, Buonocore G. New pharmacologic and therapeutic approaches for hypoxic-ischemic encephalopathy in the newborn. *J Matern Fetal Neonatal Med.* 2012;25(Suppl 1):83-8.

Shankaran S. Hypoxic-ischemic encephalopathy and novel strategies for neuroprotection. *Clin Perinatol.* 2012;39:919-29.

Thayyil S, Shankaran S, Cowan F, et al. Brain injury following whole body cooling after neonatal encephalopathy in a south Indian neonatal unit. *Pediatr Res.* 2011;70(S5):33.

Wachtel EV, Hendricks-Muñoz KD. Current management of the infant who presents with neonatal encephalopathy. *Curr Probl Pediatr Adolesc Health-care.* 2011;41:132-53.



## Chapter 16.3

# Intraventricular Hemorrhage and White Matter Injury

Shamik Trivedi, Amit M Mathur

Improved survival of very low birthweight (VLBW) (weight  $\leq 1,500$  g) neonates in the setting of only a slight decline in the rate of preterm birth has resulted in more premature infants (50% of VLBW) surviving with significant neurodevelopmental disability in cognitive, behavioral, social and motor domains, neurological consequences of intraventricular hemorrhage (IVH), cerebellar hemorrhage, and white matter injury (WMI). Neonatal units across the Indian subcontinent are seeing a higher number of extremely low birthweight (ELBW) (weight  $< 1,000$  g) admissions and continued success in survival. In one level III unit in Pune, India, ELBW neonates made up 4.8% of the whole neonatal intensive-care unit (NICU) population with a survival rate of 55.8%, which has been seen in other units across the country as well.

Intraventricular hemorrhage is an entity primarily seen in the preterm neonate; however, term neonates are affected as well. Globally, IVH continues to significantly impact morbidity and mortality in the VLBW and ELBW population. Complications of severe IVH such as posthemorrhagic ventricular dilatation (PHVD) and WMI [also referred to as periventricular leukomalacia (PVL)] are associated with a higher risk of developing neurologic sequelae. WMI is the leading cause of cerebral palsy and other motor or cognitive developmental abnormalities in the preterm infant.

## EPIDEMIOLOGY

Primarily due to the advent of antenatal corticosteroid administration and improvement in delivery of neonatal care, the incidence of IVH has declined over the past three decades worldwide. In the USA, the incidence of IVH (Papile classification—any grade) in VLBW infants is between 20% and 25%. The incidence of periventricular hemorrhagic infarction (PVHI or Grade IV IVH) is between 5% and 11% in this population. In a prospective observational study conducted at a level III NICU in Pune, India; the incidence of severe (Grade III or IV) IVH in the ELBW population was 11.5%.

The incidence of IVH is inversely proportional to birthweight and gestational age of the neonate. In ELBW infants, the incidence is 50–60% in comparison to 20–25% in VLBW infants. In regards to gestational age, IVH rates decreased 3.5% with each added week of gestation as illustrated by a population-based study of 2,896 premature infants ( $< 32$  weeks of gestation) in Switzerland using the Swiss Neonatal Network Database. In term babies, the incidence of IVH is approximately 4%.

White matter injury is the predominant brain injury of the VLBW neonate with an overall incidence of 50% in population studies conducted in the US and is more prevalent than PVHI (5–11%) in this population.

## ETIOLOGY

In the preterm neonate, IVH occurs predominately in the subependymal germinal matrix. The *germinal matrix*, a highly cellular network of vascularized tissue primarily located in the lateral ventricle, is the site of proliferating neuronal and glial

precursors that develop into oligodendrocytes and astrocytes. The density of the vasculature is the largest in the germinal matrix. It is most prominent between 24 weeks and 34 weeks of gestation initially at the body of the caudate nucleus and by 28–32 weeks over the head of the caudate nucleus posterior to the foramen of Monro. The size of the germinal matrix decreases with advancing gestational age and is rarely seen beyond 35 weeks of postmenstrual age (PMA). The vascular system in preterm infants is fragile due to an immature support structure. The support structure consists of endothelial tight junctions, astrocyte end-feet, basement membrane and pericytes. Astrocyte end-feet surround the cerebral vascular providing structural integrity with glial fibrillary acidic protein (GFAP). In preterm infants, GFAP astrocyte end-feet are less prevalent in the germinal matrix compared to the cerebral cortex. Pericytes provide structural integrity to the capillaries, venules, and arterioles. Similar to astrocyte end-feet, pericytes are not abundant in the germinal matrix. In addition, impaired autoregulation of cerebral blood flow leads to a *pressure passive state* and altered flow. These two factors play a key role in the development of an IVH (see pathogenesis section).

The etiology of WMI is complex and not completely understood but involves ischemia, inflammatory, excitotoxic and oxidative stress.

## Timing

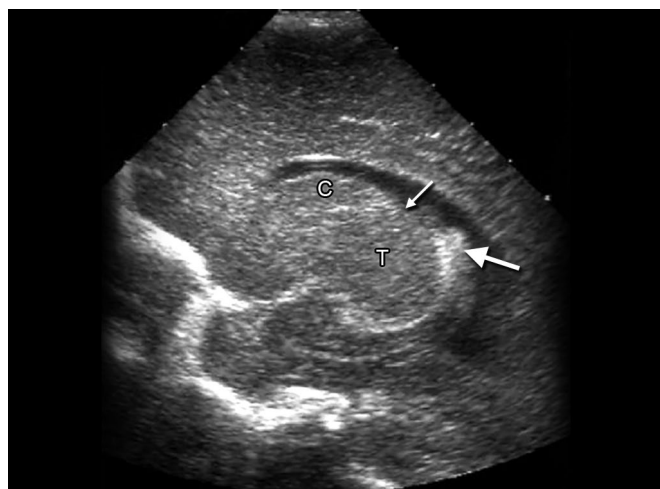
In preterm neonates, most IVH occur in the first week of life with 50% of bleeds occurring in the first 24 hours and 90% by 96 hours of life. In a study conducted at a single center in the US consisting of 1,105 ELBW neonates, 40% of the 265 infants with IVH developed the bleed within the first 5 hours. Extension of existing bleeds usually occurs within 3–5 days after the initial hemorrhage.

## Location

The majority of IVH in term infants occur due to bleeding in the *choroid plexus*, thought to be the case 35% of the time. Germinal matrix hemorrhage can be seen in about 3–4% of term infants, localized in the region of the thalamo-caudate groove, where residual subependymal germinal matrix hemorrhage remains (**Fig. 1**). WMI can be both focal and diffuse. The areas commonly affected by focal necrosis are around the foramen of Monro and the peritrigonal area of the lateral ventricles.

## The Injury

*Focal injury* can be macroscopic or microscopic necrosis in the deep periventricular white matter. Macroscopic necrosis with loss of cellular elements develops over weeks into cystic lesions seen on ultrasound (cystic WMI). Microscopic necrosis, also known as noncystic WMI, also evolves over weeks developing into glial scars that are not readily seen on cranial ultrasound (CUS). Cystic WMI is seen in approximately 5% of VLBW neonates and has decreased in prevalence over the years (**Fig. 2**). *Diffuse injury* to white matter precursor cells (OL-1 stage-pre-oligodendroglial cell) is mediated by excitotoxic, inflammatory and oxidative mechanisms. This injury results in not only a decrease in number of surviving preoligodendroglial cells but also a maturational arrest in the remaining cells due to accumulation of hyaluronic acid. Thus, these remaining cells do not mature effectively into myelin producing oligodendroglial cells thereby affecting neuronal signaling. The neuronal or axonal injury accompanying WMI affects the cerebellar white matter, thalamus, basal ganglia, cerebral cortex, and brain stem (**Fig. 3**). Axonal growth is prominent in the premature period and mature oligodendrocytes are necessary for effective axonal growth and connectivity.



**Figure 1** Cranial ultrasound (sagittal view) showing the thalamo-caudate groove (thin arrow), the choroid plexus (thick arrow) *Abbreviations: C, caudate head; T, thalamus.*



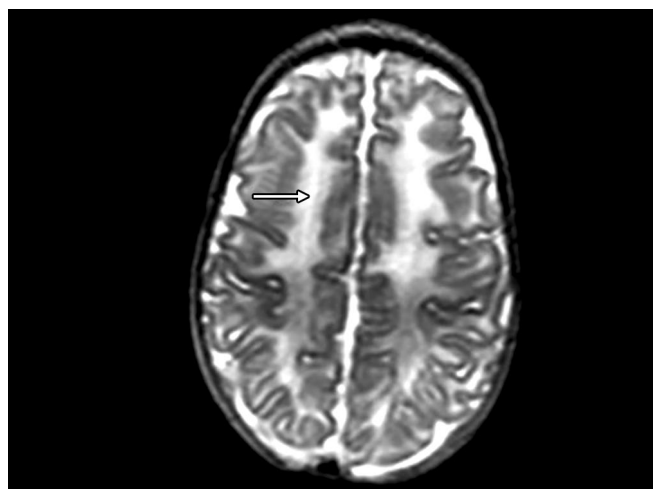
**Figure 2** Coronal cranial ultrasound demonstrating bilateral cystic white matter injury (arrows) in the anterior

## PATHOGENESIS/PATHOPHYSIOLOGY

The vascular bed supplying the germinal matrix is a rich network of arteries, veins, and capillaries. The arterial supply is from the main branches of the anterior cerebral artery, middle cerebral artery, and anterior choroidal artery. The terminal branches near the germinal matrix are in a watershed zone predisposing it to ischemic or reperfusion injury. As the fetus matures, so does the capillary network. During early gestation, the network is fragile with thin, delicate, and immature walls without the support of a basement membrane. The preterm neonate has limited ability in autoregulating cerebral blood flow producing a *pressure passive state*. Using radioactive xenon tracer and near infrared spectroscopy (NIRS), studies show that systemic blood pressure and cerebral blood flow are linear in relation. A change in systemic blood pressure directly leads to alteration in cerebral blood flow. Lack of blood flow in the immature germinal matrix vessels leads to cell death, breakdown of the vessel wall, and eventual bleeding. As the bleeding in the germinal matrix expands, it has the potential to rupture through the ependyma into the lateral ventricle producing an IVH.

Ventricular blood flows through the drainage system reaching the foramina of Magendie and Luschka and collecting in the basilar cisterns in the posterior fossa. Clot formation most often occurs at the aqueduct of Sylvius near the level of the arachnoid villi. The vascular network supplying the germinal matrix is continuous with a well-developed venous system. The smaller tributaries drain into the terminal vein, coursing alongside the germinal matrix terminating in the vein of Galen. This close relationship between vascular systems plays a key role in development of PHVI. As the ventricle fills with blood or clot, the venous drainage of the periventricular parenchyma is impeded resulting in venous congestion.

Many of the pathogenic factors seen in preterm infants also apply to term infants. Three causes seen primarily in term infants are: (1) birth trauma, (2) coagulopathy, and (3) cerebral sinovenous thrombosis. The exact relationship between trauma and development of an IVH is not fully understood. Currently, the leading theory relates to factors that increase cerebral venous pressure. Coagulopathy is more prevalent in term infants with IVH. Based on case series reports, 40% of term infants with IVH were noted to be in a hypercoagulable state or in disseminated intravascular coagulopathy (DIC). Related to coagulopathy, recent data using



**Figure 3** A T2 weighted MRI image demonstrating diffuse high signal intensity in the white matter (arrow)

CT and MRI scans show the significance of cerebral sinovenous thrombosis in the pathogenesis of IVH in term newborns.

White matter injury occurs in areas of arterial watershed zones. They are located deep in the periventricular region and are particularly vulnerable to hypoxic ischemic injury. Similar to the arterial supply of the germinal matrix, the vessels branch primarily from the middle cerebral artery with minor contribution from the anterior and posterior cerebral artery. Active periventricular vascular growth and development occur between 24 weeks and 34 weeks of gestational age. Thus, preterm neonates are at risk for injury due to the immaturity in vasculature. As in the development of IVH, the lack of cerebral blood flow autoregulation producing a *pressure passive state* plays a key role in WMI. Using NIRS, studies have demonstrated the association of longer pressure passive states with a higher incidence of WMI. Microglia are abundant in cerebral white matter and particularly susceptible to ischemia. During the reperfusion phase, they produce free radicals and cytokines that lead to further injury. Maturing oligodendrocytes are sensitive to injury from free radicals leading to cell death. Inflammation due to maternal intrauterine infection or postnatal sepsis is

also a pathogenic mechanism that can coexist with ischemia (**Table 1**). Recent insight using serial MRI scans in premature infants has revealed that WMI is associated with altered brain development anatomically in regional brain volumes involving white matter, deep nuclear gray matter, cortex and surface folding measures and in functional connectivity measures compared to term born gestational age matched controls.

## RISK FACTORS

There are multiple risk factors for developing IVH in the preterm and term infant (**Table 2**). In the prenatal period, the most important is prematurity. The lower the gestational age and birthweight, the higher incidence of IVH. If preterm delivery is unavoidable, the route and location of delivery may have an impact. Previous studies have shown that preterm neonates delivered vaginally or those who endured labor for longer than 12 hours prior to delivery have a higher incidence of IVH. In addition, preterm neonates delivered by C-section who endured labor were more likely to develop IVH. Follow-up studies have contradicted previous results showcasing no difference in the route of delivery and development of IVH in the preterm population. Tertiary care centers are normally situated in major cities making it difficult for many pregnant women to have access to specialized care. Studies have shown that delivery at a level I or II center increases the incidence of IVH compared to matched gestational age neonates born at a tertiary care center.

Once a preterm neonate is in the NICU, the primary factor is the inability to autoregulate cerebral blood flow producing a pressure passive state. A neonate with respiratory distress syndrome (RDS) requiring mechanical ventilation could have fluctuating cerebral blood flow due to the mechanics of the ventilator and fluctuations in CO<sub>2</sub> levels, which are a potent regulator of cerebral vascular tone. A study comparing permissive hypercapnia levels (PaCO<sub>2</sub> between 45 mm Hg and 55 mm Hg) compared to the control group (PaCO<sub>2</sub> between 35 mm Hg and 45 mm Hg) showed no statistical significant difference in IVH. However, in another large study, hypercarbia (PaCO<sub>2</sub> > 60 mm Hg) positively correlated with IVH in preterm infants.

Hypotension in the early neonatal period can lead to ischemia of the germinal matrix and watershed areas in the brain. Hypotension requiring inotropic support increases the risk of developing IVH even more so. Factors that lead to increased cerebral blood flow such as tracheal suctioning, rapid infusion of colloid, seizures, and pneumothorax are associated with a greater risk of developing IVH. The neonatal hematocrit is inversely related to cerebral blood flow. As an adaptive mechanism, cerebral blood flow increases to maintain cerebral oxygen delivery in an anemic neonate. Without the ability to autoregulate cerebral blood flow, increased flow to the germinal matrix can lead to IVH.

## CLINICAL FEATURES (TABLE 3)

The majority of IVH is *clinically silent* and seen 25–50% of the time. It is often detected on a screening head ultrasound on the first or second day of life. Possible clues may be a failure of the hematocrit to rise after a packed red blood cell transfusion. The second most common presentation is *saltatory* or *stepwise*. There is a mild and fluctuating encephalopathy that is difficult to appreciate. Signs will gradually appear over days consisting of increased ventilator settings, mild acidosis on a blood gas, or hyperglycemia. The least common but acute presentation is *catastrophic*. The neonate may have bradycardia, hypotension, temperature fluctuations, pallor and poor perfusion, a tense bulging fontanel or severe hypotonia. These signs develop rapidly, within minutes to hours. Neonates become apneic, requiring increased respiratory support and intubation. Eventually, seizure activity and decerebrate posturing may occur. The medical team should be prepared for urgent resuscitation and treatment.

In term infants, clinical presentation can range from the first few days of life to a month of life. If there was a significant perinatal event leading to an IVH, signs usually present early in the course. Whereas if no inciting event occurred, infants remain stable until 2–4 weeks of life. The clinical presentation is usually more severe than seen in a preterm infant. Irritability, fever, apnea, and signs of intracranial pressure consisting of a bulging fontanel and vomiting

**Table 1** Pathogenesis of white matter injury

White matter injury and altered brain development	
Ischemia	<ul style="list-style-type: none"> <li>Vascular anatomic factors—arterial border and end zones</li> <li>Vascular physiological factors—low physiological blood flow to cerebral white matter</li> <li>Pressure-passive cerebral circulation</li> <li>Systemic hypotension requiring inotropic support</li> <li>Hypocarbida (&lt; 35 mm Hg)</li> </ul>
Infection/Inflammation	<ul style="list-style-type: none"> <li>Propensity for maternal intrauterine infection and fetal systemic inflammatory response</li> <li>Propensity for postnatal infection and necrotizing enterocolitis (NEC)</li> </ul>
NICU factors	<ul style="list-style-type: none"> <li>Environment (developmental care, massage, noise, light, type of room, etc.)</li> <li>Drugs (sedation, steroids, oxygen)</li> <li>Nutrition (TPN, breastmilk)</li> <li>Stress</li> <li>Sepsis/NEC/ventilation days/BPD</li> </ul>
Social/Parental factors	<ul style="list-style-type: none"> <li>Parent visitation and holding</li> <li>Bonding</li> </ul>

**Table 2** Risk factors for intraventricular hemorrhage

Risk factors	
Prenatal	<ul style="list-style-type: none"> <li>Prematurity</li> <li>Low birthweight</li> </ul>
Intrapartum	<ul style="list-style-type: none"> <li>Route of delivery</li> <li>Level of care at delivery center (primary vs tertiary)</li> </ul>
Neonatal	<ul style="list-style-type: none"> <li>Respiratory distress syndrome</li> <li>Mechanical ventilation</li> <li>CO<sub>2</sub> levels</li> <li>Pneumothorax</li> <li>Hemodynamic instability</li> <li>Need for crystalloid/colloid infusions</li> </ul>

**Table 3** Clinical features of intraventricular hemorrhage

Presentation	Clinical features
Silent	<ul style="list-style-type: none"> <li>No presenting symptoms or signs</li> </ul>
Stepwise	<ul style="list-style-type: none"> <li>Mild fluctuating encephalopathy</li> <li>Subtle changes on physical exam</li> <li>Acidosis, electrolyte abnormalities</li> </ul>
Catastrophic	<ul style="list-style-type: none"> <li>Hemodynamic instability consisting of bradycardia, hypotension, pallor and poor perfusion</li> <li>Respiratory distress leading to apnea</li> <li>Bulging fontanel, severe hypotonia, seizures</li> </ul>



may appear. Seizures are particularly common, presenting in 50–65% of cases.

Clinical features of WMI are primarily developmental and seen after the neonatal period when delayed milestones are detected. Spastic diplegia is commonly seen with cystic WMI whereas cognitive effects seen without motor deficits present in neonates with non-cystic WMI. When there is associated neuronal or axonal injury, a wide spectrum of clinical deficiencies can develop from impairment in intelligence to falling on the spectrum of autistic disorders. Prior to discharge, increased appendicular tone, hyperreflexia, and ankle clonus consistent with upper motor neuron injury may be seen.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis is broad since the presenting signs and symptoms are not specific to IVH. Episodes of apnea and desaturation could point toward apnea of prematurity, gastroesophageal reflux, sepsis, necrotizing enterocolitis, or a central nervous system disorder. A sudden decrease in hematocrit could be the result of blood loss in the GI tract or necrotizing enterocolitis with perforation. Electrolyte abnormalities such as hyperglycemia and metabolic acidosis could be secondary to sepsis or necrotizing enterocolitis. Retractions, increased work of breathing and tachypnea could be RDS, sepsis or necrotizing enterocolitis. Physical exam findings of poor perfusion, lethargy or pallor could indicate sepsis.

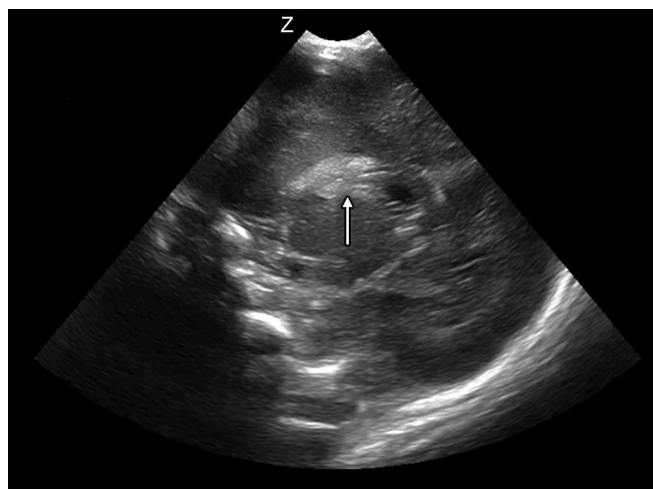
## DIAGNOSIS

Intraventricular hemorrhage is diagnosed primarily using imaging modalities. The goal is to detect IVH in high-risk infants and for surveillance of future complications. CUS is the mode of choice due to its accessibility in NICUs worldwide. It is a low-cost noninvasive bedside test that is easy to perform in a busy intensive care unit and produces high-resolution images without ionizing radiation. Using the open anterior fontanel, one is able to visualize the ventricles and surrounding parenchyma. Papile and colleagues in 1979 developed a classification system of IVH based on head CT scans stratifying findings into four grades. Grade I is defined as a germinal matrix hemorrhage, where the bleeding is restricted to the subependymal zone of the ventricle (**Fig. 4**). Grade II is a hemorrhage that breaks through the germinal matrix and begins to fill the ventricular space (**Fig. 5**). Grade III is an IVH that expands causing ventricular dilatation (**Fig. 6**). In a Grade IV hemorrhage, a triangular fan shaped echodensity is seen in the peritrigonal parenchyma (**Fig. 7**).

More recently, an updated classification system developed by Volpe takes into account the percentage of ventricle filling by the bleed. A Grade II is diagnosed when the bleed fills 10–50% of the ventricle, Grade III if it is greater than 50% of the ventricle and Grade IV if there is an intraparenchymal echogenicity now known as a PVHI.

Based on multiple studies documenting the timing of an IVH, routine screening with a head ultrasound is recommended on day 1–3 of life, 7–14 of life and then at 36–40 weeks of PMA for neonates born less than 30 weeks of gestation or less than 1,500 g (VLBW). Follow-up ultrasounds are obtained to monitor for extension of the bleed and development of common complications such as PHVD.

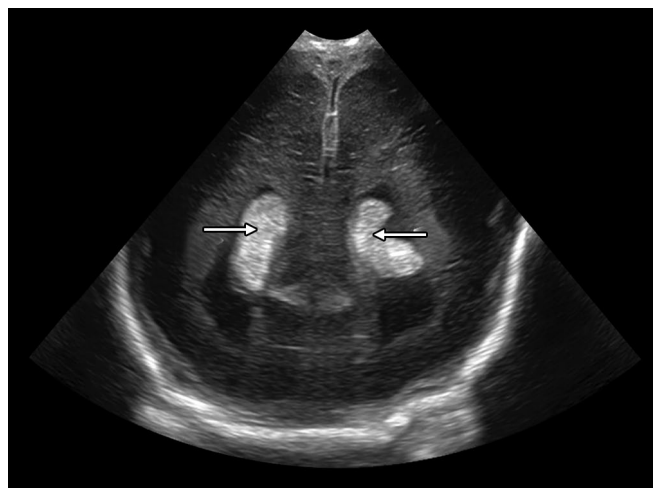
Detection of lower grade hemorrhages can be difficult using ultrasound. Inter-rater reliability of head ultrasound interpretation is very good with Grades III and IV IVH; however, it decreases significantly with Grades I and II IVH and WMI. In WMI, CUS will show bilateral linear echodensities near the lateral ventricles. However, ultrasound is unreliable for detecting small focal necrosis and myelin loss that can be visualized with MRI.



**Figure 4** Sagittal view of a Grade I IVH



**Figure 5** Coronal view of a bilateral Grade II IVH



**Figure 6** Coronal view of bilateral Grade III IVH

## MRI Studies

In tertiary NICUs in the USA, many MRI studies are completed at term equivalent age in VLBW infants to better assess brain development and delineate injury. Compared to ultrasound, MRI is



better at depicting anatomical landmarks in the brain. In addition, it has greater sensitivity and specificity in diagnosing WMI and parenchymal pathology. PVHI can be diagnosed by ultrasound; however, MRI is more accurate in determining size and exact location of the bleed. In term infants at risk of having a sinovenous thrombosis, MRI is the best modality for diagnosis. Using specific regions of the brain, such as the posterior limb of the internal capsule, term equivalent MRIs can aid in predicting future motor dysfunction. Due to advances in child life procedures, neonates tolerate MRI scans without sedation relatively well using devices like the MedVac<sup>®</sup> bag (CFI Solutions, Fenton, MI, USA). With the advent of MRI compatible ventilators and monitoring equipment, the ability to obtain an MRI in a critical neonate is easier. There are several qualitative and quantitative tools available to score neonatal brain MRI scans. However, specialized neuroradiological input is required for appropriate interpretation of neonatal MRIs.

## MANAGEMENT

As is the case of many diseases in medicine, the primary goal in management is to prevent the problem and provide supportive care. Monitoring electrolyte levels, respiratory mechanics and hemodynamic status are a few measures to play close attention to. Maximizing intravenous and/or enteral nutritional support is important for growth and healing. Weekly head circumference surveillance is helpful in monitoring for complications such as PHVD. With large IVHs, early detection and treatment of seizure activity with antiepileptics may improve long-term outcome. In the catastrophic presentation, resuscitation including intubation, volume expansion, and inotropic medication for abrupt hemodynamic change, and chest compressions may be needed to stabilize the critically ill neonate.

## COMPLICATIONS

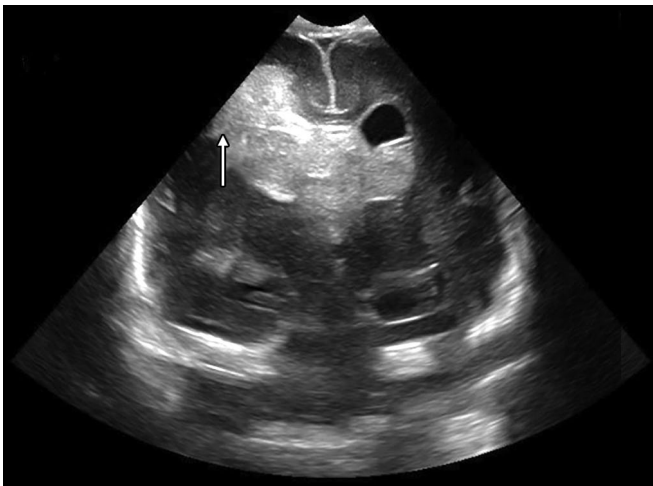
The most frequent complication of IVH is PHVD. PHVD evolves over 1–3 weeks and is most often associated with higher Grade IVH. Risk of progression to ventricular dilatation is 5% in Grade I IVH and 20% in Grade II IVH. PHVD can occur rapidly in situations where the blood clot obstructs the foramen of Monro (obstructive PHVD) but more commonly intraventricular blood results in decreased reabsorption of CSF at the arachnoid villi due to an obliterative arachnoiditis in the basal cisterns mediated by upregulated fibroblasts and deposition of extracellular matrix proteins within the subarachnoid villi.

Clinical features, such as a bulging fontanel, diastasis of the sutures and increase in head size, *do not present for weeks after ventricular dilatation* due to the higher water content and compressibility of the preterm brain and the large subarachnoid space. Thus, serial head ultrasounds (**Fig. 8**) are recommended to monitor for development of PVHD. In half of the patients, PVHD is transient and will resolve on its own. Depending on the severity of the PHVD and clinical condition of the neonate, the two options in management are reservoir or ventriculoperitoneal shunt (VP shunt) placement. Reservoirs are often first line therapy whereas a VP shunt is considered if no improvement is seen with reservoir taps by term equivalent age (**Flow chart 1**). It is estimated that neonates with Grade III IVH will require a VP shunt 18% of the time and up to 29% in Grade IV IVH (PVHI). Similar to the high risk of PHVD in preterm Grade IV IVH, 50% of term infants with large bleeds will require a VP shunt.

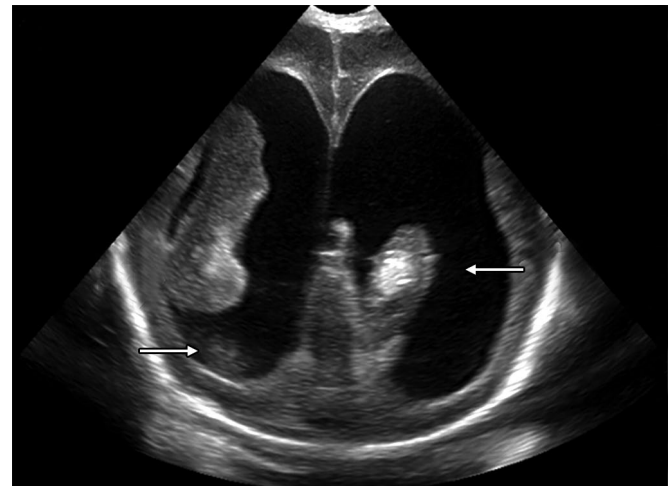
Intraparenchymal blood can irritate the surrounding cortical tissue leading to seizure activity. The majority of seizures in preterm neonates are subclinical. Continuous EEG for at least a 24 hours period in high-risk neonates is warranted to monitor for any abnormal electrical activity. Early diagnosis and treatment of seizure activity in the neonate may impact long-term neurodevelopmental outcome. PVHI is a unilateral venous infarction that forms a single large porencephalic cyst that rarely disappears over time (**Fig. 9**). Porencephalic cysts are the most common sequela of a PVHI forming over a period of 1–8 weeks. The incidence is as high as 66% in patients with a PVHI. It is often difficult to distinguish a PVHI from WMI. Destruction of developing oligodendrocytes leading to impairment of myelination affects the long-term outcome. WMI is most often an arterial disturbance that is symmetrical in nature with more diffuse cerebral WMI compared to PVHI, which is predominantly a unilateral lesion in as many as 80% of infants. WMI develops over days to weeks after delivery whereas PVHI forms much earlier in the course of injury. It progresses into multicystic injury that becomes less apparent over time.

## OUTCOME

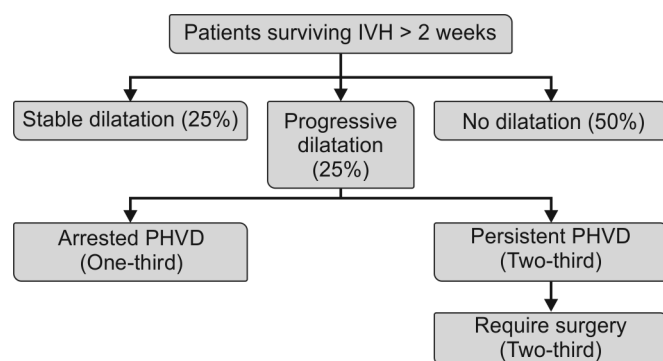
As more preterm neonates are surviving the NICU, the morbidity and mortality due to IVH remain at a steady state. In preterm neonates, Grades I and II IVHs generally resolve without significant complications. However, recent data out of Australia revealed that presence of Grades I and II IVH can be associated



**Figure 7** Coronal view of a Right Grade IV IVH



**Figure 8** Coronal Ultrasound demonstrating posthemorrhagic ventricular dilatation

**Flow chart 1** Natural course of IVH and PHVD

with poor neurodevelopmental outcome. In their cohort, preterm infants with IVH had significantly lower mental developmental (MDI) scores compared to matched infants with normal head ultrasounds. In addition, higher rates of cerebral palsy were seen in the IVH group. Neurological sequelae are seen in 35% of preterm infants with a Grade III IVH and as high as 90% in neonates with PVHI. Mortality rates increase significantly to 20% in Grade III and 50% in Grade IV. The major outcome in PVHI is motor dysfunction, specifically spastic diplegia. The spastic diplegia occurs more often in the lower extremity. In neonates with PHVD requiring VP shunt placement, Bayley Scales of Infant and Toddler Development at 2 years are significantly lower compared to PMA matched neonates without shunt placement. Term infants more often develop a higher Grade IVH (Grade III or IV). Thus, they are prone to develop neurodevelopmental complications associated with moderate to severe IVH. In published data, IVH in term infants with thalamic involvement seem to have a worse prognosis with higher risk of developing cerebral palsy.

Similar to PVHI, long-term neurological dysfunction commonly seen with WMI is spastic motor paresis and cognitive deficits. The corticospinal tracts pass through the periventricular region with the lower extremity bundles most adjacent to the lateral ventricles. Moderate to severe white matter abnormalities seen on MRI showed a statistically significant association with neurodevelopment outcomes. Specifically, cognitive and psychomotor delay, cerebral palsy and neurosensory impairment are common. Deep gray matter injury seen on MRI also correlated with cognitive delay and motor impairment.

## PREVENTION (TABLE 4)

Intraventricular hemorrhage prevention in the preterm infant is a tough goal to accomplish. The best way to prevent IVH is delaying preterm birth as long as possible. If preterm delivery is inevitable, administration of maternal corticosteroids reduces the risk of developing an IVH. Steroids are well documented to accelerate the maturity of the brain, improving the pressure passive state. In vitro studies have shown steroids up-regulate GFAP in pericytes improving vascular stability. Lung maturity is improved and the need for inotropic support is reduced. A few studies have shown that antenatal administration of magnesium sulfate may protect against IVH. The exact mechanism of the protective effect of magnesium sulfate is unknown. There is some evidence that magnesium sulfate is able to neutralize reactive oxygen species and enhances the preterm antioxidant system.



**Figure 9** T2 weighted MRI scan demonstrating a right-sided resolving PVHI (arrow), which has evolved into a porencephalic cyst that has merged with the lateral ventricle

**Table 4** Potential interventions to reduce brain injury (IVH and white matter injury) in preterm infants

Prevention of white matter injury	
Antenatal	<ul style="list-style-type: none"> <li>• Antenatal steroid use</li> <li>• Magnesium sulfate in preterm labor</li> <li>• Transportation in utero</li> </ul>
Delivery	<ul style="list-style-type: none"> <li>• Route of delivery</li> <li>• Delayed cord clamping</li> </ul>
Resuscitation	<ul style="list-style-type: none"> <li>• Temperature regulation</li> <li>• Optimize ventilation</li> </ul>
NICU	<ul style="list-style-type: none"> <li>• Head in midline and raised for 72 hours</li> <li>• Early extubation</li> <li>• Maintain target temperature</li> <li>• Maintain target PCO<sub>2</sub> levels</li> <li>• Avoid/manage blood pressure fluctuations</li> <li>• Indomethacin prophylaxis</li> <li>• Nutrition (early TPN, breastmilk)</li> <li>• Avoid postnatal steroids</li> </ul>

Once the preterm neonate is delivered, delayed cord clamping (30–90 seconds) has shown encouraging outcomes in recent studies. Higher blood pressure, better cerebral oxygenation and lesser days on the ventilator are seen in the delayed cord-clamping group with a significant reduction in IVH rates. The use of Indomethacin prophylaxis has shown promising results with a recent meta-analysis of 19 trials showing a decrease in the incidence of severe IVH (Grade III or IV). Specifically, the greatest reduction occurred in male preterm neonates less than 25 weeks of gestational age. Animal studies and postmortem autopsies of preterm infants have shown indomethacin increases key components of the basal lamina improving structural integrity of the germinal matrix vasculature. Muscle paralysis and sedation has been shown to improve the fluctuation in cerebral blood flow in preterm neonates requiring mechanical ventilation. However, there are risks that go hand in hand that need to be considered when deciding to use paralytics and sedation in this population.

### IN A NUTSHELL

1. IVH, cerebellar hemorrhage and white matter injury (WMI) are the predominant forms of brain injury seen in VLBW infants and often coexist.
2. IVH originates in the germinal matrix. The severity of IVH is Graded (I–III) depending on location and amount of blood resulting from ischemia-reperfusion injury coupled with a pressure passive cerebral blood flow. Grade IV or periventricular hemorrhagic infarction (PVHI) results from venous infarction in the peritrigonal area due to obstruction of venous drainage.
3. White matter injury can be focal or diffuse and microscopic (more common) or macroscopic (cystic). It is the predominant injury of the preterm infant.
4. IVH can be clinically silent and only detected on screening cranial ultrasound (CUS). A mastoid view of the cerebellum should be included in the standard CUS protocol. WMI and smaller cerebellar bleeds may also be clinically silent and best detected on a term equivalent MRI.
5. White matter injury involves injury to the preoligodendroglial cell (OL-1 stage) whose expression peaks between 24 weeks and 34 weeks PMA. The injury is mediated by inflammatory, excitotoxic and oxidative mechanisms and results in not only a reduction in absolute OL-1 cells but a maturational arrest of these cells.
6. IVH, depending on severity, results in destruction of the germinal matrix and posthemorrhagic ventricular dilatation (PHVD) that may require a temporizing surgical measure (reservoir) and some of these infants may require a ventriculoperitoneal shunt.
7. Anatomic characteristics of the VLBW infant brain result in PHVD occurring with minimal increase in the occipitofrontal circumference (OFC). Thus CUS screening twice a week is essential to detect ventricular dilatation that can happen rapidly with CSF flow obstruction.
8. Clinical bundles can be created to prevent IVH and reduce WMI in VLBW infants.
9. Neurodevelopmental outcomes worsen across domains with severity of IVH, especially with the need for VP shunt placement following PHVD.
10. Presence of moderate to severe white matter abnormalities on MRI at term equivalent age is associated with significant developmental delay across cognitive, motor and language domains in later childhood.

Avoiding hypothermia, hypercarbia/hypocarbia and maintaining hemodynamic stability is critical in the first week of life. Keeping the head midline with the infant supine and the head end raised by 15 degrees and avoiding volume expanders and inotropes when possible have been shown to decrease the incidence of IVH when used as a *bundle* of practice.

In order to prevent WMI, prompt recognition of impaired cerebral blood flow is essential. As stated earlier, the use of NIRS monitoring can aid in diagnosis of a pressure passive state in real time. Preventing the impaired cerebral blood flow through supportive measures described for IVH are important in WMI as well. Finally, ongoing research on the use of free radical scavengers in preventing oligodendrocyte injury could potentially improve neurodevelopmental outcomes in preterm neonates at risk.

### MORE ON THIS TOPIC

- Ballabh P. Intraventricular hemorrhage in premature infants: mechanism of disease. *Pediatric Res.* 2010;67:1-8.
- Bolisetty S, Dhawan A, Abdel-Latif M, et al. Intraventricular hemorrhage and neurodevelopmental outcomes in extreme preterm infants. *Pediatrics.* 2013;133:55-62.
- Davis AS, Hintz SR, Goldstein RF, et al. Outcomes of extremely preterm infants following severe intracranial hemorrhage. *J Perinatol.* 2013;1-6.
- Koksal N, Baytan B, Bayram Y, Nacaküçük E. Risk factors for intraventricular haemorrhage in very low birthweight infants. *Indian J Pediatr.* 2002;69:561-4.
- Mathur A, Mckinsty R. Intraventricular hemorrhage spectrum in premature neonates: evidence based neuroimaging. In: Medina L, Sanelli P, Jarvik, J. *Evidence-Based Neuroimaging Diagnosis and Treatment.* New York: 2013. pp.331-42.
- Mathur AM, Neil JJ, Inder TE. Understanding brain injury and neurodevelopmental disabilities in the preterm infant: the evolving role of advanced magnetic resonance imaging. *Semin Perinatol.* 2010;34:57-66.
- Mukhopadhyay K, Louis D, Mahajan R, Kumar P. Predictors of mortality and major morbidities in extremely low birthweight neonates. *Indian Pediatr.* 2013;50:1119-23.
- Prager A, Roychowdhury S. Magnetic resonance imaging of the neonatal brain. *Indian J Pediatr.* 2007;74:173-84.
- Volpe J. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol.* 2009;8:110-24.
- Volpe J. *Neurology of the Newborn.* 5<sup>th</sup> ed. Philadelphia; Elsevier Saunders; 2008.
- Whitelaw A. Periventricular hemorrhage: a problem still today. *Early Human Dev.* 2012;88:965-9.

# Section 17 RESPIRATORY PROBLEMS OF THE NEWBORN INFANT

Section Editor Siddarth Ramji

## Chapter 17.1

### Approach to a Neonate with Respiratory Distress

Swarna Rekha Bhat

Respiratory distress of any etiology accounts for a significant proportion of morbidity and mortality in the neonatal period. The etiology may be diverse but the basic supportive measures include oxygen and ventilator support when distress is severe. It is, therefore, important to be able to assess severity of respiratory distress to decide the treatment modality. It is equally important to be able to determine the etiology as treatment varies from simple supportive measures to surgery if the cause of distress is surgical. This section will deal with clinical approach to respiratory distress in neonates to help determine etiology and assess severity.

#### EPIDEMIOLOGY

As per the neonatal perinatal database 2002–2003, incidence of respiratory problems among intramural neonates was 5.7% of all livebirths. Among these, transient tachypnea of newborn (TTNB) accounted for 55.7% of respiratory distress, followed by meconium aspiration syndrome (MAS) accounting for 22.5% and respiratory distress syndrome (RDS) accounting for 19.9% of respiratory morbidity. Respiratory problems, particularly RDS, accounted for nearly 16% of neonatal mortality. Data from Kumar et al. suggested a similar pattern; overall incidence of respiratory problems was 6.7% of livebirths and TTNB was the most common cause (42%), followed by pneumonia (17%), MAS (10%) and RDS (9%). The same data also suggests that among surgical causes, the most common cause of respiratory morbidity was esophageal atresia with or without tracheoesophageal fistula (TEF).

#### ETIOLOGY

It is important to understand that causes of respiratory distress in neonates need not necessarily be respiratory problems, though this is the commonest cause. Breathing difficulty can occur because of respiratory, cardiac, metabolic, CNS and surgical causes. The common causes of respiratory distress are enumerated in **Table 1**. These include respiratory distress syndrome, meconium aspiration syndrome, pneumonia, pneumothorax and persistent pulmonary hypertension of newborn. This table also highlights the time of onset of respiratory distress in each of these conditions.

**Table 2** lists some of the less common causes of respiratory distress. One should think of these if usual causes are ruled out. Particularly, conditions such as primary surfactant deficiency, primary ciliary dyskinesia are rare causes. It is important to identify surgical causes as early as possible so that corrective action can be taken as soon as possible.

**Table 3** summarizes the cardiac conditions that can cause respiratory distress in neonates. One must suspect cardiac cause, if there are malformations, cyanosis, hepatomegaly or shock. Identifying these conditions is important as duct-dependent lesions will need immediate treatment with prostaglandins.

#### CLINICAL APPROACH

A neonate may present at birth or at any time subsequently in the first 28 days of life with respiratory distress. Priority is to assess the severity and decide regarding need for immediate intervention. This should be followed by a detailed history and examination to determine etiology.

**Table 1** Common causes and time of onset of respiratory distress in newborns

Condition	Predisposing factor	Onset
Respiratory distress syndrome (RDS)	More common in preterm	< 6 hours
Chronic lung disease	Preterms on ventilator	> 1 week
Transient tachypnea of newborn (TTNB)	Occurs mostly in term neonates, but can occur in preterms	< 6 hours
Meconium aspiration syndrome (MAS)	Occurs in term SGA and post-term neonates	< 6 hours
Pneumonia	Can occur in term and preterm	Any time
Pneumothorax	MAS, ventilated neonate	Any time
PPHN	Setting of MAS or asphyxia	< 6 hours
Malformations		< 6 hours
Pulmonary hypoplasia	Oligohydramnios, congenital diaphragmatic hernia	< 6 hours
Pulmonary hemorrhage	Pneumonia, sepsis, cardiac problem	Any time
Asphyxia		Any time
IEM		After 5 days
Cardiac		> 6 hours
Metabolic acidosis	Dehydration, IEM	Any time
Pleural effusion	Unusual, often can be chylous or associated with hydrops	

**Table 2** Less common causes of respiratory distress in the newborn

Small chest syndromes	Asphyxiating thoracic dystrophy Achondroplasia Osteogenesis imperfecta Thanotrophic dysplasia Campomelic dysplasia Hypophosphatasia
-----------------------	--

Contd...



Contd...

Malformations	CCAM Congenital lobar emphysema Lung cyst Pulmonary sequestration Congenital pulmonary lymphangiectasia Pulmonary alveolar proteinosis Primary ciliary dyskinesia Primary surfactant deficiency
Airway abnormality	Choanal atresia Midfacial hypoplasia Macroglossia Micrognathia Laryngeal web Tracheal stenosis Subglottic stenosis Laryngotracheomalacia
Neuromuscular diseases	SMA Myopathy
Aspiration syndromes (causes of aspiration)	<i>Sucking-swallowing incoordination:</i> GERD Neuromuscular diseases HIE Preterm Cleft palate Pierre Robin sequence TEF Laryngeal cleft

**Abbreviations:** CCAM, congenital cystic adenomatoid malformation; SMA, spinal muscular atrophy; GERD, gastroesophageal reflux disease; HIE, hypoxic-ischemic encephalopathy; TEF, tracheoesophageal fistula.

**Table 3** Cardiac causes of respiratory distress in neonates

	Condition	Time of onset
Structural heart disease	Hypoplastic left heart, interrupted aortic arch, coarctation of aorta, aortic stenosis	First week
	Truncus arteriosus, TGA, TAPVC, DOV	2–3 weeks
	VSD, AP window	After 3 weeks
AV malformations		Any time
Arrhythmias		
Myocarditis/myocardial dysfunction	Hypoxic ischemic encephalopathy, infections	
Cardiomyopathy	Other malformations, inborn errors of metabolism	

**Abbreviations:** TGA, transposition of great arteries; TAPVC, total anomalous pulmonary venous circulation; DOV, double outlet ventricle; VSD, ventricular septal defect; AP, aortopulmonary.

**Table 4** Silverman Anderson score for respiratory distress in preterm neonates

	Upper chest	Lower chest	Xiphoid retraction	Dilatation of nares	Expiratory grunt
Score 0	Synchronized respiration	None	None	None	None
Score 1	Lag on inspiration	Just visible	Just visible	Minimal	Heard with stethoscope
Score 2	See-saw movements	Marked	Marked	Marked	Heard with naked ear

Score 10 = Severe respiratory distress; Score  $\geq 7$  = Impending respiratory failure; Score 0 = No respiratory distress

## Assessing Severity of Respiratory Distress

Respiratory rate by itself will not determine the severity of respiratory distress: sometimes when there is severe distress, respiratory rates may be lower and the neonate can even become apneic. The two scoring systems usually used in the neonatal period are the Silverman Anderson score, usually used for preterm neonates and the Downe's score usually used for term neonates. The Silverman score is based predominantly on retractions and therefore may over- or underscore depending on the underlying condition (**Table 4**). The Downe's score is more comprehensive and includes need for oxygen and can be used for all neonates (**Table 5**).

If the distress is mild, monitoring is sufficient. Moderate distress would need blood gas estimation to determine degree of hypoxia and hypercarbia, and severe distress would require immediate intubation and ventilation. Neonates with moderate distress may be managed on invasive or noninvasive ventilation. Neonates with mild distress may require oxygen or noninvasive respiratory support, particularly in preterm neonates.

## Determining the Etiology

### History

If distress has occurred immediately after birth or within the first few hours of birth, details of antenatal, natal and immediate postnatal events are important. Important points to be asked in antenatal, natal and postnatal history are summarized in **Box 1**.

### Examination

**Severity of distress** As mentioned earlier, the priority is to assess severity of respiratory distress. For this, one needs to look for respiratory rate, suprasternal, intercostal, subcostal retractions, flaring of alae nasi and grunting, cyanosis, irritability or drowsiness. Increased respiratory rate not associated with distress or retractions is usually termed as tachypnea. The most likely cause of tachypnea without retractions is transient tachypnea of newborn. Milder degrees of respiratory distress will also have no retractions. Suprasternal retractions usually indicate an upper airway problem. Cyanosis, irritability or drowsiness suggest that there is some amount of hypoxia.

**General examination** Importance of checking if the baby is pre- or post-term, small for gestational age (SGA) or large for gestational

**Table 5** Downe's respiratory distress scoring system for term neonates

Score	0	1	2
RR/min	<60	60–80	>80
Cyanosis	none	in room air	In >40% oxygen
Retractions	none	mild	Moderate to severe
Grunting	none	Audible with stethoscope	Audible without stethoscope
Air entry	normal	decreased	Barely audible

Mild: 0–3; Moderate: 4–6; Severe: 7 and more

**BOX 1 Taking history in a neonate with respiratory distress***Antenatal history*

- History of decreased fetal movements may suggest neuromuscular disease
- History of oligohydramnios could indicate possibility of pulmonary hypoplasia, history of polyhydramnios could suggest TEF or maternal diabetes
- History suggestive of intrauterine infections may point towards a congenital pneumonia
- Attempt should be made to find out if an anomaly scan has been done to identify any cardiac or respiratory malformations
- Maternal diabetes may help identify polycythemia or TTNB as a cause of respiratory distress
- Maternal fever and evidence of chorioamnionitis should be asked for to see if early onset sepsis and pneumonia is causing the problem.

*Natal history*

- Prolonged rupture of membranes could lead to early onset sepsis and pneumonia
- Prolonged duration of labor, difficult delivery could suggest asphyxia as an etiology
- Meconium stained liquor would indicate MAS, asphyxia, PPHN
- Caesarian delivery is likely to be associated with TTNB
- Requirement of resuscitation would indicate: asphyxia, acidosis, pneumothorax as cause of distress.

*Postnatal history*

- *Weight and gestation:*
  - Preterm neonates are most likely to have RDS
  - Post-term neonates and term SGA neonates are more likely to have MAS
  - LGA neonates are likely to have TTNB and hypoglycemia as an etiology for tachypnea
- *Onset of respiratory distress:* This probably gives one of the most important clues for cause of respiratory distress.
  - Onset of respiratory distress immediately after birth or within first few hours is likely to suggest respiratory distress syndrome, Meconium aspiration syndrome, transient tachypnea of newborn, birth asphyxia, congenital malformations. Less frequent causes of respiratory distress occurring in the first few hours would be persistent pulmonary hypertension and pulmonary hypoplasia
  - Transient early causes of tachypnea would include delayed clearance of lung fluid, metabolic acidosis, hypothermia, hypoglycemia and polycythemia
  - Most other causes of respiratory distress occur after 6 hours of life.
- History of facial dysmorphism would indicate aspiration or upper airway cause of distress
- Frothing or persistent regurgitation can point to esophageal atresia and trachea esophageal atresia as an etiology
- Cyanosis would suggest cyanotic heart disease or PPHN
- A normal neonate deteriorating on day 5–7 would indicate possibility of inborn error of metabolism
- A normal neonate deteriorating towards end of first week could also indicate cardiac problems
- History of lethargy, poor feeding followed by respiratory distress would suggest aspiration as a cause of respiratory distress
- History of lethargy, poor feeding, grunting and cyanosis would also indicate severe distress
- History of prolonged ventilation would mean either a ventilator-associated pneumonia or chronic lung disease, particularly in a pre-term neonate.

*Abbreviations:* TEF, tracheoesophageal fistula; TTNB, transient tachypnea of newborn; MAS, meconium aspiration syndrome; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; SGA, small for gestational age; LGA, large for gestational age.

cleft palate and distress could be having aspiration pneumonia, or a neonate with features of Down's syndrome could be having a cardiac problem. Similarly, if there is micrognathia, the distress could be due to an upper airway problem or a neck mass could also be causing an upper airway obstruction. Potter facies will help identify pulmonary hypoplasia as cause of respiratory distress. A neonate who has failure to thrive or dehydration and has tachypnea is most likely to be having metabolic acidosis.

**Respiratory system examination** In respiratory system, one must look at the shape of the chest. A hyperinflated chest is most likely to occur in MAS or a congenital diaphragmatic hernia. A neonate with congenital diaphragmatic hernia in addition will have a scaphoid abdomen. If the chest is small, it could be any of the small chest syndromes. The type of sounds associated with respiratory distress is also useful; nose block, grunt or stridor, all give clues to the diagnosis.

Cyanosis is most likely to occur in a neonate with severe distress, cyanotic heart disease and PPHN. Cyanosis improving with crying has been typically described in bilateral choanal atresia. Decreased air entry bilaterally would suggest a condition like severe RDS, and unilateral decreased air entry is most likely to be due to pneumothorax, collapse or congenital lobar emphysema. It is important to check for position of heart sound as it might have shifted to the right side in diaphragmatic hernia or left-sided pneumothorax. Crepitations may be heard in pneumonia.

**Other systems** In a neonate with respiratory distress, cardiovascular examination should be done to look for murmurs, tachycardia and cardiomegaly. One must look for hepatomegaly to identify cardiac failure. A CNS examination is necessary to see if cause of tachypnea is central neurogenic hyperventilation. A neonate who has Erb palsy and distress may be due to phrenic nerve palsy. Severe hypotonia in a neonate with respiratory distress would indicate that respiratory distress could be due to neuromuscular disease.

**Pulse oximetry** Currently pulse oximetry should be considered as part of clinical examination of a neonate with respiratory distress. It is always useful to check the preductal saturation. If both preductal and postductal saturations are checked, a difference would suggest right to left shunting.

**Arterial blood gases** Blood gases should be determined for any neonate with moderate or severe respiratory distress. Blood gas assessment helps in determining etiology, severity of illness and the need for respiratory support.

**Chest X-ray** Chest skiagram is mandatory in any neonate with respiratory distress. It helps identify etiology and helps to rule in or rule out any malformations. Any chest X-ray taken in a neonate should be with a nasogastric tube *in situ*, so that by this simple test TEF or esophageal atresia can be identified.

### Causes of Transient Respiratory Distress

Conditions such as delayed lung fluid clearance, hypothermia, mild metabolic acidosis, hypoglycemia, polycythemia, amniotic fluid aspiration can cause transient respiratory distress, which disappears after correcting the underlying problem.

### Causes of Persistent Respiratory Distress

If a preterm neonate continues to require ventilatory support, one must consider chronic lung disease, ventilator-associated pneumonia or presence of a patent ductus arteriosus. In a term neonate requiring continued support, one must consider PPHN, ventilator-associated pneumonia. Cardiac disease, structural malformations, inborn errors of metabolism and rare causes of respiratory distress like primary surfactant deficiency may cause persistent distress and require continued respiratory support.

age (LGA) has already been mentioned in the history section. The next most important step in general examination would be to look for dysmorphic features and malformations. A neonate with

### Distinguishing PPHN from Cyanotic Heart Disease

Many times a neonate presents with significant respiratory distress and cyanosis. In the absence of an echocardiography, it is difficult to rule in or rule out a cardiac condition. A hyperoxia and hyperventilation test will help in distinguishing PPHN from cyanotic heart disease. In cyanotic heart disease the  $\text{PaO}_2$  will be between 100 and 150 mm Hg and usually will not exceed 100 mm Hg with the test, whereas in PPHN the  $\text{PaO}_2$  will increase beyond 100 mm Hg when hyperoxia and hyperventilation are provided. A greater than 10% difference in the pre- and postductal oxygen saturation is also useful to determine the presence of a right to left shunt.

### MORE ON THIS TOPIC

- Archer N. Cardiovascular disease. In: Rennie JM. Robertson's text book of Neonatology, 4<sup>th</sup> ed. USA: Elsevier, Churchill Livingstone; 2005. pp. 619-60.
- Jalal M, Abu-Shaweesh. Respiratory disorders in preterm and term infants. In: Martin RJ, Fanaroff AA, Walsh MC. Neonatal Perinatal Medicine—Diseases of the Fetus and Infant 9<sup>th</sup> ed. USA: Elsevier Mosby; 2011. pp. 1141-69.
- Kamath BD, MacGuirre ER, McClure EM, et al. Neonatal mortality from respiratory distress syndrome: lessons for low-resource countries. Pediatrics. 2011;127:1139

Kumar A, Bhatnagar V. Respiratory distress in neonates. Indian J Pediatr. 2005;72:425-8.

Kumar A, Bhat BV. Epidemiology of respiratory distress in newborns. Indian J Pediatr. 1996;63:93-8.

### IN A NUTSHELL

1. It is important to assess severity of respiratory distress in the newborn by using a respiratory distress score
2. Etiology can be respiratory or nonrespiratory
3. Common causes include RDS in preterm neonates and MAS and pneumonia in term neonates
4. Surgical causes must be ruled out as these are correctible by surgical intervention
5. History, particularly age of onset of respiratory distress, is useful to determine etiology
6. Pulse oximetry should be considered to be part of clinical examination in a neonate with respiratory distress
7. Chest skiagram is useful in determining the etiology of respiratory distress in the neonate and should always be taken with a nasogastric tube in situ.

## Chapter 17.2

# Neonatal Apnea

Manoj Modi

Apnea is a disorder of respiratory control characterized by an abnormal pause during spontaneous breathing. Though exact mechanisms for occurrence of apnea and associated risk factors are not completely elucidated till date, advent of molecular genetics has led to great improvement in our understanding about nature of this dreaded condition. Most common diagnosis for apnea in neonates is apnea of prematurity (AOP), which is believed to be an effect of immaturity of respiratory control.

## FETAL BREATHING AND TRANSITION AT BIRTH

During fetal life, breathing is intermittent and occurs during the low-voltage electrocortical state. Immediately after birth, as a part of extrauterine adaptation, breathing becomes continuous, irrespective of electrocortical state. The regulatory mechanisms for this transition from intrauterine life are not precisely elucidated. The continuous breathing after birth may be a result of altered threshold of peripheral and central chemoreceptors, which now trigger at lower PCO<sub>2</sub> and higher PO<sub>2</sub> of neonates. In addition, it is believed that somatic sensory stimuli after birth lead to suppression of midbrain inhibitor by increasing neuronal traffic in brainstem.

Though breathing is continuous in most term neonates, brief pauses of 5–10s, after 15–20s of regular breathing are not uncommon. This pattern of breathing is called periodic breathing. Periodic pattern of breathing is related to gestational age and has been observed for up to 25% of the breathing time in preterm neonates compared to 2–5% of time in term neonates. The occurrence of periodic breathing declines substantially by 40–50 weeks postconceptional age. This pattern of breathing is observed more often during REM sleep, though it may also occur during awake state or quite sleep. However, this breathing pattern is inconsequential, as it is not associated with any change in heart rate or oxygen saturation. These neonates require no treatment and their later outcome is excellent. AOP is considered as an extension of periodic breathing, though some researchers doubt this association.

## DEFINITION AND CLASSIFICATION

Apnea is defined as prolonged cessation of air flow, which may be associated with change in oxygen saturation and heart rate. However, there is no consensus regarding duration of respiratory pause, or degree of change in saturation and heart rate, which should be considered abnormal. The most widely used definition of AOP is cessation of respiration in preterm neonates, which lasts for more than 20s, or is accompanied by fall in oxygen saturation to less than or equal to 80% or fall in heart rate to less than two-third of baseline lasting for greater than or equal to 4s.

Traditionally, apnea in neonates is classified into three categories: central, obstructive and mixed. *Central apnea* is characterized by a complete cessation of respiratory efforts without an involvement of airway obstruction. *Obstructive apnea* is characterized by cessation of airway flow, where neonate tries to breathe against an obstructed upper airway. In *mixed apnea*, there is element of both central and obstructive apnea. Mixed apnea accounts for about 50% of all cases of apnea in premature neonates, followed by central apnea (40%) and obstructive apneas (10%).

## INCIDENCE

The incidence of AOP is inversely correlated with gestational age and birthweight. Approximately 50% of very low birthweight infants and almost 100% extremely low birthweight infants experience apnea during birth hospitalization. Incidence of AOP is 10–15% at 32–35 weeks gestation, approximately 50% at 30–31 weeks, and nearly 100% at gestation below 29 weeks. Apneas usually resolve by 40–44 weeks postmenstrual age (PMA) in most preterm neonates.

## PATHOGENESIS

The exact pathogenesis of AOP is poorly understood. It is believed to be due to functional immaturity of respiratory centers in brainstem that regulate breathing, mainly via central chemoreceptor zone. This is manifested in the form of an immature ventilatory response to hypercapnia and hypoxia and an exaggerated inhibitory response to mechanical or chemical stimulation of airway receptors. Ventilatory response of a preterm neonate is further modified by a number of other coexisting morbidity factors or disease states.

### Diminished Hypercapnic Response

Term neonates and adults respond to hypercapnea with an increase in their minute ventilation by increasing both tidal volume and respiratory rate. This ventilatory response to hypercapnea is mainly mediated through stimulation of chemosensitive zone on the ventrolateral surface of the medulla. In contrast to term neonates, hypercapnic exposure in preterm neonates is associated with prolonged expiratory duration. This altered response to hypercarbia, in preterm neonates, is attributed to structural and functional immaturity of medullary chemosensitive zone. Furthermore, in preterm infants, there is upregulation of multiple inhibitory neurotransmitter including  $\gamma$ -aminobutyric acid (GABA), adenosine, endorphins, and prostaglandins, which could be additionally implicated for this aberrant response.

### Hypoxic Depression

Preterm infants respond to a decrease in ambient oxygen with a transient increase in respiration, which is subsequently followed by a sustained respiratory depression. This biphasic response to hypoxia in preterm infants is postulated to be due to an initial stimulation of peripheral chemoreceptors, followed by an overriding depression of the central medullary receptors. It is unclear if this biphasic ventilator response to hypoxia is an initial triggering factor for development of apnea or not, hypoxia may aggravate apnea and result in delayed recovery of the infant.

### Enhanced Inhibitory Reflexes

Cessation of breathing in response to laryngeal stimulation is a protective reflex that prevents aspiration of contents in lungs. In preterm infants, there is an exaggerated response to stimulation of laryngeal mucosa, leading to prolonged apnea. The precise mechanisms for this maturational difference in laryngeal reflex-induced apnea are not known.

### Upper Airway Instability

An in-coordination between upper airway and chest wall muscle responses to chemoreceptor stimulation might be additional explanation for apnea of prematurity, particularly for mixed apnea. In mature neonates, upper airway muscle activity precedes the diaphragmatic contractility ensuring upper airway patency at peak inspiratory flow. It is believed that in preterm infants, activation of diaphragm precedes activation of upper airway, causing pharyngeal structures to collapse, leading to obstruction of upper airway during inspiratory efforts. This delayed activation of upper airway muscle may either trigger or prolong the apneic episode.



### Mechanoreceptors

The Hering-Breuer reflex is a reflex triggered to prevent overinflation of the lungs. This is mediated by stretch receptors present in the smooth muscle of the airways, which respond to excessive stretching of the lung during large inspirations by sending inhibitory signals to brainstem through vagus nerve. The strength of this reflex increases with gestation, consistent with a maturational increase of respiratory drive induced by the stretch receptors and may play a role in the reduced ventilatory drive seen in preterm infants.

### Sleep State and Apnea

Apnea of prematurity is observed more frequently during active sleep. This could be partly explained by paradoxical activity of intercostal muscles during respiration, due to spinal inhibition. This leads to inward movement of chest wall during inspiration, particularly in extremely preterm infants with a more compliant chest wall. This leads to a decrease in functional residual capacity (FRC) and impaired oxygenation, hence predisposing the preterm neonate to apnea.

### Gastroesophageal Reflux

Gastroesophageal reflux (GER) and apnea, both are common occurrence in preterm infants and both often coexist. GER is frequently attributed as cause of apneic episodes; however, role of GER in causation of apnea is debatable. Many studies have evaluated temporal relationship between apnea and GER. Findings of these studies suggest that even when apnea and GER coexist, apnea usually precede the reflux episode. Hypoxia associated with apneic episode is suggested to reduce tone of lower esophageal sphincter, predisposing to GER.

### Feeding-related Apnea

Preterm infants frequently experience apnea during feeding sessions, which are usually obstructive or mixed in nature. This could be related to immaturity of sucking-swallowing-respiration coordination. This results in onset of breathing efforts; while milk contents are still there in pharynx, leading to obstruction of airway during inspiration. In addition, there is a marked ventilatory depression during the initial continuous sucking phase of feeding. Activation of the laryngeal chemoreflex, repeated swallowing and prolonged airway obstruction may be attributed as possible factors for this ventilatory depression. This feeding-related apnea usually resolve by 44–54 weeks gestation. Infants with chronic lung disease and neurologic abnormalities have a higher propensity of feeding-related apneic episodes.

## MONITORING AND EVALUATION

As apnea are common in preterm neonates, particularly during first few days after birth, all preterm infants less than 35 weeks gestation should preferably be monitored for apneic spells for first week of life. There is a rapid decline in apneic episodes in most preterm infants after first few weeks. However, in very preterm infants, apnea may continue for 40–44 weeks postmenstrual age (PMA) warranting a continuous monitoring. All sick or unstable neonates, irrespective of their gestation should also be evaluated for apnea, till the time they become stable and alert.

Apnea may be detected by transthoracic impedance pneumography, which detects respiration by change in impedance over chest with movement of air. Electrodes are placed on either side of the chest above and below the diaphragm. With inhalation, air fills in the lungs, increasing the impedance across thoracic cavity. This is interpreted by the monitor as respiratory movement. If there is no movement of air in lungs, it is interpreted as apnea. A major limitation of impedance technology is that it cannot detect obstructive apnea. An alternative device to monitor apnea is nasal thermistor, which detects the presence of flow across nares by a

rise in temperature of thermistor, on contact with exhaled warm air. Many units do not have access of these devices and use routine pulse oximetry to diagnose apnea. An apneic episode associated with desaturation and/or bradycardia will generate an alarm, which will drag attention of caregiver. Many centers offer home apnea monitoring for neonates, who are otherwise well and meet discharge criteria but continue to have occasional episodes of apnea for prolonged period. However, this is a debatable practice as home apnea monitoring has not been shown to decrease the incidence of sudden infant death syndrome (SIDS).

Any infant having apnea should be evaluated for possible cause of apnea. Many neonatal conditions may manifest with apnea in neonates; hence, neonate should be evaluated for these conditions as appropriate. Apnea of prematurity (AOP) should always be a diagnosis of exclusion.

## Differential Diagnosis of Apnea of Prematurity

- *Temperature instability* Hypothermia, hyperthermia
- *Metabolic* Hypoglycemia, hypocalcemia, hyponatremia, hypernatremia, acidosis
- *Infections* Sepsis, pneumonia, UTI, meningitis
- *CNS* Intracranial hemorrhage, seizures, infections, other structural malformations
- *Cardiovascular* Hypertension, hypotension, hypovolemia, vagal tone, heart failure
- *Hematological* Anemia, polycythemia
- *Respiratory* RDS, pneumothorax, hypoxemia, hypercarbia, airway obstruction, BPD spells
- *Gastrointestinal* Necrotizing enterocolitis, GERD
- *Drugs* Intrapartum magnesium exposure, sedatives.

## MANAGEMENT OF APNEA

### General Measures

- *Maintain airway, breathing and circulation*
- *Avoid vigorous suctioning of oropharynx*
- *Position* Extreme flexion or extension of neck should be avoided. Prone positioning improves thoracoabdominal synchrony and stabilizes the chest wall and may reduce AOP. However, unsupervised prone nursing has been associated with an increased risk of SIDS; hence, an infant being nursed in prone position should not be left unattended and should be on continuous monitoring.
- *Kinesthetic stimulation* Tactile stimulation is the most common intervention offered to a neonate having an apneic episode. This simple intervention most likely works by generating excitatory, nonspecific neuronal activity in the brainstem center and stimulate respiratory activity. Due to same logic, some units use oscillating mattresses and various other ways to provide continuous kinesthetic stimulation to neonates having recurrent apnea.
- *Maintain euthermia* Hypothermia and hyperthermia both are risk factors for AOP and should be treated promptly.
- *Check and correct hypoglycemia, hypocalcemia and electrolyte imbalance*
- *Sensory stimulation* Avoid exposure to obnoxious odors as these lead to a decrease in respiratory drive. Pleasant odors, such as rose scent or smell of mother's milk elicit an increased respiratory drive.

## Pharmacological Treatment

### Methylxanthines

Methylxanthines are most commonly used medications for treatment of neonatal apnea. There is no definite consensus on when to start pharmacological treatment. Most often treatment

is started when apneic spells are recurring, nonresponsive to supportive measures or if an apneic spell requires bag and mask ventilation. There is no benefit of prophylactic use of xanthenes for prevention of apnea of prematurity.

**Methylxanthines** are central respiratory stimulants that increase CO<sub>2</sub> sensitivity and, hence, lead to improved tidal and minute volumes and blood gas values. These also increase diaphragmatic function and decrease muscle fatigue. The mechanism of these actions is competitive antagonism of adenosine receptors. Adenosine acts as an inhibitory neuroregulator in the central nervous system and is released during hypoxia. Theophylline and caffeine are two commonly available xanthine preparations for treatment of apnea in neonates.

**Theophylline** Theophylline is available in oral and intravenous preparations. The intravenous form is aminophylline, a complex of theophylline and ethylenediamine. Mean half-life of theophylline is approximately 30 hours. Treatment usually is initiated with a loading dose followed by maintenance therapy. The loading dose is 5–6 mg/kg, followed by 1–2 mg/kg every 8 hours. A therapeutic effect is seen at plasma concentration of at least 5 mg/L, although a target plasma concentration is around 10 mg/L. Plasma concentration of theophylline may vary widely at the same dosage levels, and therapeutic index is low, necessitating frequent monitoring and dose adjustments. Toxicity usually starts after plasma concentration of 20 mg/L. Common adverse effects include tachycardia, cardiac dysrhythmias, abdominal distention, feed intolerance, seizures, hyperglycemia and electrolyte imbalances.

**Caffeine** Caffeine is available for both oral and intravenous use and has some advantages over theophylline. It is associated with less adverse effects, and has long half-life, leading to once a day dosing. It has higher therapeutic index with wide margin of safety; hence, routine monitoring of drug level is not required. The recommended dose of caffeine citrate is 20 mg/kg loading, followed 24 hours later by 5.0 mg/kg IV or PO q 24 hours. If apnea recurs, maintenance dose may be increased stepwise, up to 12.5–15 mg/kg/day. Side effects are unusual at usual dose range. Commonly observed adverse effects are jitteriness, tachycardia and occasionally feed intolerance.

### Concerns with Methylxanthines

**Effect on neurological development** The methylxanthines are adenosine receptor antagonists. Adenosine is believed to be neuro-protective during ischemia. It is postulated that methylxanthines may actually worsen hypoxic tissue damage in infants at risk of recurrent hypoxemia. However, a large multicentric trial (CAP trial) has established safety of caffeine therapy in neonates with birth weight 500–1250 g. Caffeine therapy was associated with reduced incidence of BPD and lesser duration of mechanical ventilation. Five years follow-up of the study revealed no difference in the composite outcome of death or severe impairment but there was statistically significant improvement in motor coordination and visual perception in caffeine-treated group.

**Effect on growth** Another concern regarding use of methylxanthines is its effect on growth of preterm neonates. Methylxanthines increase oxygen consumption in preterm neonates by 20–25%. A single 5 mg/kg dose of theophylline increases energy expenditure by 15 kJ/kg per day; this may have an effect on growth of preterm infant. In CAP trial, daily weight gain of caffeine-treated infants was less during the first 3 weeks of therapy. However, there was no difference by 4 weeks age. By 18–24 months age, the mean percentiles for weight, height and head circumference did not differ between caffeine and placebo.

### Doxapram

Doxapram is another drug used for apnea in neonates. Mechanism of action appears to be related to stimulation of carotid

chemoreceptors at lower doses and to direct stimulation of central respiratory control neurons at higher doses. The intravenous loading dose for doxapram is 2.5–3.0 mg/kg over 15 min followed by a continuous infusion of 1.0 mg/kg titrated to the lowest responsive dose (maximum dose 2.5 mg/kg/h). At low doses as used in AOP, significant side effects are uncommon but increased blood pressure and other side effects of catecholamine stimulation can occur, including lowering seizure threshold, gastrointestinal disturbances and even heart block. A single small study on doxapram showed decrease in apnea in first 48 hours of initiation of medication; however, the effect was not sustained. There are concerns about safety of doxapram use in neonates. Doxapram has been shown to decrease the cerebral blood flow in preterm neonates and some studies have shown mental developmental delay with prolonged use of doxapram. In view of a lack of evidence for benefits and possible neurological toxicity, doxapram should not be used as primary therapy and should be kept as reserve drug for treatment of apnea.

## Nonpharmacological Measures

### Ventilation

Some premature infants continue to have apnea while on methylxanthine therapy. In these infants, use of nasal continuous positive airway pressure (CPAP) may reduce incidence and frequency of apnea. CPAP is hypothesized to work by several mechanisms, including improvement of PaO<sub>2</sub> by increasing FRC, splinting of the upper airway and stabilization of compliant chest wall of preterm neonates eliminating thoracoabdominal dyssynchrony. Potential adverse effects of CPAP include barotrauma, abdominal distension, feeding intolerance and local nasal trauma. CPAP should be considered if infant continues to have apnea while on xanthine therapy; there is no role of prophylactic CPAP for prevention of apnea of prematurity. If apnea persists on nasal CPAP, infant is intubated and put on invasive ventilation. Some investigators have suggested nasal intermittent positive pressure ventilation (NIPPV) as a missing link between nasal CPAP and invasive ventilation. Two trials have compared nasal CPAP to nasal IPPV. However, both trials have shown different results. One study showed no difference in apneas whereas the other showed NIPPV to be more effective in reducing apneas.

### Kangaroo Mother Care

Kangaroo mother care, also known as skin-to-skin contact, is a widely prevalent practice, where a hemodynamically stable neonate is kept in close contact with skin of mother/caregiver. However, the effect of this approach for the treatment of AOP remains controversial. A randomized controlled trial showed that infants receiving kangaroo care had fewer apneic and bradycardic events than those who did not receive kangaroo care. In another study, researchers found that apneic and bradycardic events were increased during kangaroo care.

### CO<sub>2</sub> Inhalation

A fall in CO<sub>2</sub> levels below a threshold leads to an apnea and a rise in CO<sub>2</sub> above the apnea threshold will reduce or abolish apnea. This has led researchers to investigate the role of CO<sub>2</sub> inhalation in prevention or treatment of apnea of prematurity. Recently, a randomized controlled trial of theophylline versus CO<sub>2</sub> inhalation for treatment of AOP showed that inhalation of a low CO<sub>2</sub> concentration (0.8%) in premature infants was as effective as theophylline in decreasing apnea. No adverse effects of CO<sub>2</sub> inhalation on cerebral blood flow velocity were observed. However, feasibility and long-term safety of this intervention is yet to be established and CO<sub>2</sub> inhalation still remains an experimental tool.

### Blood Transfusion

Anemia is associated with decreased oxygen content of blood and has been suggested to increase the risk of apnea. Neonates with idiopathic apnea and coexisting anemia are transfused with packed cells. Transfusion is usually considered if hematocrit is <25% and infant has episodes of apnea and bradycardia that are frequent or severe while on methylxanthine therapy. However, benefit of such practice is debated and studies have reported no difference in frequency of apnea before or after transfusion though one randomized trial of liberal or restrictive transfusion practices reported higher frequency of apnea in restrictive group.

### CONSEQUENCES OF NEONATAL APNEA

Brief apnea, which resolves quickly, may not be a threat to physiological well-being. A significant apnea is that associated with hypoxia, hypercarbia, bradycardia and changes in blood pressure. A prolonged apnea may lead to cerebral hypoperfusion, which may result in hypoxic-ischemic insult to developing brain of preterm infant. This initial hypoperfusion and hypoxia might be followed by a transient compensatory hyperperfusion with an associated potential reperfusion injury. These concerns warrant neurological follow-up of infants experiencing these events. However, the long-term consequences of recurrent apnea and bradycardia are difficult to ascertain due to confounding effect of coexistence of other common neurological morbidities.

Many studies have reported a relationship between number of apnea days and neurodevelopmental impairment. However, these studies did not establish whether apnea is a cause of or results from underlying cerebral dysfunction in preterm infants or if both apnea and lower neurodevelopmental indices have a common underlying cause.

### IN A NUTSHELL

1. Apnea is a common condition in preterm neonates, usually caused by an immaturity of respiratory control in brainstem.
2. Apnea of prematurity is most common diagnosis for apnea in neonates. However, it should be a diagnosis of exclusion, after evaluation of other differentials for apnea.
3. Xanthines are mainstay of pharmacotherapy for apnea.

### MORE ON THIS TOPIC

- DiFiore JM. Neonatal cardiorespiratory monitoring techniques. *Semin Neonatol.* 2004;9:195-203.
- Hansen TN, Corbet A. Control of breathing. In: Tausch HW, Ballard RA, Gleason CA. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia: WB Saunders; 2005. pp. 616-33.
- Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. *Cochrane Database Syst Rev.* 2010;12:CD000140.
- Holditch-Davis D, Scher M, Schwartz T. Respiratory development in preterm infants. *J Perinatol.* 2004;24:631-9.
- Martin RJ, Jalal M, Abu-Shaweesh, Baird TM. Pathophysiologic mechanisms underlying apnea of prematurity. *Neo Reviews.* 2002;3:59-65.
- Mathew OP. Apnea of prematurity: pathogenesis and management strategies. *J Perinatol.* 2011;31:302-10.
- Schmidt B, Anderson PJ, Doyle LW, et al; Caffeine for Apnea of Prematurity (CAP) Trial Investigators. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA.* 2012;307:275-82.
- Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy. *N Engl J Med.* 2007;357:1893-902.
- Stokowski LA. A primer on apnea of prematurity. *Adv Neonatal Care.* 2005;5:155-70.
- Steer PA, Henderson-Smart DJ. Caffeine versus theophylline for apnea in preterm infants. *Cochrane Database Syst Rev.* 2001; CD000273.
- Zhao J, Gonzalez F, Dezhi M. Apnea of prematurity: from cause to treatment. *Eur J Pediatr.* 2011;170:1097-105.

## Chapter 17.3

# Neonatal Ventilation

Sourabh Dutta

The advent of neonatal intensive care has also resulted in improved respiratory support for neonates and consequently improved survival. But neonates have a physiology distinct from infants and adults and more so if they are born preterm. It is, therefore, important that pediatricians understand the physiology of neonatal ventilation.

### WHAT ARE VENTILATORS?

The most commonly used basic neonatal ventilators are the so-called *timed cycled*, *continuous flow*, *pressure-controlled* ventilators (**Fig. 1**). An endotracheal tube is the interface device through which the ventilator delivers gases to the newborn infant. *Time-cycled* means that the ventilator switches from inspiration to expiration based on a set time. *Pressure-controlled* means that the physician decides the pressure that is to be delivered and the tidal volume is a measured parameter. This is in contrast to *volume-controlled* ventilation where the physician decides the volume to be delivered. *Continuous flow* refers to flow of gases in the ventilator circuit. While the flow of gases in the ventilator circuit is continuous, the flow of gases through the endotracheal tube transiently ceases and reverses direction in each respiratory cycle.

### VENTILATOR PARAMETERS

In conventional ventilation, there are six parameters we are primarily concerned with (**Table 1**).

#### Gas Flow

Gas flows from a region of high pressure to low pressure. This is shown graphically in **Figure 2**.

The flow of gases is governed by Poiseuille's law which states:

$$\text{Flow} = [\pi \times (P_1 - P_2) \times \text{radius}^4] \div (8 \times \text{viscosity} \times \text{length})$$

Therefore, the flow of gases through an endotracheal tube increases when the difference between  $P_1$  and  $P_2$  increases, when the radius of the endotracheal tube increases, when the length of the endotracheal tube decreases and when the viscosity of the gas mixture decreases. The flow of gases through the endotracheal tube decreases when the pressure difference decreases, the radius decreases, the length of endotracheal tube increases and the viscosity of the gas mixture increases. For all practical purposes, the viscosity of the gas mixture is a constant.

### Spontaneous Breathing versus Ventilator Breaths

#### Spontaneous Breathing

To understand how a ventilator works, it is important to understand how spontaneous breathing takes place. At the onset of a spontaneous breath, the rib cage moves outwards and the diaphragm moves downwards to create a negative intrathoracic pressure with respect to the atmospheric pressure. This difference in pressure results in the flow of atmospheric air into the lungs. The magnitude of flow depends on the pressure gradient, the radius of the glottis and the length of the air passages. During exhalation, the rib cage and diaphragm move inwards to create a slight positive intrathoracic pressure and this results in the flow of gases from the lungs out through the nares into the atmosphere. The glottis partially closes during normal breathing. This creates a physiological positive end-expiratory pressure (PEEP) which is

around 3 cm  $H_2O$ . The normal respiratory rate (RR) ranges from 20 to 60 breaths per minute.

#### Ventilator Breaths

Unlike spontaneous breathing, which is negative pressure ventilation, the mechanical ventilation provided by a ventilator is positive pressure ventilation. The baseline pressure in the ventilator circuit, endotracheal tube and air passages of the neonate is the PEEP. Periodically, the pressure inside the ventilator circuit is rapidly increased to reach the peak inspiratory pressure (PIP). This creates a pressure gradient (PIP-PEEP) which drives gases from the ventilator circuit through the endotracheal tube into the lungs of the newborn infant. If the ventilator pressure is increased almost instantaneously to reach the PIP, it is called square wave ventilation, whereas if the ventilator pressure is made to rise slowly, it is called sine wave ventilation.

The flow of gases continues till such time that the pressure inside the lungs equilibrates with the pressure inside the ventilator circuit (PIP). The magnitude of the flow through the endotracheal tube is dependent upon the pressure gradient, the internal radius of the endotracheal tube and the combined length of the endotracheal tube and the air passages of the neonate. The duration over which the pressure in the ventilator circuit rises and is held at the level of the PIP is called inspiratory time ( $T_i$ ). Once the  $T_i$  is complete, in a time-cycled ventilator, the pressure inside the ventilator circuit reduces instantaneously to the level of PEEP. Since the pressure inside the lungs is still at the level of PIP, the pressure gradient now reverses and gases flow out of the lungs into the ventilator circuit. The flow continues till such time that the pressure in the lungs equilibrates with that of the ventilator circuit (PEEP). These phenomena are shown graphically in **Figures 3A and B**. Note that the flow of gases into the lungs does not occur throughout the  $T_i$ ; and, similarly, the flow of gases out of the lungs does not go on throughout the expiratory time ( $T_e$ ), because in both instances pressure equilibrates before the  $T_i$  and  $T_e$  are completed. Spontaneous breathing can continue superimposed on the mechanical breath cycle.

#### Compliance

Compliance is defined as the change in volume per unit change in pressure (see pressure-volume curve in **Figure 4**). The change in pressure over one ventilator cycle ( $\Delta P$ ) is essentially PIP minus PEEP. The change in volume during one breath is the ventilator tidal volume. The normal tidal volume is 4–8 mL/kg, with the median figure being around 5 mL/kg. Therefore, compliance is the tidal volume divided by the difference between PIP and PEEP. Respiratory distress syndrome (RDS) is a typical example of a disease with low compliance. In RDS, a given change in pressure results in a lower tidal volume compared to a normal lung.

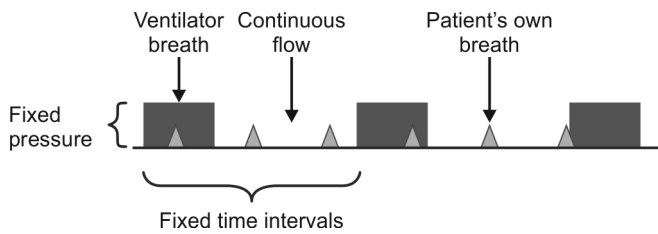
#### Resistance

Just as the resistance of an electric wire is equal to the voltage difference divided by the flow of current, the resistance of a tube to the flow of gases is equal to the pressure difference divided by the flow rate of gases. We have already seen that the flow of gases is directly proportionate to the pressure difference and radius to the 4th order of magnitude and inversely proportionate to the length (with viscosity being a constant). Thus, resistance is directly proportionate to the length of the tube and inversely proportionate to the radius to the 4th order of magnitude. Since the radius is raised to the 4th power, minor changes in the internal radius of the endotracheal tube or air passages (due to secretions, blood or fluid) can result in huge changes in resistance.

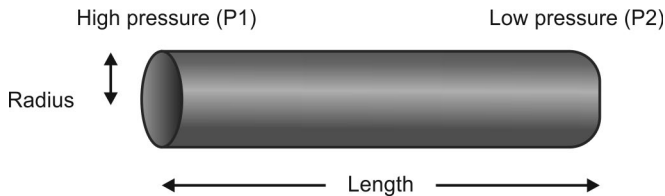
#### Time Constant

We have seen earlier that it takes some time for pressure to equilibrate between the ventilator circuit and the lungs (i.e., the alveoli). The pressure changes at the level of the alveoli seem





**Figure 1** Ventilator breaths and spontaneous breaths on continuous flow



**Figure 2** Factors affecting flow of gases from high-pressure end to low-pressure end of a tube

to lag behind the pressure change in the ventilator. The term 'time constant' gives us an idea of the time taken for pressure to equilibrate between the proximal airway and the alveoli.

1 Time constant = Compliance  $\times$  Resistance.

At the onset of inspiration, there is a certain pressure difference between the proximal airway and the alveoli. It takes 1 time constant for the rise in alveolar pressure to cover 63% of this pressure difference. Once 63% of the pressure difference is achieved, it requires another time constant for the alveolar pressure to reach 63% of the remaining pressure difference and so on. Thus, the equilibration of pressures is not a linear process but it follows first-order kinetics. As can be seen in **Figure 5**, it takes approximately 3 time constants to achieve 95% equilibration. Therefore, the  $T_i$  on the ventilator is generally set at 3 times the expected  $T_i$  constant. 95% equilibration is considered to be safe because extending the  $T_i$  beyond 3 time constants may result in overdistention.

A mirror image process occurs during expiration. The time constant during expiration is longer than inspiration because the radii of distal airways narrow during expiration, and the glottis remains partially closed during expiration. This is the reason why—both during spontaneous breathing as well as during mechanical ventilation—the time taken for expiration is longer than the time taken for inspiration.

If the  $T_i$  is set at less than 3  $T_i$  constants, it results in delivery of inadequate tidal volume; whereas, if it is set at a value greater than 3 time constants, it results in overdistention of the alveoli. If the  $T_e$  is set at less than 3  $T_e$  constants, it results in incomplete emptying of the alveoli and gas trapping within the lungs. Gas trapping over several mechanical breaths results in an unintended pressure

buildup at the end of expiration and this unintended pressure is called inadvertent PEEP.

A normal newborn lung has a compliance of 1.5–2 mL/cm  $H_2O$ /kg and a normal term newborn lung has a resistance of 0.03 cm  $H_2O$ /mL/s. A full-term 3 kg neonate will have a compliance of approximately 5 mL/cm  $H_2O$ . Therefore, the normal time constant is approximately 0.15s.

### Mean Airway Pressure

The maintenance of adequate levels of partial pressure of oxygen in arterial blood ( $PaO_2$ ) is called oxygenation. Oxygenation is proportionate to  $FiO_2$  and mean airway pressure (MAP). MAP is calculated by the area under the pressure-time curve per second of the respiratory cycle (**Fig. 6**). The area under the pressure-time curve of one respiratory cycle is  $(PIP \times T_i) + (PEEP \times T_e)$ . This is easy to understand because each of the boxes (the box made by the PIP and the box made by the PEEP) is rectangle. The time taken for each respiratory cycle is  $T_i + T_e$ .

Thus,  $MAP = [(PIP \times T_i) + (PEEP \times T_e)] \div [T_i + T_e]$ .

In sine wave ventilation, the PIP box is not a rectangle, and to correct for that, a constant  $k$  is included in the equation which is always less than 1.

The modified formula is:

$$MAP = [(k \times PIP \times T_i) + (PEEP \times T_e)] \div [T_i + T_e]$$

It is evident from this formula that the following interventions (in decreasing order of effectiveness) can increase the MAP:

- Increasing the PEEP
- Increasing the PIP
- Increasing the  $T_i$
- Shifting from sine wave to square wave ventilation
- Decreasing the  $T_i + T_e$ ; i.e., increasing the RR. Among all these parameters, increasing the RR has the least effect on MAP.

### Minute Ventilation

The removal of carbon dioxide from the lungs depends directly upon the minute ventilation.

$$\text{Minute ventilation} = \text{Tidal volume} \times \text{RR}$$

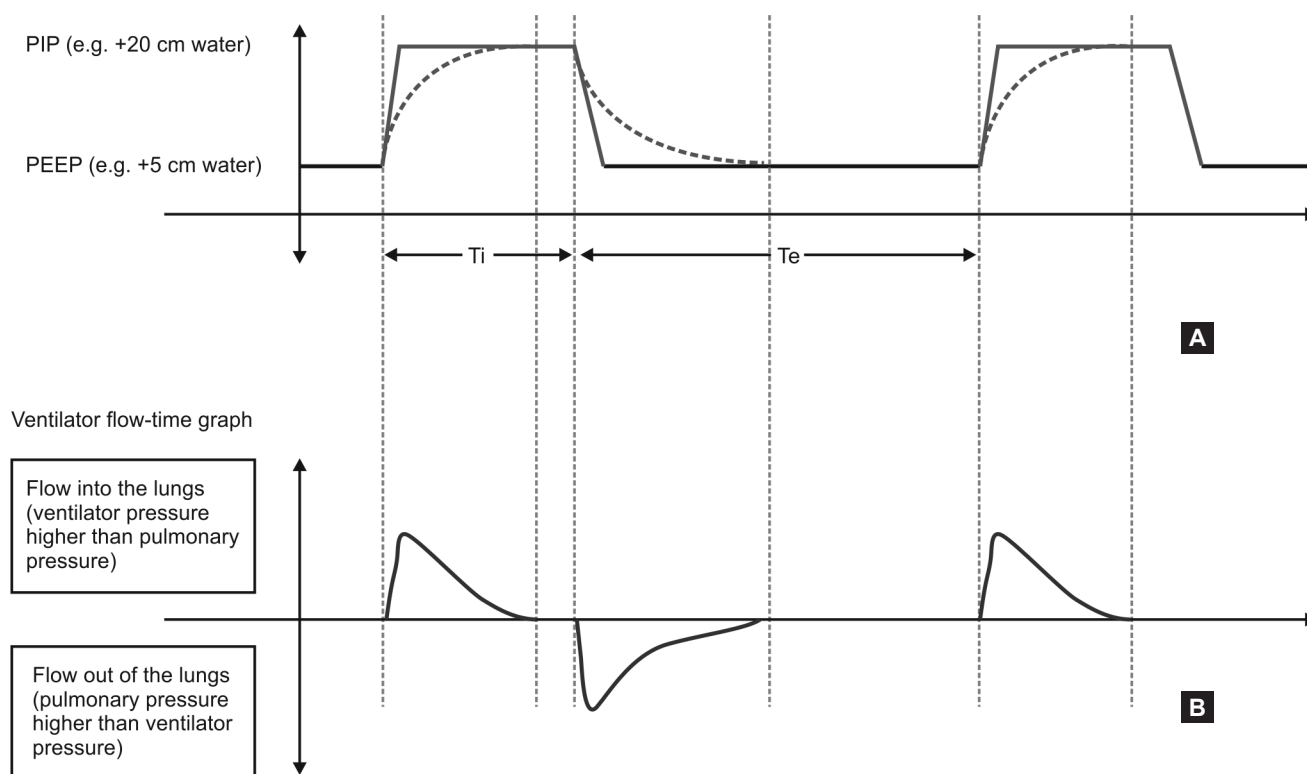
As can be seen from the pressure-volume curve in **Figure 4**, the greater the difference between PIP and PEEP (i.e.,  $\Delta P$ ), the greater is the tidal volume. Therefore, tidal volume can be increased either by increasing the PIP or by decreasing the PEEP or by doing both simultaneously. Minute ventilation can be increased by increasing the  $\Delta P$  or increasing the RR.

### MODES OF VENTILATION

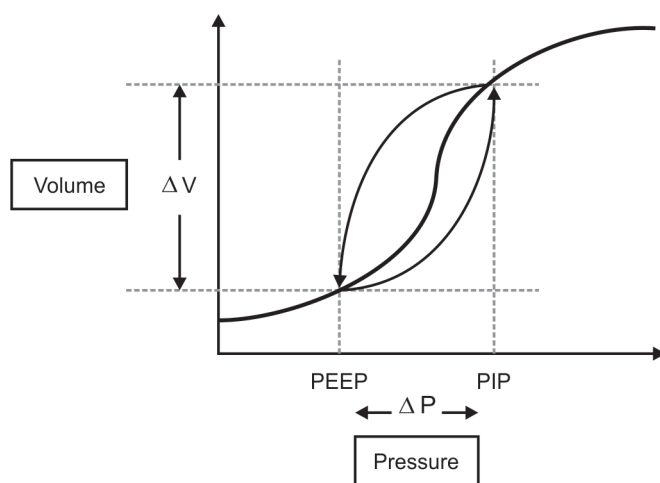
Modern day ventilators have a bewildering array of modes of ventilation. It will not be possible to cover all modes in a textbook for postgraduates. This chapter will attempt to touch upon intermittent mandatory ventilation (IMV), patients triggered modes of ventilation such as synchronized intermittent mandatory

**Table 1** Parameters adjustable on ventilators

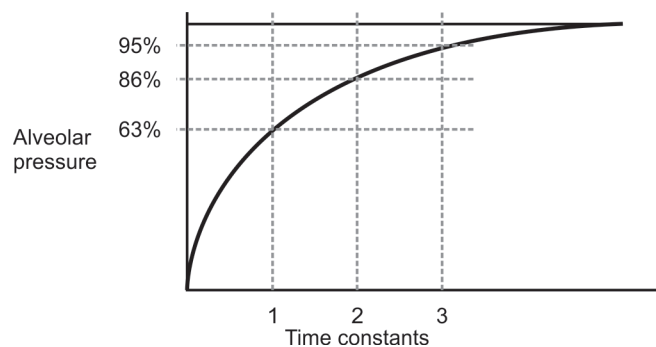
Parameter	Abbreviation	Explanation
Peak inspiratory pressure	PIP	Maximum pressure achieved by the ventilator during the inspiratory phase
Positive end-expiratory pressure	PEEP	Pressure maintained by the ventilator during the expiratory phase. This is the minimum pressure achieved during the respiratory cycle
Fraction of inspired oxygen	$FiO_2$	Fraction of inspired gases that comprises of oxygen
Inspiratory time	$T_i$	Time available for the ventilator to push gases into the lungs during the inspiratory phase of the respiratory cycle
Respiratory rate	RR	The number of mechanical breaths provided by the ventilator over 1 min. The expiratory time ( $T_e$ ) can be derived from the RR and $T_i$
Flow	F	The liters of gas that flow through the ventilator circuit per minute



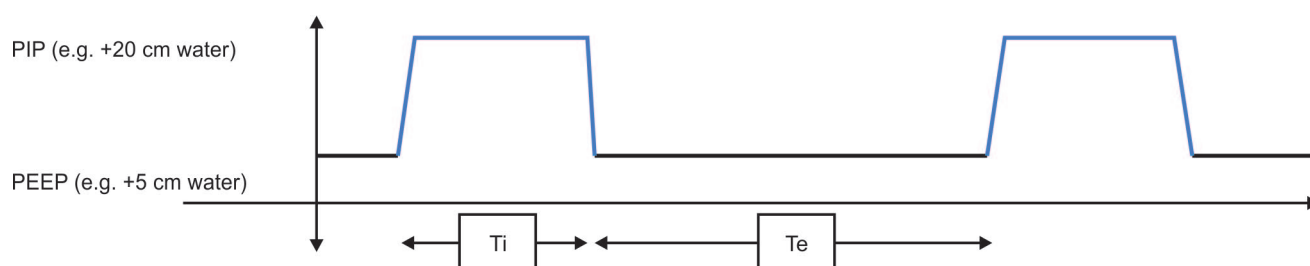
**Figures 3A and B** (A) Ventilator pressure-time graph; and (B) Ventilator flow-time graph  
Abbreviations:  $T_i$ , inspiratory time;  $T_e$ , expiratory time.



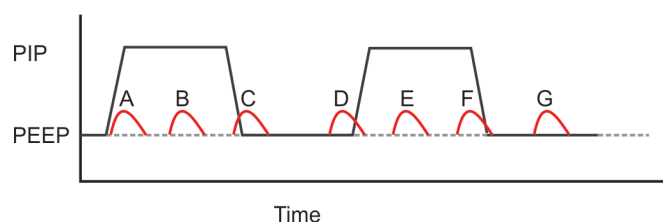
**Figure 4** Pressure-volume curve of a lung



**Figure 5** Equilibration of pressure versus time constant



**Figure 6** Mechanical ventilator breaths  
Abbreviations:  $T_i$ , inspiratory time;  $T_e$ , expiratory time.



**Figure 7** Asynchrony between spontaneous breaths and mechanical breaths

Abbreviations: PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure.

ventilation (SIMV), assist-control ventilation (ACV) and pressure support ventilation (PSV).

### Intermittent Mandatory Ventilation

In IMV, the mechanical breaths are provided at fixed intervals by the ventilator (intermittent) and the number of such breaths is also fixed (mandatory). As shown in **Figure 7**, in IMV, there is no synchronization of the spontaneous breaths of the patient (shown as blue colored breaths: A to G) with the ventilator breaths. There is dyssynchrony with respect to the start of each ventilator breath, the end of each ventilator breath and the total number of ventilator breaths. If any spontaneous breath happens to coincide with a ventilator breath, it is just a matter of random chance. Note that the start of the spontaneous breath A happens to coincide with the start of a mechanical ventilator breath and the end of spontaneous breath F happens to coincide with the end of a ventilator breath.

Note that the inspiratory phase of spontaneous breath C is superimposed on the expiratory phase of a mechanical breath, whereas

the expiratory phase of spontaneous breath D is superimposed on the inspiratory phase of a mechanical breath. When this form of dyssynchrony occurs, it results in sudden changes in intrapulmonary pressure; and may predispose to air leaks and increased work of breathing. Spontaneous breaths B and E are superimposed upon mechanical breaths. This results in an inadvertently high-tidal volume which can result in air leaks. Spontaneous breath G is superimposed upon the PEEP. This is akin to providing endotracheal continuous positive airway pressure (CPAP) in which the patient has to work hard to draw gases through a narrow tube.

### Triggered Modes of Ventilation

#### *Synchronized Intermittent Mandatory Ventilation*

In SIMV, the number of mechanical breaths is mandatory but wherever possible the onset of a mechanical breath is made to synchronize with a spontaneous breath. Each mandatory breath has a trigger window prior to the scheduled onset of the mandatory breath. If a spontaneous breath is initiated within this trigger window period, it triggers off a mechanical breath. Spontaneous breaths occurring in excess of the mandatory rate will not trigger a mechanical breath. If the patient is apneic, the ventilator simply delivers the fixed number of mandatory breaths at the scheduled intervals. In SIMV, the physician fixes the number of mandatory breaths (RR), PIP, PEEP,  $T_i$ , flow,  $FiO_2$  and the trigger sensitivity. The onset of the mandatory breaths is decided by the patient. The total number of ventilator breaths is not decided by the patient.

#### *Assisted Controlled Ventilation*

Every spontaneous breath triggers a mechanical breath that supports the spontaneous breath. This is the assist component of ventilation. The physician fixes the PIP, PEEP,  $T_i$ , flow,  $FiO_2$  and the trigger sensitivity. To cater to a situation where the patient may

**Table 2** Adjusting ventilator settings using blood gas measurements

$PaO_2$	$PaCO_2$	Change in single parameter required (and reasons thereof)	Alternate option (and situation where indicated)
Hyperoxia	Normal	Decrease $FiO_2$ (to normalize oxygenation without affecting minute ventilation)	Decrease PIP and PEEP by equal amount keeping $\Delta P$ constant (in situations where ventilator pressures are high and $FiO_2$ is already low)
Hypoxia	Normal	Increase $FiO_2$ (to normalize oxygenation without affecting minute ventilation)	Increase PIP and PEEP by equal amount keeping $\Delta P$ constant (in situations where ventilator pressures are low and $FiO_2$ is already high)
Normal	Hypercarbia	Increase RR (to normalize minute ventilation with no or minimal effect on oxygenation)	Increase PIP and decrease $FiO_2$ to offset the effect of PIP on oxygenation (in situations where tidal volume is low and should be increased to normalize minute ventilation)
Normal	Hypocarbia	Decrease RR (to normalize minute ventilation with no or minimal effect on oxygenation)	Decrease PIP and increase $FiO_2$ to offset the effect of PIP on oxygenation (in situations where the tidal volume is high and should be decreased to normalize minute ventilation)
Hyperoxia	Hypercarbia	Decrease PEEP (to decrease MAP and increase $\Delta P$ )	Decrease $FiO_2$ and increase RR (in situations where lung is underinflated; decreasing PEEP may cause derecruitment or tidal volume is already high)
Hyperoxia	Hypocarbia	Decrease PIP (to decrease MAP and decrease $\Delta P$ )	Decrease $FiO_2$ and decrease RR (in situations where tidal volume is already low)
Hypoxia	Hypercarbia	Increase PIP (to increase MAP and increase $\Delta P$ )	Increase $FiO_2$ and increase RR (in situations where tidal volume is already high)
Hypoxia	Hypocarbia	Increase PEEP (to increase MAP and decrease $\Delta P$ )	Increase $FiO_2$ and decrease RR (in situations where tidal volume is already low or lung is hyperinflated)

Abbreviations:  $PaO_2$ , partial pressure of oxygen in arterial blood;  $PaCO_2$ , partial pressure of carbon dioxide in arterial blood;  $FiO_2$ , fraction of inspired oxygen; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; RR, respiratory rate; MAP, mean airway pressure.

become apneic, there is a provision for a backup rate of mechanical breaths—this is the control component of ventilation. The control rate is set lower than the usual RR of the neonate and is only intended as a safety measure in case of apnea. In ACV, the onset of ventilator breaths and the total number of ventilator breaths are decided by the patient.

### Pressure Support Ventilation

Pressure support ventilation originated in adult ventilation as a means to decrease the work of breathing in intubated patients who were receiving CPAP. Spontaneous breathing on endotracheal CPAP is like breathing through a straw because the tidal volume of the spontaneous breath is drawn through a narrow endotracheal tube. In PSV, every spontaneous breath is supported by a so-called pressure boost which raises the pressure to a level lower than the usual PIP that is provided in mechanical ventilation. The purpose of this pressure boost is simply to overcome the work of breathing and not to provide the entire tidal volume via the mechanical breath. The patient is expected to generate the tidal volume. The onset of the PSV breath is triggered by the patient. An additional unique feature of PSV is that the ventilator measures the spontaneous inspiratory flow rate of the patient in real-time and terminates the mechanical breath when the patient's inspiratory flow rate drops to less than a certain fraction (often 15%) of the peak inspiratory flow rate. The drop in flow rate to less than 15% is an indicator to the ventilator that the patient spontaneous breath is about to finish. Thus, in PSV, the onset of ventilator breaths, the number of ventilator breaths and the Ti of ventilator breaths are decided by the patient.

## VENTILATOR SETTINGS

### Initial Settings

Three common clinical conditions—apnea of prematurity, RDS and meconium aspiration syndrome (MAS) will be used to exemplify the basis for selecting the initial ventilator settings.

#### Apnea

In apnea of prematurity, the lungs are essentially normal. The presence of an endotracheal tube bypasses the glottis. As discussed earlier, in spontaneous breathing, the partially closed glottis generates a physiological PEEP of 3 cm H<sub>2</sub>O. In apnea ventilation, the PEEP should, therefore, be set at 3 cm H<sub>2</sub>O. The time constant of a normal neonatal lung is approximately 0.15s. Therefore, the Ti should be set at 0.45s. To achieve a tidal volume of 5–10 mL/kg, the PIP required would be approximately 7–10 cm H<sub>2</sub>O. This can be derived from the fact that the normal compliance is 1.5–2 mL/cm H<sub>2</sub>O/kg and compliance equals  $\Delta V/\Delta P$ . FiO<sub>2</sub> should be set at 0.21 because the transfer of oxygen across the lungs into the pulmonary vasculature is normal. The RR must be set at 20/min which is the lower limit of normal.

#### Respiratory Distress Syndrome

The functional residual capacity (FRC) of a neonatal lung with RDS is lower than a normal lung. To restore the FRC, the PEEP should be approximately 5 cm H<sub>2</sub>O. The typical compliance of a neonatal lung with RDS drops to approximately 25% of that of a normal lung. On plugging in the values, the typical starting PIP to achieve a tidal volume of 5 mL/kg in a neonate with RDS is 15 cm H<sub>2</sub>O. The lungs are stiffer in a neonate with RDS; hence, the compliance is less. This is partly counterbalanced by the increased resistance in a premature baby because of the narrow airways. The net result is that the time constant is lower than in a normal lung. The Ti required in RDS is generally varies between 0.3s and 0.35s. The FiO<sub>2</sub> has to be adjusted to maintain normal saturation. Higher RRs (around 50–60/min) are recommended to decrease lung injury.

### Meconium Aspiration Syndrome

Meconium aspiration syndrome is characterized by a combination of areas of hyperinflation and areas of atelectasis. The PEEP is selected anywhere in the range of 3–5 cm H<sub>2</sub>O, depending on whether hyperinflation or atelectasis is dominant. Meconium partially blocks the air passages and increases bronchial hyperactivity; therefore, MAS behaves like an obstructive lung disease with increased airway resistance. This is counterbalanced by some decrease in compliance because of secondary deactivation of surfactant. The net result is that the time constant is longer than in the case of RDS. As in the case of any obstructive lung disease, the Te constant is affected out of proportion to the Ti constant. To allow for adequate Te and prevent gas trapping, the RR has to be maintained in the range of 40–45/min. The Ti is limited to 0.4s leaving the rest of the respiratory cycle for the Te. Persistent pulmonary hypertension of the newborn (PPHN) is an important complication of MAS in the initial phase of the disease. To prevent PPHN, it is important to avoid hypercarbia and hypoxia. Therefore, adequate minute ventilation and FiO<sub>2</sub> are required.

### Adjustment of Settings

Ventilator settings are adjusted based upon arterial blood gas findings (Table 2), clinical findings, pulmonary functions and the expected course of the disease.

#### Based on Arterial Blood Gases

We can easily derive the ventilator changes required for different combinations of PaO<sub>2</sub> and partial pressure of carbon dioxide in arterial blood (PaCO<sub>2</sub>) from what we have learnt in the sections on oxygenation and minute ventilation. The guiding principle is that a change in a single parameter is generally preferred to making changes in two or more parameters simultaneously, unless there are compelling reasons to make two changes.

### Reducing Ventilator Support

The prerequisites for reducing ventilator support include improvement in the basic disease, stable ventilator settings for about 8–12 hours and acceptable blood gas values. It is a good principle to reduce parameters which are associated with more barotrauma and volutrauma such as the PIP. To be able to extubate the baby, the infant must have good spontaneous breathing effort, must be off sedation, and must have manageable secretions.

## MORE ON THIS TOPIC

- Davis RP, Mychaliska GB. Neonatal pulmonary physiology. *Semin Pediatr Surg.* 2013;22:179–84.
- Goldsmith JP, Karotkin EH. Assisted Ventilation of the Neonate. 5th ed. Philadelphia: Elsevier; 2011.
- Khilnani P. Pediatric and Neonatal Mechanical Ventilation, 2nd ed. New Delhi: Jaypee Brothers Medical Publishers; 2011.

### IN A NUTSHELL

1. The ventilator parameters that are usually adjusted to compensate for changes in pulmonary mechanics include PIP, PEEP, FiO<sub>2</sub>, Ti, rate and gas flow.
2. The patient triggered modes of ventilation include SIMV, ACV and PSV.
3. Ventilator adjustments are based on a combination of clinical assessment, blood gas values and chest skiagrams.
4. Reduction of ventilator support needs the basic disease to be improving, stable blood gases, good spontaneous breathing efforts by the baby, and manageable secretions.



## Chapter 17.4

# Hyaline Membrane Disease

Praveen Kumar, Anuj Bhatti

Hyaline membrane disease (HMD) is the most important cause of respiratory distress in preterm infants. Untreated, it carries a high mortality and morbidity. Advancements in neonatal intensive care, respiratory support and availability of surfactant replacement therapy (SRT) have brought down the mortality and morbidity dramatically in the developed world. However, it still is an antecedent of serious morbidity in extremely low birthweight infants.

Hyaline membrane disease is named so because of the appearance of pinkish waxy hyaline membranes composed of fibrinous material, proteins and dead cells which are seen to line the collapsed alveoli of infants dying from this disease. The term is often used synonymously and interchangeably with respiratory distress syndrome (RDS) which is a clinical diagnosis.

## EPIDEMIOLOGY

Hyaline membrane disease is typically a disease of preterm infants as it is primarily due to the deficiency of surfactant and structural immaturity of the lung related to prematurity. The incidence of HMD is inversely related to gestation. It is 60% in less than 30 weeks of gestation, 43% in 30–34 weeks of gestation and 5–6% in greater than 34 weeks of gestation. This is because of the progressive maturation of the developing lung and increasing surfactant production with advancing gestation. Other risk factors associated with increased incidence of HMD are perinatal asphyxia, maternal diabetes, lack of labor, absence of antenatal steroid administration and male gender. Small for gestational age infants as well as infants exposed to maternal chorioamnionitis have more chances of severe and chronic lung damage. Relatively mature and term infants can occasionally develop HMD due to genetic conditions causing deficient production of surfactant proteins.

## PATHOPHYSIOLOGY

The central feature of HMD is surfactant deficiency, which results in increased surface tension. Surface tension is a contractive tendency of the surface of a liquid that allows it to resist an external force. In other words, at air-liquid interface, the molecules of the liquid

are always under tension with a tendency to contract; so that they form a sphere of minimal radius. According to *Laplace's law* (Fig. 1), the pressure required to inflate a sphere is directly proportional to surface tension and inversely proportional to the radius of the bubble. If we apply this corollary to the inflation of alveoli at birth, the work done by the infant will be more if the surface tension is increased and the alveoli are collapsed (decreased radius). In other words, the compliance (distensibility) of the lung tissue will be less, i.e., pressure required for a unit change in volume of alveoli will be more (compliance = change in volume/change in pressure). Lung surfactant is required to reduce the surface tension at the air-liquid interface. Moreover, as the radius of the bubble decreases, the need for the surfactant to reduce surface tension increases. In other words, surfactant helps to maintain functional residual capacity (FRC). FRC is the volume of the air left in lungs after normal expiration. In normal lung, at end of expiration there is still air present in the lungs. In infants with HMD, alveoli collapse at the end of expiration. So, during the next breath, higher pressures need to be generated resulting in increased work of breathing.

The production of surfactant starts in type II pneumocytes during the terminal sac stage of lung development. Surfactant in the type II pneumocytes appears in the form of lamellar bodies in the cytoplasm at about 20 weeks of gestation. These lamellar bodies are secreted into the alveolar fluid to form tubular myelins. These are then adsorbed at the alveolar surface liquid-air interface. Surfactant proteins B and C (SP-B and SP-C) are essential for transition into monolayer at air-liquid interface. Absence of SP-B and SP-C is associated with fatal neonatal respiratory distress at birth (pulmonary alveolar proteinosis). Pulmonary surfactant is composed of lipids (90%) and protein (10%) (Fig. 2). The main phospholipid in the surfactant is dipalmitoylphosphatidylcholine (DPPC), also called lecithin. It decreases the surface tension because of its unique structure which consists of a hydrophilic head and a hydrophobic tail (Fig. 3). Lecithin, being a saturated lipid, is in gel form at body temperature. So, for efficient adsorption at the air-liquid interface, it has to be converted into fluid form. This is helped by the presence of other unsaturated lipids. Other lipids help in the uptake, spreading and redistribution at smallest airways.

Lung injury due to positive pressure ventilation at birth or later is also an important contributory factor in the evolution of HMD. Positive pressure or overstretching of alveoli causes lung fluid to leak into the alveoli, which inactivates the surfactant. Establishing and maintaining appropriate FRC immediately after birth noninvasively (*keeping the lung open*) can minimize this injury substantially.

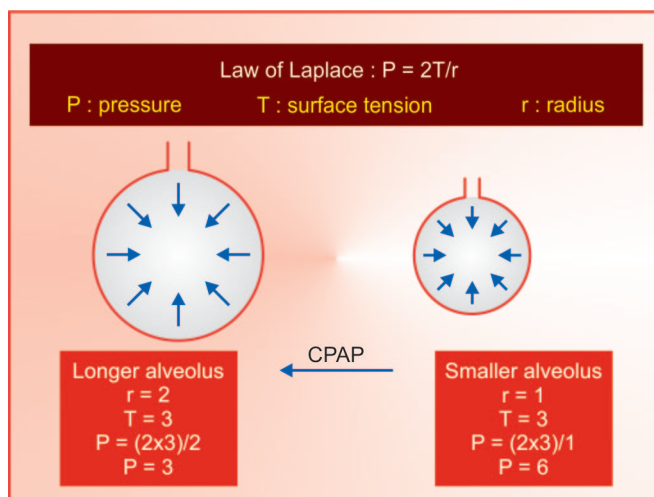


Figure 1 Laplace's law

Source: Professor Ashok K Deorari, AIIMS, New Delhi.

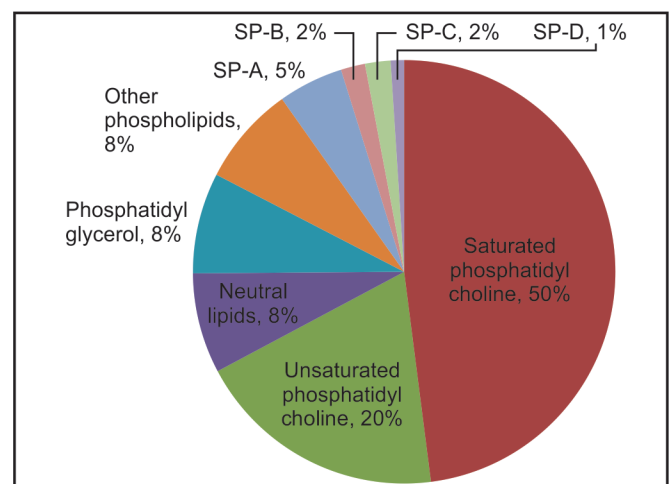
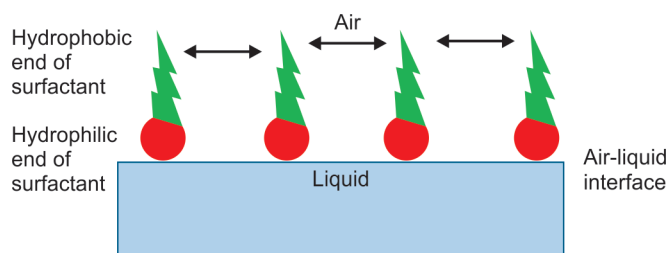


Figure 2 Surfactant composition



**Figure 3** Air-liquid interface with surfactant. Lecithin (DPPC) gets adsorbed at air-liquid interface with hydrophilic head (red) towards the liquid medium and hydrophobic tail (green) towards the air. Once adsorbed, the hydrophilic tails repel each other, thus decreasing the surface tension

## CLINICAL FEATURES

Tachypnea (respiratory rate more than 60/min), increased work of breathing and grunt are the cardinal features of HMD. The onset of the symptoms could be anytime soon after birth to within 6 hours after birth. Surfactant deficient lungs of the preterm baby require larger negative intrathoracic pressure to reopen collapsed alveoli during the phase of inspiration. This leads to use of accessory muscles of respiration leading to intercostal retractions, nasal flaring and head bobbing. Because the rib cage in premature infants is very compliant (soft), the sternum may deeply retract during inspiration. During expiration, the infant tries to maintain FRC (to prevent alveolar collapse) by expiring through partially closed glottis. This is manifested as grunt. Cyanosis or low oxygen saturation may be present due to inadequate oxygenation. Infant can appear pale due to acidosis because of inadequate removal of carbon dioxide (respiratory acidosis). This may be confused with the pallor due to blood loss at delivery. Lethargy and apnea can result due to increase work of breathing, cyanosis and acidosis. Extremely low birthweight and asphyxiated babies with HMD may developed apnea immediately following birth rather than progressing through above signs and symptoms. The progress of respiratory distress can be prospectively followed by using objective scoring systems like Silverman-Anderson and Downes' scores outlined in Chapter 17.1.

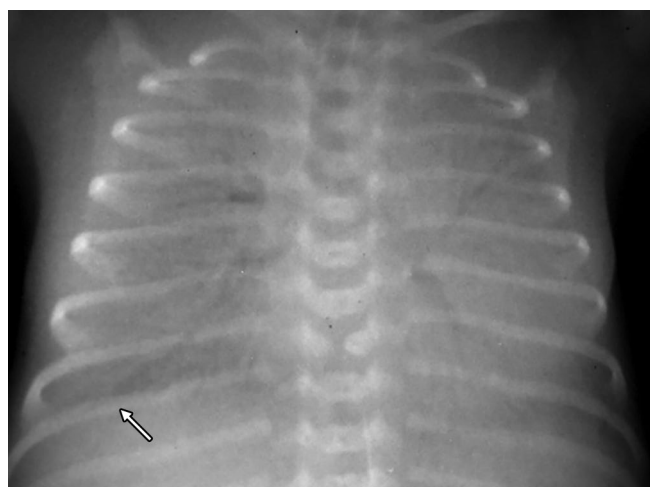
## Clinical Course

Typically, the disease presents within 6 hours of birth. If left untreated, the disease worsens for 24–48 hours and then begins to improve as the natural surfactant production begins. The infant, if survives, usually recovers in 5–7 days. Very preterm infants will not be able to make it without support. If surfactant is given and/or early continuous positive airway pressure (CPAP) is applied, the clinical course is altered and recovery is faster.

## INVESTIGATIONS

### Chest Radiograph

The classical findings in HMD include low volume lungs, reticulogranular shadows, air bronchograms, diffuse ground glass appearance and complete white-out (**Fig. 4**). The reticulogranular pattern is because of microatelectasis in the background of open small airways. Large airways beyond second- and third-generation branches are more visible due to engorged peribronchial lymphatics and fluid-filled or collapsed alveoli, resulting in air bronchograms. Widespread collapse of lung fields can lead to diffuse and homogeneous dense shadows. These radiographic findings are usually present shortly after birth but occasionally do not reach maximum severity until 12–24 hours of life. Moreover, the



**Figure 4** Chest X-ray of an infant with hyaline membrane disease (HMD): low lung volumes, homogeneous opacities, ground glass appearance. Air bronchograms can be seen (white arrow)

classical radiological findings may not be observed if exogenous surfactant has been given and/or adequate positive end-expiratory pressure (PEEP) has been applied right from the beginning.

## Arterial Blood Gas Analysis

Blood gas is essential because with clinical assessment and pulse oximetry alone, one would not be able to assess partial arterial carbon dioxide pressure ( $\text{PaCO}_2$ ) and pH. In the initial stages of respiratory distress, arterial blood gas (ABG) may be normal or show hypoxia with normal  $\text{PaCO}_2$  (sometimes  $\text{PaCO}_2$  may be decreased in early stages due to severe tachypnea). As the respiratory distress worsens and baby tires down,  $\text{PaCO}_2$  starts to increase, leading to respiratory acidosis. There is also a component of metabolic acidosis due to increased work of breathing. Furthermore, as the oxygen delivery to the tissues is compromised, lactic acid may accumulate, leading to mixed respiratory and metabolic acidosis.

## Assessment of Gas Exchange

Though the blood gas parameters indicate oxygenation and ventilation at a single point of time, these parameters alone are not sufficient to evaluate gas exchange. Interpretation of partial arterial oxygen pressure ( $\text{PaO}_2$ ) without fractional inspired oxygen concentration ( $\text{FiO}_2$ ) is misleading. Hence, the gas exchange should be assessed using: (1) alveolar-arterial oxygen gradient ( $\text{A-aDO}_2$ ); (2) arterial to alveolar oxygen ratio (a/A ratio); and (3) oxygenation index (OI).

**Alveolar-arterial oxygen diffusion gradient** This is calculated as shown below:

$$\begin{aligned} \text{A-aDO}_2 &= \text{PAO}_2 - \text{PaO}_2 \text{ (P alveolar - P arterial oxygen pressure)} \\ &= [\text{PiO}_2 - \text{PACO}_2] - \text{PaO}_2 \\ &= [(\text{PB} - \text{PW}) \times \text{FiO}_2 - \text{PACO}_2] - \text{PaO}_2 \\ &= [(760 - 47) \times \text{FiO}_2 - \text{PACO}_2] - \text{PaO}_2 \end{aligned}$$

( $\text{PAO}_2$ , partial alveolar oxygen pressure;  $\text{PaO}_2$ , partial arterial oxygen pressure;  $\text{PiO}_2$ , partial inspired oxygen pressure; PB, barometric pressure; PW, water vapour pressure;  $\text{FiO}_2$ , fractional inspired oxygen concentration;  $\text{PACO}_2$ , partial alveolar carbon dioxide pressure;  $\text{PaCO}_2$ , partial arterial carbon dioxide pressure.)

Normally it ranges between 5 and 15 while breathing room air.  $\text{A-aDO}_2$  is considered to be abnormal if it is more than 40.

**Arterial to alveolar oxygen ratio** Ratio of  $\text{PaO}_2$  to partial alveolar oxygen pressure ( $\text{PAO}_2$ ). It is considered to be a better indicator of

gas exchange as the ratio is usually not affected by changes in  $\text{FiO}_2$ . The interpretation of this ratio is depicted below:

1. Greater than 0.8—normal
2. Less than 0.6—indicates need for oxygen therapy
3. Less than 0.15—severe hypoxemia.

**Oxygenation index** Recommended in babies who are mechanically ventilated as this index includes mean airway pressure (MAP).

$$\text{OI} = (\text{MAP} \times \text{FiO}_2) / \text{PaO}_2$$

The interpretation of this index is as below:

1. OI 25–40—severe respiratory failure; mortality risk is 50–60%
2. OI greater than 40—mortality risk is greater than 80%.

### Gastric Aspirate Shake Test

This is useful in assessing the risk of RDS in neonates with respiratory distress who are less than 34 weeks of gestation or have risk factors for RDS. In a glass test tube with dimensions of 82 mm × 10.25 mm and 4 mL capacity, 0.5 mL of gastric aspirate is taken and mixed with 0.5 mL of absolute alcohol. The tube is shaken vigorously for 15 sec and allowed to stand for 15 min. If at least one complete rim of bubbles is present all the way round the meniscus, the risk of RDS is less than 1%, whereas complete absence of bubbles is associated with a 50–60% risk. Shake test interpretation is as follows:

- Negative test is no bubbles
- 1+ is very small bubbles in the meniscus extending one-third or less of distance around the test tube
- 2+ is single rim of bubbles extending one-third to all around the test tube
- 3+ is a rim of bubbles all the way around the test tube with a double row in some areas
- 4+ is a double row or more of bubbles all the way around the test tube.

3+ and 4+ indicate adequate lung surfactant. The shake test is only an ancillary investigation and the decision to give surfactant should be based upon the severity of respiratory distress and oxygen requirement.

### Investigations for Sepsis

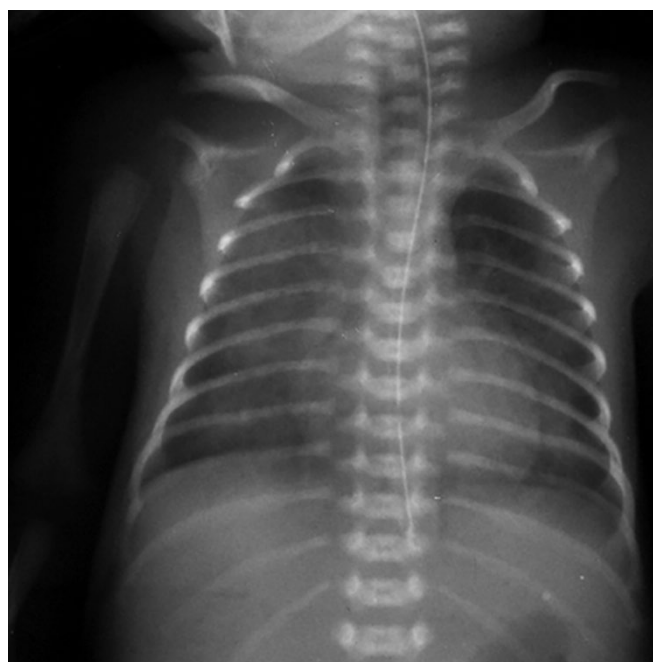
As it may be impossible to rule out infection at the onset in a sick preterm infant, most infants would undergo a blood culture and sepsis screen which may include C-reactive protein (CRP), micro-ESR, total leukocyte count (TLC), absolute neutrophil count (ANC) and immature to total leukocyte ratio (ITR).

### Other Investigations

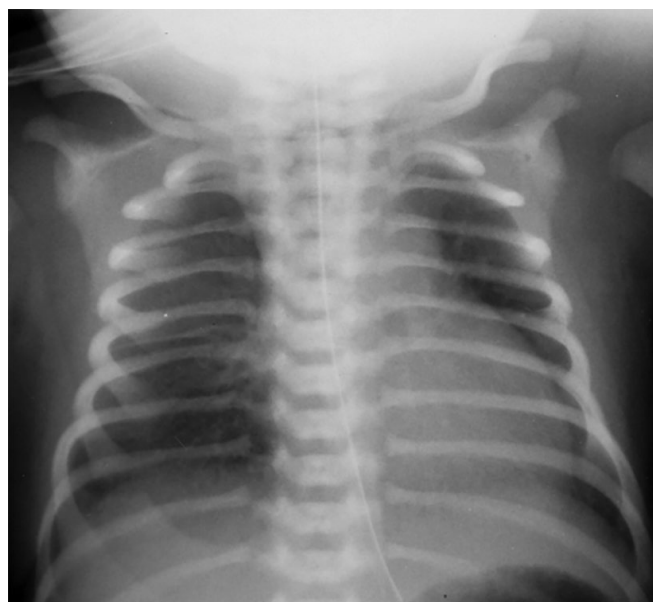
Blood glucose, ionized calcium, hemoglobin (Hb) or packed cell volume (PCV), electrolytes.

### DIFFERENTIAL DIAGNOSIS

Congenital pneumonia is the closest differential diagnosis. Onset of pneumonia can be soon after birth but could be delayed beyond 6 hours. Pneumonia and HMD may also coexist (pneumonia can further lead to secondary surfactant deficiency). Maternal history of clinical and histological chorioamnionitis can point towards the differential diagnosis of pneumonia. Moreover, pneumonia can present with inhomogeneous shadows in the chest X-ray as against the typical homogeneous shadows seen in HMD (**Fig. 5**). Transient tachypnea of the newborn usually presents with mild tachypnea without retractions or grunt and resolves within 24–48 hours of life. The chest X-ray shows adequate to mildly increased lung volume with prominent fissures, streaky opacities and occasionally small effusions (**Fig. 6**). Obstructive total anomalous pulmonary venous return can have cyanosis with silent tachypnea and chest X-ray may mimic HMD.



**Figure 5** Chest X-ray of pneumonia: normal lung volumes, nonhomogeneous and patchy opacities



**Figure 6** Chest X-ray of infant with transient tachypnea of the newborn (TTNB): normal lung volumes, prominent major fissure and streaky opacities

### MANAGEMENT

#### Delivery Room Management

Special considerations should be made in the resuscitation of extremely low birthweight babies. For transition from fetal to neonatal life, newborn must replace lung fluid with air, establishing FRC in the lung. This is very difficult for the extreme preterm infant. So, during the resuscitation, the aim should be to *open the lungs* and subsequently *keep the lungs open* along with adequate oxygenation. This can be achieved by using devices which can provide CPAP or PEEP. These ventilation devices include: T-piece



resuscitator, flow inflating bag or a CPAP device. Recent cumulative evidence suggests that these infants should be placed on CPAP immediately after birth instead of intubation or leaving them on oxygen alone. Such a strategy reduces the need for surfactant and mechanical ventilation. There is also a reduction in the combined outcome of death or bronchopulmonary dysplasia (BPD).

### Initial Respiratory Support

The initial support can be in the form of oxygen alone, CPAP or mechanical ventilation. Early CPAP is the first choice of support. One should aim to avoid intubation as far as possible as intubation is the single most important factor leading to BPD.

#### Nasal Continuous Positive Airway Pressure

Continuous positive airway pressure helps in keeping the lungs (alveoli) inflated, especially during the phase of expiration. It should be kept in mind that CPAP works only in spontaneously breathing infants and will not provide inflating pressure (pressure required to inhale till maximum spontaneous inspiration). The system consists of a heated and humidified blended gas source, a nasal interface, a patient circuit and the pressure-generation apparatus (Fig. 7). As flow of gases is very high in the CPAP circuit, gases should be humidified to 100% and heated to a temperature of 37°C.

**Nasal interface (Fig. 8)** Continuous positive airway pressure is usually delivered to infants using nasal prongs or new generation nasal masks. Other interfaces which have been used are nasopharyngeal tubes, endotracheal tubes, pressurized plastic bags, head-box enclosures and tight-fitting face masks. In a systematic review assessing the efficacy of various interfaces for CPAP, short binasal prongs were found to be more effective than single prong in reducing the rate of reintubation. Furthermore, authors concluded that the improvement in respiratory parameters with short binasal prongs suggests they are more effective than nasopharyngeal CPAP in the treatment of early RDS. The short and wide binasal prongs also have the least resistance. Nasal injury is the commonest complication with nasal prongs. If the interface is not managed appropriately, serious erosions, perforations and disfigurement can occur. The incidence can be decreased by using appropriately fitting prongs, avoiding undue pressure on the nasal interface, properly supporting the CPAP tubing, keeping a distance of 2–3 mm between the nasal prong and nasal septum, applying lubrication, massage and skin protective dressings at contact points. Recently, two new interfaces have been introduced: (1) nasal mask; and (2) RAM's cannula. RAM's cannula consists of a binasal prong like the oxygen prongs and tubings but with a diameter much wider than conventional oxygen prong. This may be more comfortable for the infant and make nursing easier. New generation soft nasal masks have been shown to provide adequate nasal seal without increasing the injury. Alternating nasal mask with nasal prongs may minimize injury.

**Pressure-generating apparatus** Continuous positive airway pressure can be generated by the following devices:

- Expiratory flow valve (conventional ventilator) [ventilator-derived CPAP (VCPAP)]
- Underwater tube bubble CPAP (BCPAP)
- Variable flow CPAP [infant flow driver (IFD)]
- Heated humidified high-flow nasal cannulae (HHFNC)

Continuous positive airway pressure devices have traditionally been classified according to the pressure-generating apparatus and techniques used to control gas flow to the patient. There are two broad categories: (1) *constant flow devices*; and (2) *variable flow devices*. In *constant flow* devices, the flow is set by the clinician, and pressure is generated by controlling the resistance at the expiratory end of the tube. Conventional ventilators provide the simplest way to generate CPAP by controlling the expiratory valve

which generates PEEP. The advantage is that same machine can be used to provide mechanical ventilation. But ventilators are more expensive than stand-alone CPAP equipment. The most popular technique of generating CPAP is *bubble* CPAP. Devices which use fluidic control mechanisms to regulate the CPAP have been described as *variable flow devices*. Mechanisms within the CPAP pressure fluidic generator allow for additional gas delivery to the patient during inspiration in order to maintain a consistent airway pressure. During expiration also, the exhaled gases can escape through the additional tube, minimizing the work of breathing.

#### Bubble CPAP

The BCPAP system consists of a blended, humidified gas source (4–6 L/min) attached to nasal prongs by a length of inspiratory circuit. A separate length of expiratory circuit tubing is attached from the nasal interface, thus allowing egress of exhaled gases and system bias flow into a water seal column of sterile H<sub>2</sub>O/0.25% acetic acid mixture. The CPAP level is determined by the distance the distal end of the expiratory tubing is placed below the water seal surface (5 cm below surface = 5 cm H<sub>2</sub>O). But, the actual pressure delivered is flow-dependent with higher flow leading to higher CPAP pressure than the intended submerged length of tube.

The level of CPAP should be individualized to the baby's disease. As a general guideline, start CPAP of 5 cm H<sub>2</sub>O and FiO<sub>2</sub> of 0.5 to maintain normal pulse oximeter oxygen saturation (SpO<sub>2</sub>). Subsequent titration can be done based on the clinical improvement, blood gases and lung volume on chest radiograph. An orogastric tube (OGT) should be inserted to decompress the stomach. The signs of overinflation should be monitored—inadequate cardiac output (prolonged capillary filling time (CFT), reduced urine output, metabolic acidosis) and hyperinflated chest. Periodic inspection of the local area is important because patient interface can lead to septal and mucosal injury. CPAP is said to have failed when on a CPAP of 8–9 cm of H<sub>2</sub>O and FiO<sub>2</sub> of 60–70%, the infant has continuing desaturations, increased work of breathing, apnea or develops respiratory or metabolic acidosis.

#### Nasal Intermittent Positive Pressure Ventilation

Nasal intermittent positive pressure ventilation (NIPPV) has come up in the recent years as another alternative to CPAP or as a bridge between CPAP and mechanical ventilation. Apart from providing the PEEP, it also provides maximal inspiratory pressure at predetermined rates. Thus, it can be used in preterms who are not spontaneously breathing or who have failed maximal settings on CPAP. It has been seen that NIPPV has better success than CPAP in avoiding intubation when used as initial support and can avoid intubation in a significant proportion of those who fail CPAP. The main limitations relate to the amount of pressure that can be transmitted to the lungs because of several natural leaks and distension of stomach and intestines.

### Mechanical Ventilation

This used to be the mainstay of management of HMD. However, it was realized that it led to barotrauma, volutrauma, BPD and many other complications. Currently mechanical ventilation should be restricted for infants without any respiratory effort, those who have failed noninvasive modes of support or those with severe multisystem involvement. Even when it is used, the efforts should be to use it for minimum duration and extubate the infant at the earliest. The details of mechanical ventilation are discussed elsewhere. For best results with minimum damage, it is useful to follow the laws of ventilator efficiency (LOVE). These state that one needs to know the baby, the disease, the machine and have an EXIT strategy.

### Surfactant Replacement Therapy

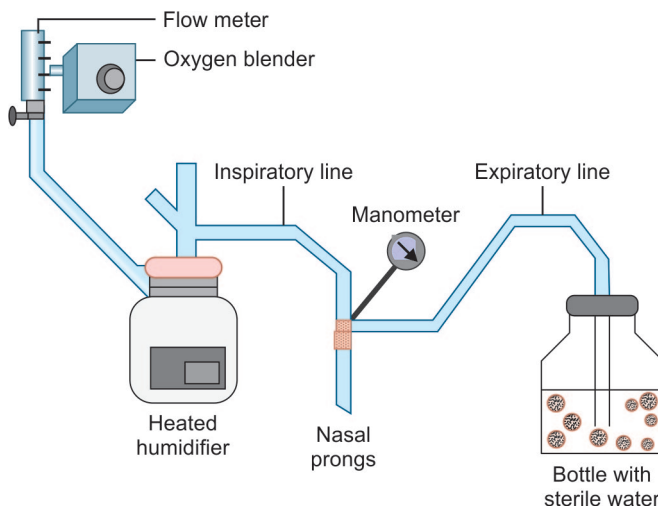
Exogenous surfactant reduces the risk of mortality, air leaks and the combined outcome of BPD or death. Natural surfactants are



faster acting with lower incidence of pneumothorax and mortality as compared to first-generation artificial surfactant. As a result, the first-generation artificial surfactants are no longer available. Natural surfactants are derived from animal sources. Commonly available surfactant preparations in India are shown in **Table 1**. All commonly available brands are equally efficacious in similar doses. The difference lies in the volume to be administered because of different concentrations. Newer generation synthetic surfactants have been developed to alleviate the theoretical concerns of immunologic or infectious complications from animal-derived surfactant. These new products have synthetic peptides or proteins, such as KL4 in lucinactant, which mimics the actions of natural surfactant-associated proteins SP-B and SP-C. Lucinactant has been shown to be superior to older synthetic surfactants and is as efficacious as the animal-derived surfactants.

### Route of Administration

Surfactant is administered through the endotracheal tube either via side port (if present) or with help of a catheter inserted into the endotracheal tube. For infants on CPAP, the



**Figure 7** Components of continuous positive airway pressure  
Source: Professor Ashok K Deorari, AIIMS, New Delhi.

surfactant is administered by INSURE (INTubate, SURfactant and Extubate) technique. This involves intubation of the baby for the administration of surfactant and then extubating to CPAP within few minutes. The concept of INSURE is linked to the finding that a single dose of surfactant is enough if given early. Moreover, extubating the baby to CPAP further helps in keeping the lungs open. Since traditional method of surfactant instillation requires intubation, efforts have been made to find alternative methods of giving surfactant. Among such methods, which have been shown to be effective, are instillation via a feeding tube or vascular catheter inserted directly into the endotracheal tube. Lot of work is undergoing to produce an aerosolized form of surfactant and a device required for that so that even the insertion of feeding tube or vascular catheter into the endotracheal tube can be avoided.

### Timing of Surfactant

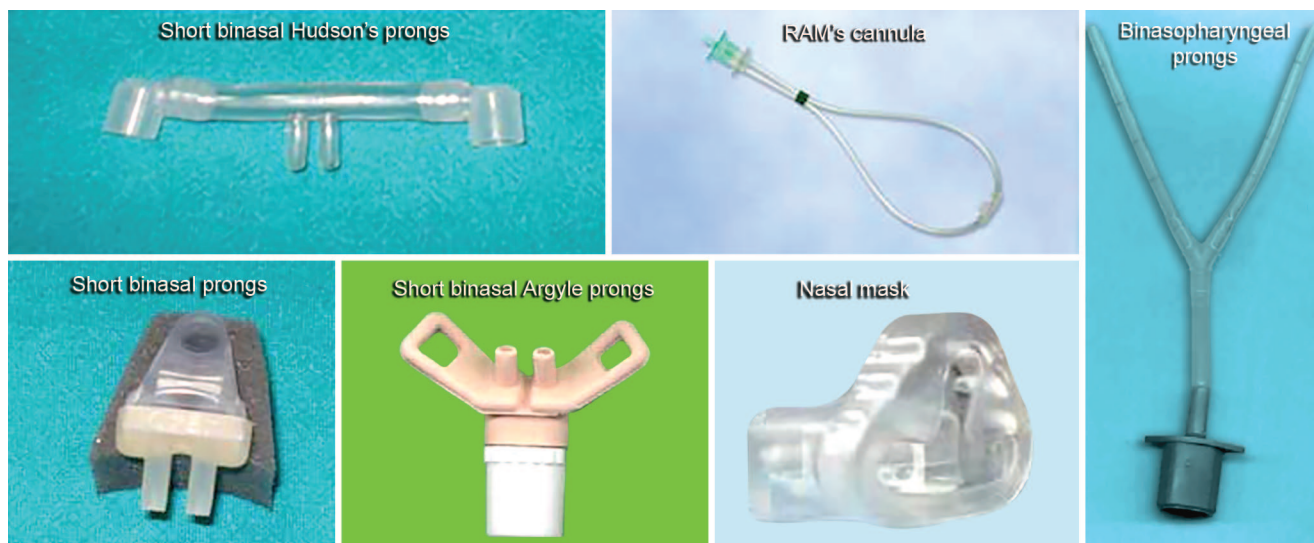
The practice has changed over the last decade. The earlier practice of giving prophylactic surfactant to extreme preterm neonates has been given up as intubation for instillation of surfactant even for short duration has been shown to initiate the inflammatory cascade leading to BPD and with very early application of CPAP, nearly half of the infants never require surfactant. Hence, the current practice is to give early rescue surfactant only if the infant requires intubation or the oxygen requirement persists to be more than 30–35% on adequate CPAP.

### Aftercare

Clinical care after surfactant administration is very important. Natural surfactant can dramatically improve the lung compliance within minutes. As a result, there is danger of overventilation and overoxygenation, which can lead to pneumothorax and oxygen toxicity. So, after surfactant administration, a close watch should be kept on pulse oximetry and  $\text{PaCO}_2$ . Similarly, tidal volumes (if baby is on ventilator) and chest movement should be closely monitored (pressures on the ventilator should be titrated accordingly). Volume-targeted ventilation is better than pressure-targeted ventilation in this scenario. As the lung compliance improves, the pressures automatically decrease in response to improving tidal volumes. This results in decreased barotrauma and air leaks.

### Supportive Therapy

The outcome of the infant is determined in a large part by the essential supportive monitoring and treatment directed towards all



**Figure 8** Various nasal interfaces used with continuous positive airway pressure

organ systems. An expert and efficient nursing care is very crucial for success of management.

**Thermoneutral environment** The neonate should be nursed in a thermoneutral environment. Hypothermia will initiate the cascade of pulmonary vasoconstriction and aggravate hypoxemia. Baby's temperature should be maintained between 36.5°C and 37.5°C. Very low birthweight neonates need incubator for maintenance of their temperature and for providing adequate humidity.

**Fluid and electrolyte balance** Fluids and normal acid-base balance should be maintained. Preterm babies have higher insensible water loss (40–100 mL/kg/day). Fluid intake should be titrated accurately by recording serial weight, intake/output, serum sodium and urine-specific gravity.

**Appropriate antibiotics** should be started in all cases of suspected sepsis or pneumonia. However, they should be stopped once the 48 hours blood culture is sterile and the infant does not have clinical features of sepsis, even if the infant continues to be on respiratory support.

**Calcium and glucose** homeostasis should be ensured.

**Maintain normal mean arterial pressure** Blood pressure and peripheral circulation should be monitored closely and nomograms used to define hypotension. Correct hypotension by using appropriate fluid volumes and inotropes if necessary.

**Hypovolemia and anemia** are to be treated adequately as necessary. Hematocrit should be maintained above 40% in the acute phase of the disease.

**Oral feeding** is withheld initially. Once the baby stabilizes on the respiratory support gavage feeding should be started and increased as per protocol and tolerance.

## PREVENTION

Prevention of prematurity seems to be most logical intervention to prevent HMD. Every effort should be done to prolong the pregnancy to at least 35 weeks. The decision to terminate pregnancy, in view of deteriorating maternal condition (e.g., uncontrolled hypertension) or fetal risk (e.g., reversed Doppler flows or chorioamnionitis), should be taken by the combined team of experts which includes obstetrician and neonatologist. Delivery should be conducted preferably in a center where there is facility for level III neonatal care, rather than transporting the baby after delivery (*transfer in utero*).

## Antenatal Steroids

Antenatal steroids are the cornerstone for the prevention of HMD. Treatment with antenatal steroids is associated with a significant reduction in neonatal death, HMD, intraventricular hemorrhage and necrotizing enterocolitis without increase in maternal risks. It is recommended that the treatment be used from 24 weeks to 34 weeks of gestation. Although the beneficial effects were found to be greatest if treatment was begun more than 24 hours before delivery, there is also a benefit if given for less than 24 hours. Hence, all women presenting with possible preterm labor between

24 weeks and 34 weeks should be administered a dose of antenatal steroid even if delivery is imminent and before referral.

Betamethasone is the preferred steroid as it leads to greater reduction in risk of death than dexamethasone and decreased risk of cystic periventricular leukomalacia (PVL) in the infant. Antenatal betamethasone is given in a dose of 12 mg intramuscular injection/dose, in two doses 24 hours apart. If betamethasone is not available, dexamethasone can be used in the dose of 6 mg per dose 12 hourly for four doses. It is identical in biologic activity to betamethasone. The beneficial effects of antenatal steroids start to wean off after 1 week of administration. Controversies exist regarding repeating the course of antenatal steroids in case baby is not delivered within a week. Repeated weekly courses of antenatal steroids result in modest improvements in incidence and severity of RDS, but there are serious concerns regarding smaller birthweight and head circumference. Hence, currently routine use of repeated doses of antenatal corticosteroids should be avoided. It is being explored whether a single dose can be repeated safely. It must be remembered that the cost of surfactant is considerably higher than antenatal steroids. Antenatal steroids provide more benefits on a wide range of organ systems and should be utilized more effectively.

## COMPLICATIONS

The complications may occur because of the disease itself but are mainly contributed by the treatments required.

### Respiratory

Pneumonia due to secondary acquired infections is the commonest complication. Air leaks are also common, though they have reduced in frequency in recent years due to better ventilators and ventilatory strategies. They include pulmonary interstitial emphysema, pneumothorax, pneumomediastinum and pneumopericardium. Inappropriate ventilation settings are the most common risk factors associated with air leaks. Hemorrhagic pulmonary edema (pulmonary hemorrhage) can be seen in extremely low birth babies. It is postulated that due to left ventricular failure and excessive shunting of blood from left to right across patent ductus arteriosus, there is rupture of pulmonary capillaries. Moreover, dramatic improvement in the lung compliance following surfactant therapy without concomitant decrease in ventilator settings may be contributory. It is manifested as pink frothy fluid in the endotracheal tube with simultaneous increase in ventilatory requirements on day 1 to 3 of life. BPD, the most dreaded complication is discussed elsewhere.

### Nonrespiratory Complications

Infants with HMD, especially those who are ventilated are prone to develop acquired sepsis, intraventricular hemorrhage, PVL, necrotizing enterocolitis and retinopathy of prematurity. They are also at risk for neurodevelopmental sequelae like cerebral palsy, vision and hearing defects, and developmental delay. These complications are mainly due to prematurity but can have an important contribution of the respiratory disease and the treatments used for it.

**Table 1** Surfactant preparations available in India

Brand	Source	Volume available and cost	Dosage recommended	Interval between doses	Maximum doses
Survanta (Abbott)	Bovine minced	8 mL (₹ 11,000) and 4 mL (₹ 6,000) vial	100 mg/kg = 4 mL/kg	6 hours	2
Curosurf (Nicholas/Abbott)	Porcine minced	1.5 mL (₹ 7,000) and 3 mL (₹ 13,000) vial	100 mg/kg = 1.25 mL/kg	12 hours	2
Neosurf (Cipla)	Bovine lavage	5mL (₹ 5,000), and 3 mL (₹ 3,000) vial	135 mg/kg = 5 mL/kg	12 hours	3

**IN A NUTSHELL**

1. Hyaline membrane disease is the most important cause of respiratory distress in preterm neonates. The incidence is inversely related to gestation.
2. The clinical features of HMD are related to surfactant deficiency and manifest as tachypnea, intercostal retractions and grunt.
3. Early CPAP support is the mainstay of treatment. It decreases the need for surfactant and mechanical ventilation. In extreme preterm infants, CPAP should be considered soon after birth in the delivery room.
4. Surfactant should be used as early rescue in infants who need intubation and those who continue to need more than 30–35% oxygen in spite of adequate CPAP support. If surfactant is required for an infant on CPAP, it should be given by INSURE technique or another minimally invasive method.
5. Intubation should be avoided as far as possible. NIPPV can help in many infants failing CPAP.
6. Infants with HMD needing respiratory support are at high risk of respiratory and nonrespiratory complications and sequelae.
7. Antenatal steroids are highly cost-effective in decreasing the incidence of HMD and its complications. They must be given to all women with threatened preterm delivery from 24 weeks to 34 weeks of gestation.

**MORE ON THIS TOPIC**

- Deorari AK, Kumar P, Murki S. Workshop on CPAP: Science, Evidence & Practice. New Delhi: 2013.
- Kahn DJ, Courtney SE, Steele AM, Habib RH. Unpredictability of delivered bubble nasal continuous positive airway pressure: role of bias flow magnitude and nares-prong air leaks. *Pediatr Res*. 2007;62:343-7.
- Kahn DJ, Habib RH, Courtney SE. Effects of flow amplitudes on intraprong pressures during bubble versus ventilator-generated nasal continuous positive airway pressure in premature infants. *Pediatrics*. 2008;122:1009-13.
- Murki S, Deorari A, Vidyasagar D. Use of CPAP and surfactant therapy in newborns with respiratory distress syndrome. *Indian J Pediatr*. 2014;81:481-8.
- Pfister RH, Soll RF. Initial respiratory support of preterm infants: the role of CPAP, the INSURE method, and noninvasive ventilation. *Clin Perinatol*. 2012;39:459-81.
- Vidyasagar D, Velaphi S, Bhat VB. Surfactant replacement therapy in developing countries. *Neonatology*. 2011;99:355-66.

## Chapter 17.5

# Transient Tachypnea of the Newborn

Srinivas Murki

Transient tachypnea of newborn (TTN) is one of the most common causes of respiratory distress in the newborn. It is reported to occur in 0.6%, of term (gestation > 36 weeks) and 6.5% of late preterm (gestation 34–36 weeks) infants. Although most infants have an uneventful course, some may require respiratory support including continuous positive airway pressure (CPAP) or ventilation, prolonged oxygen supplementation and increased duration of hospital stay. Survival is almost universal in these infants. Recent data suggest an increased risk of wheezing episodes in infants or children with neonatal TTN.

## PATHOPHYSIOLOGY

During fetal life, fluid is secreted into the alveoli to maintain growth and function. Fetal lung volume approximates the functional residual capacity that is established after birth as the lung is aerated. Retained lung fluid immediately after birth precludes aeration of the alveoli, establishment of functional residual capacity and thereby a normal in utero to postnatal transition. Fluid fills the alveoli and moves into the interstitium that is eventually cleared by the lymphatics and blood vessels. This results in newborn developing respiratory distress immediately after birth. Possible reasons for the retention of lung fluid are as follows:

- *Delayed normal switch of the fetal chloride secretory channel* to postnatal sodium (ENaC) and water absorbing channel in the lung epithelium. Increased levels of catecholamine and other hormones in late gestation promote the switching of the chloride secreting channel to sodium absorbing channel. Increased postnatal oxygen tension augments the gene expression and function ability of the ENaC channel. Antenatal glucocorticoids augment the expression of ENaC channel.
- *Delayed passive absorption of lung fluid* Oncotic pressure differences between the alveoli, interstitium and blood vessels promote passive absorption of the lung fluid. This absorption occurs along the aquaporin-5 water channels. There is an increased expression of these channels after birth in newborns with TTN.
- *Vaginal squeeze* The vaginal squeeze during labor contributes to a small fraction of the extrusion of the lung fluid at birth.
- *Inadequate surfactant function* Infants with TTN in comparison with those without TTN have lesser surfactant function as evidenced by lower lamellar body count in their gastric aspirates.

## RISK FACTORS

- *Late preterm infants* Lower the gestation, higher is the risk. Infants born at 34 weeks are at higher risk of developing TTN than those born at 37 weeks.
- *Infant of diabetic mother* TTN is more common in these infants secondary to delayed fluid absorption and higher incidence of cesarean delivery.
- *Male infant* Testosterone may affect the expression and function of the ENaC channel in the alveolar epithelium.
- *Cesarean section* Although in comparison with vaginal delivery, incidence and severity of TTN is more in cesarean section, TTN is more common if the cesarean section occurs before onset of labor than otherwise.

- Infants who are *growth restricted* or large for gestation
- *Maternal asthma*

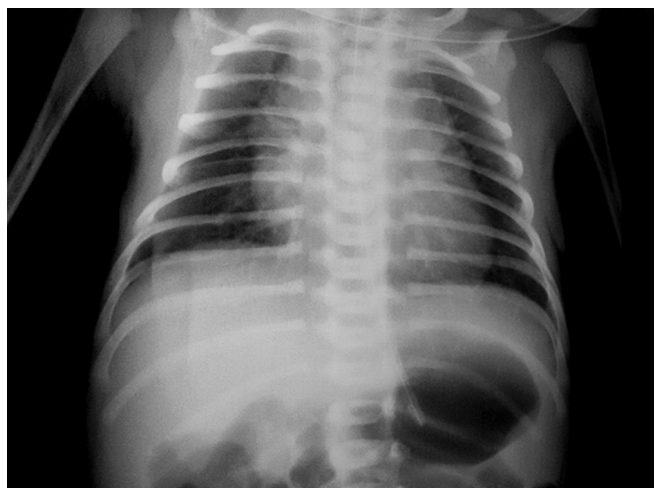
## CLINICAL FEATURES

Infants with TTN present with respiratory distress immediately after birth or within the first 6 hours of life. In many, the severity of distress improves with time. Tachypnea (respiratory rate > 60/min), normal or increased chest expansion, mild or moderate chest recessions, nasal flaring, grunting, occasional crepitation and increased oxygen requirement are the classical clinical signs. Saturations improve with oxygen supplementation and rarely infants may require CPAP or ventilation to improve oxygenation and reduce the work of breathing. The distress is usually passive by 24 hours and in some it may persist till 72 hours of life. Resolution of grunting and chest recessions precedes the normalization of respiratory rate.

## DIAGNOSIS

### Chest Skiagram

There may be evidence of hyperinflation and may also be of normal volume in some cases. The perihilar vascular markings may be prominent (which is probably due to lymphatic engorgement) and there may be evidence of fluid in the fissures (**Fig. 1**). Occasionally there may be associated cardiomegaly. The chest radiograph usually clears by 3–7 days.



**Figure 1** Prominent perihilar markings, fluid in the horizontal fissure and cardiomegaly in a newborn with transient tachypnea of newborn

## Differential Diagnosis

Respiratory distress syndrome, pneumonia, asphyxial lung injury, pneumothorax and congenital heart disease are the common conditions that would need to be differentiated from TTN.

### Pneumonia

Onset of respiratory distress may be immediately after birth or later in the first 24 hours of life. Maternal fever, foul-smelling liquor, maternal urinary tract infections, prolonged rupture of membranes, prolonged duration of labor and mother on antibiotics are the usually recognized antecedent risk factors. Chest X-ray may show infiltrates in one or more zones of lung.

### Congenital Heart Disease

Persistent pulmonary hypertension, obstructive lesions such as critical aorta stenosis and obstructed total anomalous pulmonary



venous connection may present as respiratory distress with onset from birth. High oxygen requirement, oxygen liability, normal lung fields and cardiomegaly are features suggestive of pulmonary hypertension. Low volume pulses, murmurs, cardiomegaly and good volume lungs or congested lungs are features suggestive of congenital heart disease.

### Respiratory Distress Syndrome

Preterm or late preterm infant, onset of respiratory distress at birth with progressive worsening, and radiological findings of small volume lungs, reticulogranularity and air bronchograms, differentiates respiratory distress syndrome (or hyaline membrane disease) from TTN.

### Pneumothorax

Early onset of respiratory distress with progressive worsening, differential air entry on auscultation of chest, positive transillumination test and chest X-ray are useful in differentiating pneumothorax from TTN.

## MANAGEMENT

Management is mostly supportive. Maintaining thermoneutral environment, intravenous fluids, early nutrition and oxygen supplementation form the mainstay of therapy. There is no role of antibiotics in TTN unless pneumonia or sepsis is suspected.

### Respiratory Support

All infants with respiratory distress should be connected to a pulse oximeter and severity of distress monitored with Downe's score or Silverman Anderson score. Oxygen is administered to maintain saturations between 90% and 95%. Fractional inspired oxygen concentration ( $\text{FiO}_2$ ) needs to be monitored and tailored to maintain oxygenation in the acceptable range of 90–95%. Supplemental oxygen should be provided only as long as the infant needs it and one should avoid excess and prolonged oxygen therapy. Infants with progressively worsening respiratory distress and increased oxygen requirement need to be supported with nasal continuous positive airway pressure. CPAP is indicated if the Silverman score more than 5 or Downe's score is more than 5 and/or  $\text{FiO}_2$  requirement is more than 0.60. Those with persisting or progressive respiratory distress should be screened for infections (pneumonia or early onset sepsis) and congenital heart disease (by 2-D echocardiography).

Infants delivered in facilities without respiratory support care such as CPAP or mechanical ventilation should be referred to tertiary care neonatal units if there is persistent and worsening respiratory distress at 6 hours of life, or radiological findings not consistent with TTN on the chest X-ray.

### Fluids and Feeding

There is no evidence that fluid restriction or diuretic therapy alters the course of disease. Most of these infants would not be able to

suck on the breast due to their respiratory distress, and, therefore, would need to be provided intravenous dextrose in the initial few hours or during the first day of life. Some of these infants who cannot feed on their own but have mild-moderate respiratory distress could be fed expressed breastmilk by orogastric tube.

## PREVENTION

Antenatal steroids given to mothers with elective cesarean section before 37 weeks of gestation may reduce the incidence and severity of respiratory distress in late preterm infants. However, this should not be a routine practice unless more evidence is available. When termination of pregnancy is elective, it preferably should occur at or after 39 weeks of gestation.

### IN A NUTSHELL

1. Transient tachypnea of newborn is the most common cause of respiratory distress in term and late preterm infants.
2. Retained lung fluid leads to lower functional residual capacity, which in turn results in hypoxia and increased work of breathing.
3. Late preterm birth, maternal diabetes, elective cesarean are the main risk factors for TTN.
4. Tachypnea, chest recessions, grunting with onset of respiratory distress within the first few hours of birth with gradual and spontaneous resolution differentiates TTN from other disorders with respiratory distress in the newborn.
5. Persistent respiratory distress with increased oxygen requirement should alert the clinician to rule out early onset sepsis and congenital cardiac diseases.

## MORE ON THIS TOPIC

- Guglani L, Lakshminrusimha S, Ryan RM. Transient tachypnea of the newborn. *Pediatr Rev.* 2008;29:e59-65.
- Hibbard JU, Wilkins I, Sun L, et al. Respiratory morbidity in late preterm births. *JAMA.* 2010;304:419-25.
- Kassab M, Khriesat WM, Bawadi H, Anabrees J. Furosemide for transient tachypnoea of the newborn. *Cochrane Database Syst Rev.* 2013;6:CD003064.
- Liem JJ, Huq SI, Ekuma O, et al. Transient tachypnea of the newborn may be an early clinical manifestation of wheezing symptoms. *J Pediatr.* 2007;151:29-33.
- Li Y, Marcoux M-O, Gineste M, et al. Expression of water and ion transporters in tracheal aspirates from neonates with respiratory distress. *Acta Paediatr.* 2009;98:1729-37.
- Levine EM, Ghai V, Barton JJ, Strom CM. Mode of delivery and risk of respiratory diseases in newborns. *Obstet Gynecol.* 2001;97:439-42.
- Machado LU, Fiori HH, Baldisserotto M, et al. Surfactant deficiency in transient tachypnea of the newborn. *J Pediatr.* 2011;159:750-4.
- Yurdakök M. Transient tachypnea of the newborn: what is new? *J Matern Fetal Neonatal Med.* 2010;Suppl 3:24-6.

## Chapter 17.6

# Meconium Aspiration Syndrome

Naveen Jain

Meconium (desquamated intestinal epithelium, skin, lanugo hair, amniotic fluid) may be passed into the amniotic fluid before or during delivery of baby in some pregnancies. Meconium aspiration syndrome (MAS) refers to a syndrome of respiratory stress that occurs in some of these babies (mostly term/post-term) born through meconium-stained amniotic fluid (MSAF). A fraction of babies with MAS can progress to severe hypoxemic respiratory failure.

## EPIDEMIOLOGY

Reported incidence of MSAF is about 10% of all pregnancies. The incidence has decreased a little in the last decade due to improved fetal monitoring and timely termination of pregnancy. About 5% of babies born through MSAF develop respiratory distress due to MAS.

## ETIOLOGY

Meconium-stained amniotic fluid is more common in post-term pregnancy; however, current obstetric practices seem not to allow pregnancies to go beyond term gestation. It can also be seen in growth-retarded fetuses, which experience placental insufficiency. Breech presentation is associated with passage of meconium during labor. Meconium passage may be a sign of fetal stress. Fetal hypoxia and acidosis can increase gut motility (higher levels of hormone motilin demonstrated) of fetus. Rarely, it is reported to be a sign of fetal diarrhea when there is fetal infection with listeriosis.

## PATHOPHYSIOLOGY

Although *aspiration* of meconium and associated chemical pneumonitis, surfactant inactivation, airleaks and collapses due to mechanical obstruction are apparent direct causes of respiratory distress, persistent pulmonary hypertension (MAS-PPHN) is the determinant of severity. When perinatal asphyxia is the cause of MAS, multi-organ dysfunction due to hypoxia, ischemia worsens the outcome. On some occasions, secondary bacterial infection may complicate the course.

## CLINICAL FEATURES

The diagnosis is essentially clinical-respiratory distress at birth or within hours in setting of MSAF. Investigations are only necessary to manage the respiratory and multisystem symptoms. Most recommend is close observation for respiratory distress for at least 6 hours, if baby is delivered through MSAF.

Meconium staining of umbilical cord/nail points to MSAF when the information is not available in noninstitutional birth. If the baby was depressed and intubated, finding meconium on endotracheal suction is evidence of MAS.

Babies with MAS may have two dominant patterns of lung involvement. In the more common presentation, the lungs are nonhomogeneously atelectatic (patchy shadows) (**Fig. 1**) or overinflated due to meconium plugs and ball valve effect respectively. Such babies have a splinted and prominent chest wall. In some babies, surfactant inactivation is the dominating pathology; these babies behave like respiratory distress syndrome (RDS) with tachypnea, retractions and oxygen need. X-ray chest can be typical *white out* like in RDS. In babies with RDS-like picture, surfactant therapy may be beneficial.



**Figure 1** Coarse nodular opacities in a neonate with meconium aspiration syndrome (MAS)

Tachypnea is common in MAS and can last for 2–3 weeks in some babies even after clinical improvement. Chest X-ray and arterial blood gas will help optimize respiratory care. Oxygenation indices calculated from  $\text{PaO}_2$ ,  $\text{FiO}_2$  and mean airway pressure (MAP) can objectively guide scaling therapies to high frequency ventilation, use of inhaled nitric oxide and extracorporeal membrane oxygenation (ECMO) in babies with severe hypoxemic respiratory failure.

Blood cultures must be taken before starting antibiotics in symptomatic baby/baby with X-ray changes. As meconium is *sterile* and inflammatory markers like C-reactive protein (CRP) and complete blood count (CBC) may be false positive, clear decision on discontinuing antibiotics is difficult.

## DIFFERENTIAL DIAGNOSIS

Respiratory distress in newborn, born through MSAF may be manifestation of infection (congenital pneumonia), fetal hypoxia (PPHN, pulmonary infarct/hemorrhage). MSAF may be an incidental event in babies with congenital malformations like congenital diaphragmatic hernia or other malformations causing respiratory distress in a term born neonate and only an antenatal sonography or postnatal X-ray may point to primary disease.

1. *Transient tachypnea of newborn* Some of the babies born through MSAF may settle down in hours and have no typical X-ray changes.
2. *Early onset sepsis/congenital pneumonia* The commonest cause of respiratory distress in term born babies is infection. The stress of infection may cause the fetus to pass meconium in utero. The diagnosis of infection must be excluded with surety by cultures and negative inflammatory markers to safely stop antibiotics.
3. *Asphyxial lung injury* Fetal distress, asphyxia and meconium staining of liquor and aspiration are overlapping clinical situations. Asphyxia can cause lung injury due to infarct, hemorrhage, protein leaks and surfactant insufficiency and

present the same as MAS. It may not be clinically possible to distinguish or confirm even by labs. Physiology directed therapy is preferred to pointing to pathological babies of respiratory distress/failure.

4. **Congenital malformations** Like congenital diaphragmatic hernia, unlike in preterm babies, where RDS (respiratory distress due to surfactant insufficiency) outnumbers all other causes, in term born babies, congenital malformation is an important cause especially if there is no infection or asphyxia setting. An X-ray must be done in all term born babies with respiratory distress.

## COMPLICATIONS

Neonates with MAS usually also have hypoxic-ischemic encephalopathy (HIE) as a comorbidity. But in addition, MAS itself can be associated with several other complications; major ones include airleaks (**Fig. 2**), PPHN and infection.

**Pulmonary airleaks** It is one of the most frequent complications and has been reported in up to 15% of neonates with MAS who are not mechanically ventilated. In mechanically ventilated neonates with MAS, this could be as high as 50%. Pneumothorax may be unilateral or bilateral and can result in rapid deterioration in the baby's condition. The incidence of airleaks with MAS has decreased with improved ventilators, ventilation techniques with shorter inspiratory time, possibly better synchronization, use of surfactant and less aggressive ventilation with support of high frequency and nitric oxide. Intercostals drainage may be required if X-ray confirms a pneumothorax.

**Persistent pulmonary hypertension (PPHN)** The incidence varies and reported to be as high as 40%.

**Infection** This is a complication seen more often with ventilated neonates.

## MANAGEMENT

### Initial Management

The severity of respiratory distress may be underestimated in term babies. It is, therefore, important to observe and monitor all infants

born through MSAF for hypoxia or respiratory distress for at least 6 hours.

**Minimal handling** These babies must be minimally handled because they run the risk of going into severe hypoxia when agitated.

**Thermal environment** This must be maintained in a thermoneutral environment.

**Glucose and fluids** It is important that these babies are provided intravenous fluid as symptomatic babies would feed poorly and may become hypoglycemic. It is important that blood sugars are monitored to maintain euglycemia.

## Respiratory Support

### Oxygen Therapy

Most babies when noted to be hypoxic can be managed by providing supplemental oxygen therapy by a headbox. Some of these babies may need  $\text{FiO}_2$  of over 60% for several days. Those babies who need rapid increase in oxygen concentration to maintain  $\text{SaO}_2$  are candidates for mechanical ventilation.

### Acid-base Homeostasis

It is important to maintain acid-base homeostasis. Severe metabolic acidosis may precipitate PPHN and, therefore, may need alkali therapy. Evidence of respiratory failure (raised  $\text{paCO}_2$ ) is an indication for mechanical ventilation.

### Ventilation

Respiratory distress can vary in severity—in some cases, only tachypnea and mild hypoxia requiring oxygen by hood may settle in few days. In at least 30% babies, severe respiratory distress may require ventilation. If babies have severe respiratory distress requiring high ventilator pressures or air leaks with high  $\text{PaCO}_2$ , high frequency ventilation may be used. If there is coexisting PPHN causing severe hypoxia confirmed by echocardiography, inhaled nitric oxide may be required.

### Surfactant

If baby is on high respiratory support and X-ray is RDS-like, surfactant therapy may be considered. Meta-analysis of four trials enrolling 326 infants showed no effect on mortality. The risk of requiring ECMO was significantly reduced in a meta-analysis of two trials ( $n = 208$ ); (typical relative risk 0.64, 95% CI:0.46, 0.91; typical risk difference -0.17, 95% CI:-0.30,-0.04); number needed to treat to benefit 6 (95% CI:3, 25). One trial ( $n = 40$ ) reported a statistically significant reduction in the length of hospital stay [mean difference—8 days (95% CI:14, 3 days)]. There were no reductions in duration of assisted ventilation, duration of supplemental oxygen, pneumothorax, pulmonary interstitial emphysema, air leaks, chronic lung disease and need for oxygen at discharge. Studies have described the use of higher doses of surfactant than for RDS, surfactant lavage with variable short-term benefits. In infants with MAS, lung lavage with diluted surfactant may be beneficial. Meta-analysis of two studies did not show a decrease in mortality or the use of ECMO. For the composite outcome of death or use of ECMO, a significant effect favored the lavage group (typical relative risk 0.33, 95% CI:0.11 to 0.96; typical risk difference -0.19, 95% CI:0.34 to -0.03; number needed to benefit (NNTB)).

### Steroids

In published trials, no benefits of steroid therapy in the management of MAS were demonstrated.

## OUTCOME

In babies with MAS, comorbidities like PPHN, asphyxia, bacterial pneumonia and airleaks determine the risk of progressive



**Figure 2** Unilateral pneumothorax in a neonate with MAS

respiratory failure and multiorgan injury. Mortality in MAS-PPHN is much higher than babies ventilated for RDS/pneumonia. Need for higher device support like high frequency and iNO must guide early referral.

## PREVENTION

Fetal monitoring, avoiding post-term deliveries have decreased the incidence of MAS. It is not proven whether therapies like amnioinfusion have influence on incidence or severity of MAS.

### IN A NUTSHELL

1. MAS is seen mostly in post-term neonates or those with placental insufficiency
2. All babies born through MSAF must be monitored for at least 6 hours for respiratory distress
3. Persistent pulmonary hypertension and airleaks are common complications in babies with MAS
4. High-frequency ventilation and inhaled nitric oxide may be beneficial in severe hypoxic respiratory failure.

## MORE ON THIS TOPIC

- al-Mateen KB, Dailey K, Grimes MM, Gutcher GR. Improved oxygenation with exogenous surfactant administration in experimental meconium aspiration syndrome. *Pediatr Pulmonol*. 1994;17:75-80.
- El Shahed AI, Dargaville P, Ohlsson A, Soll RF. Surfactant for meconium aspiration syndrome in full-term/near-term infants. *Cochrane Database Syst Rev*. 2007;3:CD002054.
- Hahn S, Choi HJ, Soll R, Dargaville PA. Lung lavage for meconium aspiration syndrome in newborn infants. *Cochrane Database Syst Rev*. 2013;4:CD003486.
- Halliday HL. Endotracheal intubation at birth for preventing morbidity and mortality in vigorous, meconium-stained infants born at term. *Cochrane Database Syst Rev*. 2001;1:CD000500.
- Ward M, Sinn J. Steroid therapy for meconium aspiration syndrome in newborn infants. *Cochrane Database Syst Rev*. 2003;4:CD003485.
- Wiswell TE, Gannon CM, Jacob J, et al. Delivery room management of the apparently vigorous meconium-stained neonate: results of the multicenter, international collaborative trial. *Pediatrics*. 2000;105:1-7.
- Wiswell TE, Henley MA. Intratracheal suctioning, systemic infection, and the meconium aspiration syndrome. *Pediatrics*. 1992;89:203-6.



## Chapter 17.7

# Pulmonary Air Leaks in the Newborn

Manish Balde, Sanjay Wazir

Pulmonary air leaks are most frequent in the newborn period than any other time in life. These are a result of overdistension of alveoli causing tissue rupture at the alveolar bases and leakage of air into the extra-alveolar spaces where it is not normally present. The resulting disorders depend upon the location of the air and ease with which the gas can move. The most common conditions are pneumothorax, pneumomediastinum, pulmonary interstitial emphysema and pneumopericardium. Rarer forms are pneumoperitoneum and subcutaneous emphysema.

### INCIDENCE

One percent of babies develop spontaneous pneumothorax at birth. Mostly are unilateral with right side more frequently involved than the left side. The incidence depends upon the factors including birthweight, the presence of lung disease and the method of detection. The incidence is increased in preterm infants, who often have pulmonary disease. In a report from the Vermont Oxford database, pneumothorax was reported in 6.3% of 26,007 infants with birthweight 500–1500 g in 1999. In India, in a recent study from Manipal Hospital, there were equal number of term and preterm babies with pneumothorax and incidentally only half of those were related to ventilation. The reported mortality is about 40%, and most of the cases are present in the first 48 hours.

### PNEUMOTHORAX

This condition results in collection of air between the visceral and parietal pleura and significant accumulation of air results in collapse of the lung (Fig. 1).

### Etiology

#### Spontaneous

Most cases are present early. The most common causes are:

- High transpulmonary pressures generated in the first few breaths.

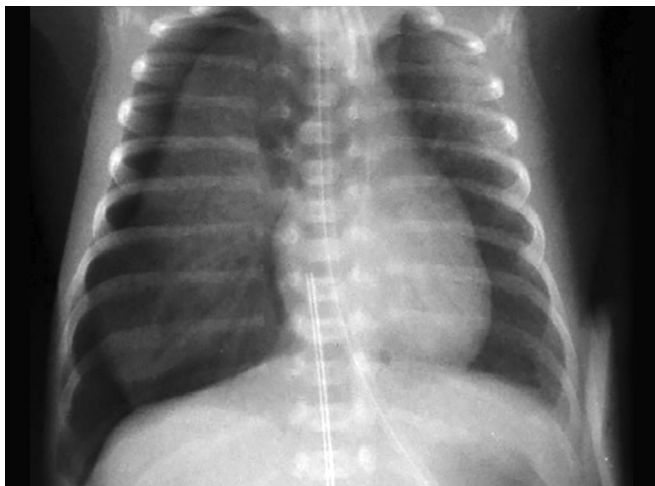


Figure 1 Right-sided pneumothorax with collapsed lung

- Rupture of a congenital bulla.
- Familial spontaneous pneumothorax—runs in the families, but mode of inheritance is not very clear, rare entity.

### Pulmonary Disorders

Pneumothorax is common in meconium aspiration syndrome (MAS) (10–30%), pulmonary hypoplasia and severe hyaline membrane disease requiring significant peak inspiratory pressures during mechanical ventilation.

### Direct Injury

By a suction catheter advanced into the right main bronchus and has also been associated with central venous catheter placement.

### Surfactant

Synthetic surfactants, although no longer used now, but were associated with increased incidence of air leaks than natural surfactants. In a recent large retrospective study from the Pediatrix database of 51,282 preterm infants (median gestational age 30 weeks), who received surfactant therapy between 2005 and 2010, there were no significant differences amongst the three natural preparations after adjusted analysis in the outcomes of air leak syndromes.

### Inspired Gas Temperature

Maintaining the temperature of the inspired gases in very low birth weight (VLBW) babies to more than 36.5°C, resulted in 70% reduction in the rate of pneumothorax, probably because of improved clearance of secretions at higher temperature and humidity.

### Ventilatory Strategies

High mean airway pressure (MAP) especially more than 12, high positive end-expiratory pressure (PEEP), Long inspiratory time (> 0.5 sec) and inspiratory time longer than expiratory time (I:E ratio) more than 1:1 is associated with higher risk of air leaks. Volume ventilation has been shown, in a recent meta-analysis, to have reduced rates of air leaks than the pressure controlled mode and also regular monitoring of tidal volumes on the graphics section of the ventilator results in lesser air leaks.

### Muscle Relaxants

For ventilated preterm infants with evidence of asynchronous respiratory efforts, neuromuscular paralysis with pancuronium seems to result in a trend toward lesser air leaks. The routine use of pancuronium or any other neuromuscular blocking agent in ventilated newborn infants cannot be recommended based on current evidence and lack of data on long-term neurological and pulmonary outcomes. Similarly, the routine use of opioids in mechanically ventilated babies is not recommended at present.

### Modes of Ventilation

- *High-frequency positive pressure ventilation (HFPPV)* Although the impact of breath rates upward of 80 per minute has not been systematically compared to lower rates, but ventilating at 60/min as compared to 30–40/min has resulted in approximately 30% reduction in the frequency of air leaks. However, the impact of these studies in the current era may be difficult to apply as these studies were done in an era where antenatal steroids and postnatal surfactant usage was not very common.
- *Patient-triggered ventilation (PTV)* If the baby's attempts to breathe are synchronized with the mechanical breaths from the ventilator, less pressure may be needed. This could reduce the chance of air leak. A meta-analysis of six studies however has shown no benefit of PTV in prevention of air leaks. The results

of this meta-analysis might have been skewed because of the study of Baumer et al. where more than 900 babies showed an increased incidence of air leaks with PTV. The babies in this trial were supported by a ventilator which used an airway pressure trigger. In very premature babies, airway pressure trigger has a long trigger delay which results in inflation extending into the active expiration and higher rate of asynchrony. This data would have to be looked at again in light of better sensing devices, incorporation of flow triggers rather than pressure triggers and use of termination sensitivities in the current ventilators.

- **High-frequency ventilation** Both high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV) can provide adequate gas exchange using extremely low tidal volume and supraphysiologic rate in neonates with acute pulmonary dysfunction, and they are considered to have the potential to reduce the risks of air leak syndrome in neonates. However, there is still no conclusive evidence that HFOV or HFJV can help to reduce new air leaks in published neonatal clinical trials.

### Clinical Features

There are three kinds of presentation of a pneumothorax:

1. **Asymptomatic** Small pneumothorax can be completely asymptomatic and picked up only on a routine chest X-ray.
2. **Respiratory deterioration** Sudden worsening of the respiratory status in a neonate who was stable otherwise or on ventilator.
3. **Signs of cardiovascular compromise** In case of large tension pneumothorax (**Fig. 2**), there is initial tachycardia followed by bradycardia, narrowing of pulse pressure and hypotension and decreased capillary refill time.

The findings could include asymmetrical chest with prominence on the affected side, decreased breath sounds on the affected side, shift of the point of maximal cardiac impulse away from the affected side and distant heart sounds. Cyanotic upper half with paler lower half can be seen in case of tension pneumothorax. An early sign may be a sudden decrease of voltage of the QRS complex on the oscilloscopic cardiac tracing.

### Diagnosis

#### Blood Gas

Hypoxemia and marked hypercarbia with resultant respiratory acidosis.

#### Transillumination

Transillumination of the chest with high intensity fiberoptic probe in a darkened room may help make the diagnosis. When the

fiberoptic probe is placed along the posterior axillary line on the side, the whole chest *lightens up* on the side of the pneumothorax (**Fig. 3**). This however could be unreliable in extremely premature babies because of the small chest, term babies with chest wall edema, severe subcutaneous emphysema in a premature infant with **pulmonary interstitial emphysema (PIE)**.

### Chest Radiograph

**Anteroposterior view** Findings include (i) shift of the mediastinum away from the pneumothorax; (ii) depression of diaphragm on the side of the pneumothorax; (iii) affected side appears hyperlucent; and (iv) air in the pleural space outlining the visceral pleura with collapse of lung on that side.

**Lateral decubitus view** A very small pneumothorax may only be appreciated in lateral decubitus view with the affected side up.

**Ultrasound of the chest** The absence of lung sliding (seashore sign), stratosphere sign and comet tails confirm the presence of pneumothorax.

### Differential Diagnosis

Other air leaks like pneumomediastinum, congenital diaphragmatic hernia, congenital lobar emphysema, congenital cystic adenomatoid malformation and pulmonary cysts.

### Management

#### Asymptomatic Pneumothorax

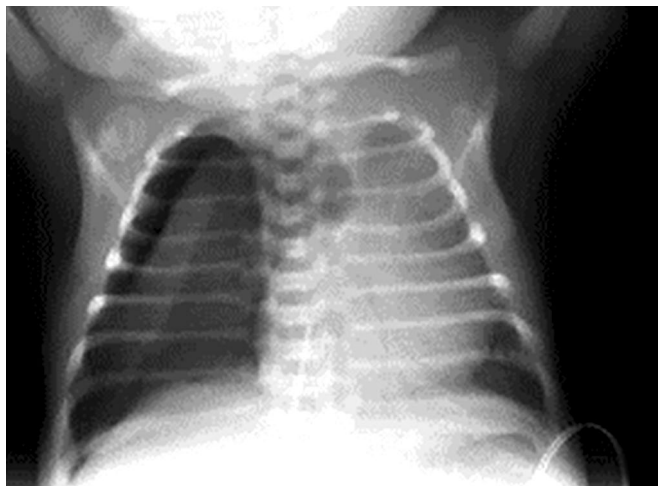
Infants without a continuous air leak or respiratory distress and who have no underlying lung disease or have no need for assisted ventilation may be observed closely without specific treatment. The pneumothorax will typically resolve in one to two days.

#### Oxygen Treatment

Animal studies have shown that the use of higher inspired oxygen concentration up to 50% may hasten the resolution of small pneumothorax. This intervention is, however, not recommended because of risk of hyperoxia, especially in a preterm infant. Oxygen therapy should be tailored based on oxygen saturation targets.

#### Conservative Management in Ventilated Babies

In mechanically ventilated infants, ventilator settings should be adjusted to minimize MAP by reducing peak inspiratory pressure, PEEP and inspiratory duration. In some cases of infants who do not



**Figure 2** Right-sided tension pneumothorax



**Figure 3** Transillumination of chest in pneumothorax

require high ventilatory settings, spontaneous resolution may occur without chest tube placement. In a retrospective study from Israel, which included 136 VLBW babies, 101 babies (74%) were treated initially with a chest tube and 35 babies (26%) without a chest tube. Of those who did not receive a chest tube initially, 14 were treated with needle aspiration and 21 with expectant treatment.

### Thoracocentesis

This is an emergency treatment for symptomatic pneumothorax. It may be the only intervention required in an infant who is not mechanically ventilated and may be a temporary measure in an infant who is mechanically ventilated. The site of puncture should be at the second intercostal space along the midclavicular line on the suspected side.

### Chest Tube Placement

For definitive drainage in tension pneumothorax or in case of significant deterioration in a mechanically ventilated baby, insertion of a chest tube is necessary. The position of the chest tube and resolution of the pneumothorax should be confirmed by chest radiography. Negative suction applied to the drainage bottle can help evacuate air in cases of large pneumothoraces (Fig. 4).

### Recalcitrant Pneumothorax

This is a difficult situation and some suggested therapies could be:

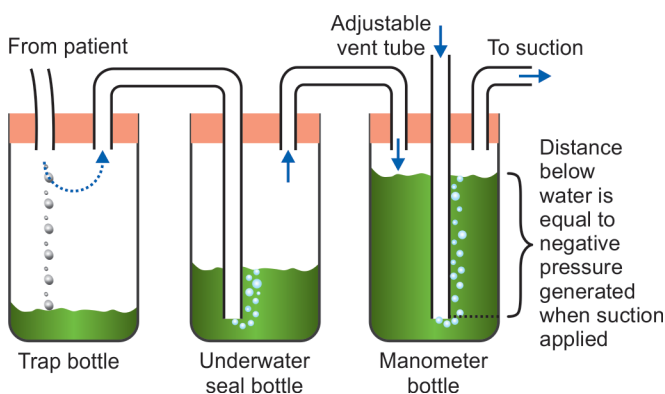
- High-frequency ventilation using a low volume strategy to lower the MAP, although the evidence for this is not very strong.
- Unilateral lung intubation for duration of 48 hours may be tried.
- Fibrin glue such as cryoseal C has been injected in the chest tube with marked reduction in the air leak, although this therapy is associated with significant adverse effects.
- Occlusion of the right main bronchus with a Fogarty catheter produced rapid improvement in a 26 weeks gestation infant who had a nonresolving pneumothorax.

## PULMONARY INTERSTITIAL EMPHYSEMA (PIE)

It consists of air trapped in the perivascular tissues of the lung from the alveolar over distension.

### Incidence

*Pulmonary interstitial emphysema* was believed to occur exclusively in the VLBW infants on ventilatory support in the first 48–72 hours of life. However, there have been case reports of PIE in late preterms on continuous positive airway pressure (CPAP) and in term infants.



**Figure 4** Three-bottle technique for pneumothorax drainage

## Pathophysiology

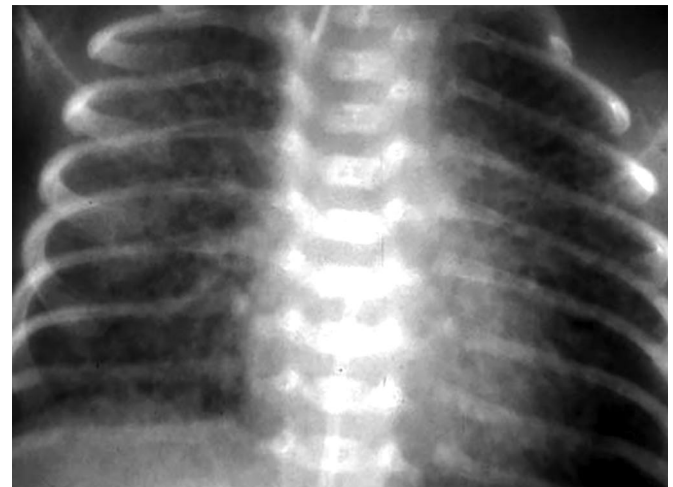
Pulmonary interstitial emphysema may precede the development of pneumothorax or other air leaks. It results from the dissection of air into the perivascular tissue of the lung due to rupture of the over distended alveoli. This interstitial air moves in the connective tissue plane and around the vascular axis. Minimising pulmonary over distension should reduce the risk of PIE. The condition could be unilateral or bilateral.

## Clinical Features

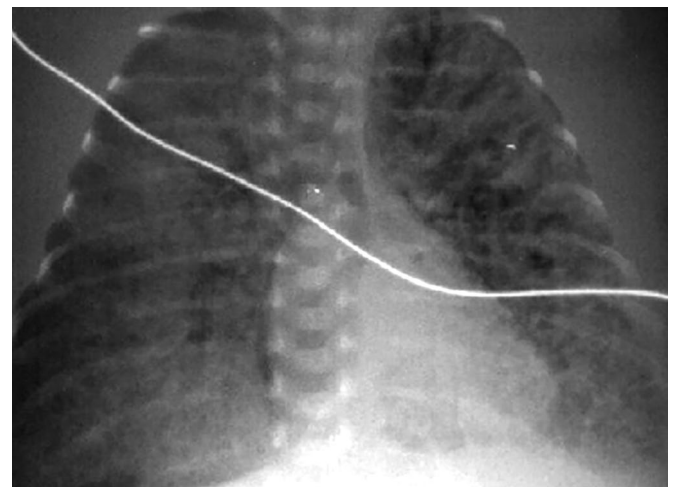
It usually presents within first few days of life with gradually worsening of hypercarbia and hypoxemia. Increase in ventilatory settings does not improve the hypercarbia. Over distension of the lung may cause vascular compression, resulting in decreased venous return and impaired cardiac output.

## Diagnosis

On a chest X-ray, interstitial air can appear as either cyst-like (Fig. 5) or linear radiolucencies (Fig. 6). The former are approximately 1–4 mm in size. The linear radiolucencies are coarse, nonbranching, streaks that are seen in both the peripheral and medial lung fields. Transillumination of the chest would produce picture similar to the large pneumothorax.



**Figure 5** Pulmonary interstitial emphysema (multiple small cysts in both the lung fields; more prominent on the right side)



**Figure 6** Pulmonary interstitial emphysema (Linear hyperlucent streaks in upper left lobe)



## Differential Diagnosis

The chest X-ray can be confused with lobar emphysema or if more localised with cystic adenomatoid malformation of the lung. Linear translucencies can be confused with air bronchograms in a severe respiratory distress syndrome (RDS), but in that case, the translucencies do not extend toward the periphery of the lung.

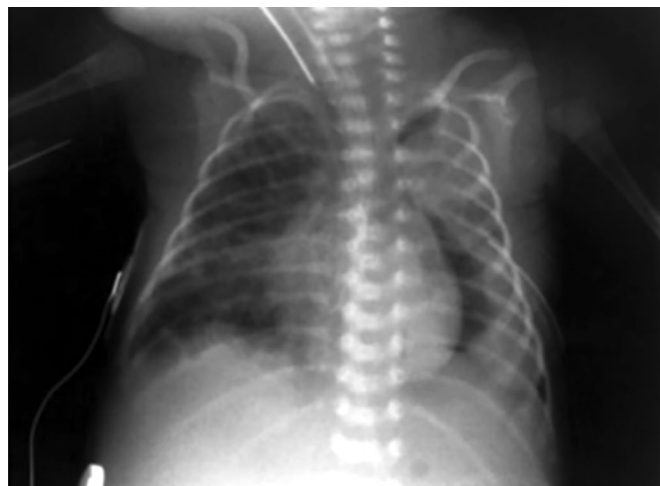
## Management

### Generalized PIE

- Sedation/analgesia** In a neonate who is having obvious asynchrony on the ventilator, we would need to sedate or use opioids to reduce the risk of extension of PIE to pneumothorax.
- Ventilatory management** Decreasing the MAP as much as possible is a goal. This can be achieved by reducing the peak inspiratory pressure, PEEP or inspiratory duration. The inspired oxygen concentration should be increased to compensate for the decreased MAP. High-frequency ventilation is often utilized in this scenario, but there is no sufficient conclusive evidence of its benefit.

### Localized PIE

- Shorter inspiratory times** This has been used to direct the delivered volume preferentially toward units of the lung with relatively normal time constants, while avoiding inflation of longer time-constant emphysematous areas. However, because of limited volume delivery with such a manoeuvre, this is likely not to be tolerated for long.
- Selective intubation of contralateral lung** Intubation of the right main bronchus is easy because of anatomical reasons and can be achieved by just intubating a little deeper. Intubation of the left main bronchus is facilitated by positioning the bevel on the end of the endotracheal tube so that the long part of the tube is directed toward the main bronchus to be intubated. Turning the infant's head to the right moves the tip of the endotracheal tube to the contralateral side of the trachea and thus the left main bronchus is intubated. Cutting a hole in the tube reduces the risk of upper lobe collapse. Duration of this should be 48 hours, although it can be extended up to 5 days in case of nonresolution. Similar results can be achieved by blocking the right main bronchus with a fogarty catheter.
- Lateral decubitus position** In such a position, the uppermost lung receives the greater proportion of the ventilation; hence, by underventilation, decompression of the dependent lung is encouraged.



**Figure 7** Pneumomediastinum

## PNEUMOMEDIASTINUM

This is a condition consisting of air in the mediastinal space.

### Clinical Features

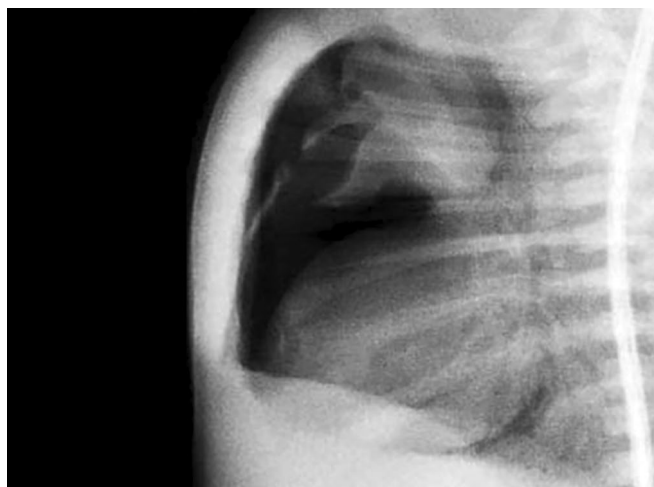
Most cases of pneumomediastinum are asymptomatic. Large collections of air may result in tachypnea and cyanosis. Pneumomediastinum is usually suspected on the routine newborn examination when the heart sounds are distant.

### Diagnosis

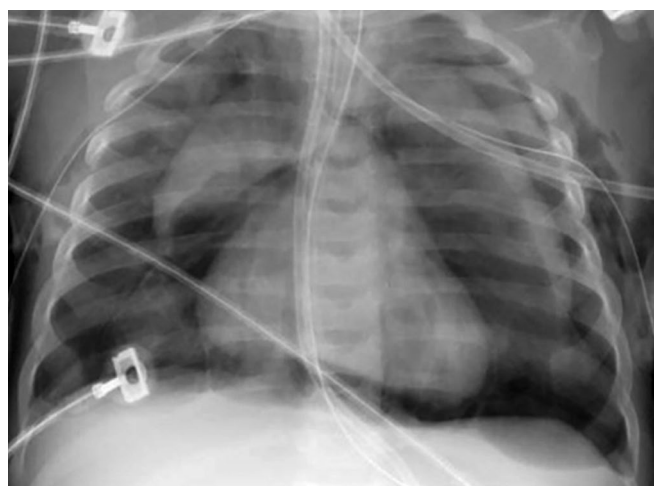
The diagnosis is made on a chest radiograph. If the amount of air is large, the pneumomediastinum can usually be appreciated on an anteroposterior view as a halo of air around the lateral border of heart (**Fig. 7**) or on a lateral view as a retrosternal or superior mediastinal radiolucency (**Fig. 8**). It is most reliably seen on a left anterior oblique view, in which even minimal air in the mediastinum surrounds the thymus and lifts it from the cardiac shadow, resulting in the characteristic *spinnaker sail* sign (**Fig. 9**).

### Management

Pneumomediastinum usually resolves spontaneously, and requires no specific treatment. The patient should be observed



**Figure 8** Pneumomediastinum lateral chest X-ray (showing air behind the sternum)



**Figure 9** Pneumomediastinum (Spinnaker Sail Sign)



closely for evidence of cardiorespiratory compromise and development of other air leaks, especially pneumothorax. Drainage is recommended for rare cases of tension pneumomediastinum, causing cardiovascular compromise. Attempts, however, at draining mediastinal air are often unsuccessful despite needling or tube drainage and indeed may cause complications, such as phrenic nerve damage. If the infant requires ongoing ventilatory support, use of a lower airway MAP should be attempted.

## PNEUMOPERICARDIUM

This condition is characterized by air in the pericardial space, which could potentially result in cardiac tamponade.

### Etiology

- Spontaneous
- Associated with ventilation in preterm babies
- Congenital absence of left pericardium—either partial or complete—is a rare condition. The complete absence is usually asymptomatic throughout life. Radiographic findings of complete absence of the left pericardium include an unusual cardiac silhouette with elongation of the left heart border, leftward shift and clockwise rotation of the heart, a radiolucent cleft between the ascending aorta and the main pulmonary artery and lucency separating the heart and the left hemidiaphragm. The first two findings related to the abnormal mobility of the heart, the later two result from interposition of lung that is normally restricted by the left pericardium.

### Clinical Features

The typical presentation is the abrupt onset of hemodynamic compromise due to cardiac tamponade. Acute collapse may be preceded by tachycardia and a narrowed pulse pressure. Findings on physical examination include bradycardia, hypotension, increased respiratory distress and cyanosis. The heart sounds may be muffled or distant. Some infants have a pericardial knock or a characteristic mill wheel-like murmur. The electrocardiogram may show low voltages with a small QRS complex.

### Diagnosis

Gas can be seen completely surrounding the heart, outlining the base of the great vessels and contained within the pericardium (**Fig. 10**). Gas does not rise above the upper border of the pericardium, whereas with a pneumomediastinum air is seen anterior to the heart with hyperlucency behind the sternum. Air is seen inferior to the diaphragmatic surface of the heart and this also differentiates this abnormality from a pneumomediastinum. Air behind the heart is virtually diagnostic of a pneumopericardium.

### Management

If it is completely asymptomatic, then they should be left alone with a little oxygen to maintain saturation in the target range of 90–95%. If the baby has features of cardiovascular compromise, it is better to do a needle aspiration by pericardiocentesis.

## OTHER AIR LEAKS

Pneumoperitoneum and subcutaneous emphysema are uncommon types of air leak. Pneumoperitoneum may occur when extrapulmonary air decompresses into the peritoneal cavity. The diagnosis is made on an abdominal radiograph and usually has little clinical significance. However, it must be differentiated from intraperitoneal air due to a perforated viscus.

Subcutaneous emphysema typically occurs in the face, neck or supraclavicular region. It typically presents as crepitus detected by palpation. It usually has no clinical significance, although large air collections in the neck may cause tracheal compromise.

### IN A NUTSHELL

- Air leaks are not uncommon causes of neonatal respiratory distress.
- A common cause is assisted ventilation; they can also occur spontaneously.
- Air can accumulate in the pleura (pneumothorax), in the lung interstitium (pulmonary interstitial emphysema), in the mediastinum or pericardium.
- In ventilated neonates with sudden cardiovascular compromise, pulmonary air leaks must always be suspected.
- Transillumination at the bedside is a useful diagnostic aid for pulmonary air leaks in the newborn.
- Pulmonary air leaks can rarely present as pneumoperitoneum.

### MORE ON THIS TOPIC

Carey B. Neonatal airleaks: pneumothorax, pneumomediastinum, pulmonary-interstitial emphysema, pneumopericardium. *Neonatal Netw.* 1999;18: 81-4.

Jeng MJ, Lee YS, Tsao PC, Soong WJ. Neonatal air leak syndrome and the role of high-frequency ventilation in its prevention. *J Chin Med Assoc.* 2012;75:551-9.

Joseph LJ, Bromiker R, Toker O, et al. Unilateral lung intubation for pulmonary air leak syndrome in neonates: a case series and a review of the literature. *Am J Perinatol.* 2011;28:151-6.

Kitsommart R, Martins B, Bottino MN, Sant'Anna GM. Expectant management of pneumothorax in preterm infants receiving assisted ventilation: report of 4 cases and review of the literature. *Respir Care.* 2012;57:789-93.

Lichtenstein DA, Mauriat P. Lung ultrasound in the critically ill neonate. *Curr Pediatr Rev.* 2012;8:217-223.

Ramesh Bhat Y, Ramdas V. Predisposing factors, incidence and mortality of pneumothorax in neonates. *Minerva Pediatr.* 2013;65:383-8.



**Figure 10** Pneumopericardium (note the air on the base of heart)

## Chapter 17.8

# Persistent Pulmonary Hypertension (PPHN)

Neeraj Gupta

Persistent pulmonary hypertension of the newborn (PPHN) is a disease which is characterized by failure to achieve or sustain the normal decrease in pulmonary vascular resistance (PVR) at birth. Elevated PVR results in extrapulmonary shunting of deoxygenated blood via fetal channels (ductus arteriosus and foramen ovale) to systemic circulation resulting in hypoxemic respiratory failure and multi-organ dysfunction. PPHN is a serious disease with significant morbidity and mortality and is primarily restricted to term and post-term infants. Recently, it has also been described in preterm infants with bronchopulmonary dysplasia (BPD). Advent of inhaled nitric oxide (iNO), along with better understanding of disease at molecular level has revolutionized its management over last one decade.

## NORMAL FETAL CIRCULATION AND TRANSITION AT BIRTH

Placenta, but not the lungs, serves as the organ of gas exchange inside the fetus. High PVR during fetal life actually helps in gas exchange by diverting most of the right ventricular output through ductus arteriosus to the descending aorta and to the placenta circulation. Blood returning from the placenta is rich in oxygen and is directed from the right atrium through the foramen ovale into the left atrium, whereas that from the brain and heart having low oxygen content is directed from the right atrium into the right ventricle. Only 10–20% of the combined ventricular output is directed to pulmonary vascular bed in the human fetus.

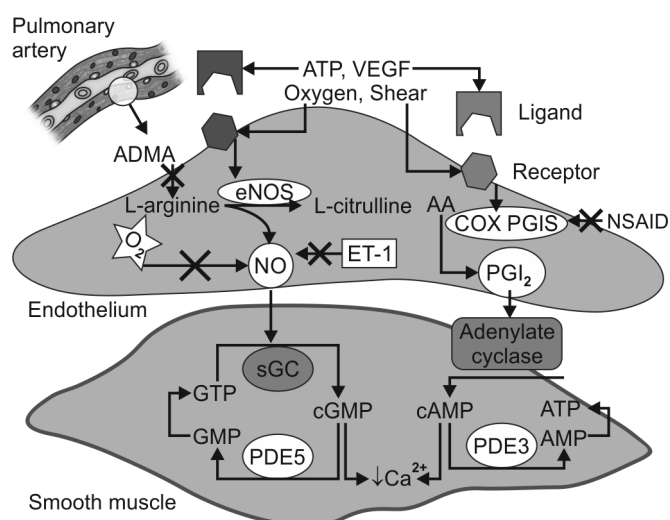
Mechanical compression of small pulmonary arterioles by fluid-filled alveoli, low arterial oxygen levels, elevated levels of pulmonary vasoconstrictors [endothelin-1 (ET-1), leukotrienes and thromboxane] and relative lack of vasodilators [nitric oxide (NO) and prostacyclin (PGI<sub>2</sub>)] maintains high PVR during fetal period. PVR increases with increasing gestational age despite the increasing surface area of pulmonary vascular bed suggesting active pulmonary vasoconstriction during late gestation. ET-1 is a potent vasoconstrictor and is synthesized by pulmonary vascular endothelial cells. It acts on two types of receptors, ETA (present on smooth muscle cells) and ETB (present on vascular endothelial cells). Stimulation of ETA receptors results in vasoconstriction via calcium influx whereas ETB causes vasodilation via stimulating NO release from endothelial cells. Selective blockade of ETA receptors leads to pulmonary vasodilation inside the fetus.

Initiation of respiration at birth replaces fluid-filled alveoli with air resulting in increased arterial oxygen tension. This results in rapid and marked decrease in PVR shortly after birth, leading to 8–10 folds increase in pulmonary blood flow. This leads to increase in pulmonary venous return and left atrial pressure promoting closure of foramen ovale. Simultaneous clamping of umbilical cord removes low resistance placental circulation, thus increasing systemic vascular resistance (SVR). The resulting decline in PVR or SVR ratio leads to steady increase in pulmonary blood flow and oxygen uptake in the lung. As soon as PVR falls below systemic levels, blood flow through ductus arteriosus reverses. This is followed by functional closure of ductus arteriosus

within first several hours after birth. Closure results in separation of pulmonary from systemic circulation leading to establishment of normal postnatal circulatory pattern. PVR continues to drop at a relatively slower rate over the next several weeks to reach adult levels.

This process of transition at birth depends on several factors. Increase in arterial oxygen tension is the most important among them which decreases PVR. Clearance of fetal lung fluid, expansion of the lung to normal resting volume and shear stress resulting from increased pulmonary blood flow also contributes to pulmonary vasodilation. All these factors promote release of pulmonary vasodilators including NO and PGI<sub>2</sub> (Fig. 1).

NO production is primarily mediated by increase in arterial oxygen saturation. Oxygen stimulates endothelial nitric oxide synthase (eNOS) which converts L-arginine to L-citrulline inside the endothelial cells of pulmonary artery and releases NO. Increase in synthesis and release of ATP from red blood cells also indirectly stimulates NO production inside endothelial cells. NO stimulates soluble guanylate cyclase (sGC) in the vascular smooth muscle cell, resulting in conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). An increase in intracellular cGMP levels causes vascular smooth muscle relaxation by decreasing calcium influx. Type 5 phosphodiesterase (PDE-5) in the vascular smooth muscle cell degrades cGMP, thus limiting vasodilation. Reactive oxygen species (ROS) like superoxide may cause pulmonary vasoconstriction by scavenging NO molecules inside endothelial cells. NO is not stored inside the cells. Its increased synthesis at birth reflects increased



**Figure 1** Mechanism of endothelium-dependent pulmonary vasodilation at birth. Nitric oxide (NO) and prostacyclin (PGI<sub>2</sub>) are released in response to birth-related stimuli. NO and PGI<sub>2</sub> increase the cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) levels in the smooth muscle cell. Type 5 and type 3 phosphodiesterases (PDEs) degrade these cyclic nucleotides. A decrease in intracellular Ca<sup>2+</sup> levels leads to relaxation of vascular smooth muscle. NO levels are decreased by asymmetric dimethyl arginine (ADMA), superoxide (O<sub>2</sub><sup>-</sup>), and ET-1. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclo-oxygenase (COX). AA, arachidonic acid; eNOS, endothelial nitric oxide synthase; GMP, guanosine monophosphate; GTP, guanosine triphosphate; PGI<sub>2</sub>, prostacyclin; sGC, soluble guanylate cyclase; VEGF, vascular endothelial growth factor.

Source: Berger S, Konduri GG. Pulmonary hypertension in children: the twenty-first century. *Pediatr Clin North Am.* 2006;53:961-87. Reproduced with permission from Elsevier.

production of eNOS enzyme, which primarily takes place during late gestation period inside the fetus. NO also promotes growth of pulmonary vessels in utero in response to vascular endothelial growth factor (VEGF).

Prostacyclin is another potent pulmonary vasodilator. Stimulus at birth converts arachidonic acid to PGI<sub>2</sub> with the help of cyclooxygenase enzyme. PGI<sub>2</sub> acts in a similar fashion like NO-cGMP pathway and activates the enzyme adenylate cyclase in the vascular smooth muscle cell, which converts ATP to cyclic adenosine monophosphate (cAMP). An increase in intracellular cAMP levels causes vascular smooth muscle relaxation by decreasing calcium influx. Type 3 phosphodiesterase (PDE-3) like PDE-5 keeps a check on cGMP levels, thus limiting vasodilation. Thus, intervention which increases arterial oxygen saturation, NO, sGC, PGI<sub>2</sub> levels and decreases activity of PDE-5 and PDE-3, will have potential role in the management of PPHN. Similarly, blockade of ETA receptors and inhibitors of ROS will also help in decreasing PVR.

## EPIDEMIOLOGY

The prevalence of PPHN varies from 0.4 to 6.8 per 1,000 livebirths in developed countries. However, there is lack of data from developing countries. It is likely that PPHN occurs more frequently in this setting due to high incidence of perinatal asphyxia and meconium aspiration syndrome (MAS). PPHN primarily affects infants who are more than or equal to 34 weeks gestation although a very small proportion of very preterm infants also develop this disease.

## ETIOLOGY

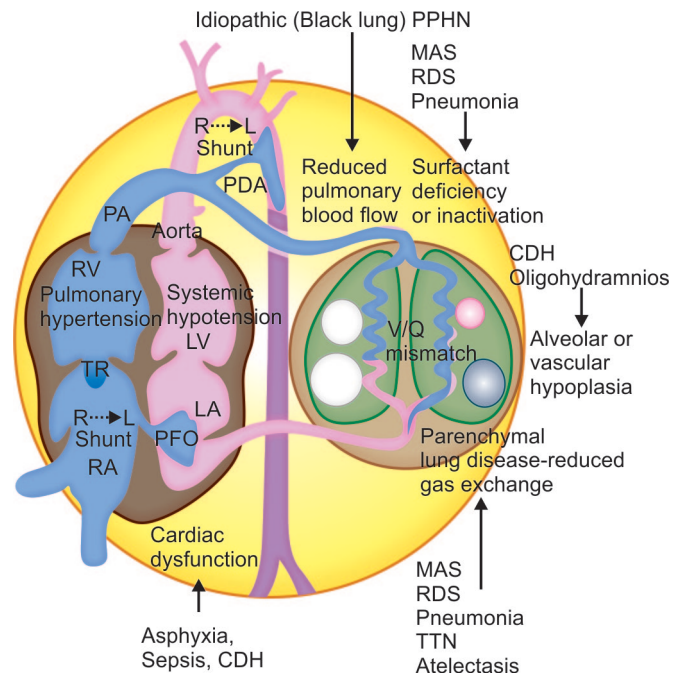
Pulmonary hypertension of the newborn may be idiopathic (10%) or secondary to diverse neonatal conditions (**Fig. 2**). Perinatal asphyxia and MAS are two most common associated diagnoses. Others include various pulmonary parenchymal diseases including respiratory distress syndrome (RDS), transient tachypnea of newborn, pneumonia and/or sepsis. Pulmonary hypoplasia secondary to congenital diaphragmatic hernia (CDH) also leads to development of PPHN. Rare causes of intractable PPHN includes alveolar capillary dysplasia (ACD) and RDS secondary to mutations in surfactant protein B gene or ATP-binding cassette protein member 3.

Various antenatal and perinatal risk factors have been reported in association with PPHN. These include maternal smoking, consumption of aspirin or any other nonsteroidal anti-inflammatory drugs (NSAIDs) during pregnancy, intake of selective serotonin reuptake inhibitors (SSRIs), maternal fever, prolonged rupture of membranes, meconium-stained amniotic fluid and birth by cesarean delivery.

Recently, genetic predisposition has also been associated with increased risk of PPHN. These include specific polymorphism of carbamoyl phosphate synthetase gene, diminished expression of eNOS expression and variations in corticotropin-releasing hormone and its binding protein.

## PATHOGENESIS

Pulmonary hypertension of the newborn is a syndrome which is characterized by sustained elevation of PVR leading to right to left extrapulmonary shunting of blood across ductus arteriosus and/or foramen ovale to systemic circulation resulting in hypoxemia. Three types of abnormalities of the pulmonary vasculature occur in PPHN: underdevelopment, maldevelopment or vascular remodeling, and maladaptation (**Box 1**). However, this compartmentalization is imprecise and most patients actually have overlapping changes.



**Figure 2** Various etiological factors causing PPHN and hemodynamic changes in PPHN. Surfactant deficiency (RDS) or inactivation (MAS or pneumonia) results in parenchymal lung disease and ventilation-perfusion (V/Q) mismatch. Increased PVR results in reduced pulmonary blood flow and right-to-left shunt through PDA and/or PFO. Pulmonary hypertension is often associated with systemic hypotension with septal deviation to the left. Cardiac dysfunction secondary to asphyxia, sepsis or CDH may complicate PPHN. Parenchymal lung disease secondary to RDS, pneumonia, transient tachypnea of newborn (TTN), pneumonia, and atelectasis can result in V/Q mismatch and hypoxemia and PPHN. Idiopathic or “black-lung” PPHN is not associated with parenchymal lung disease and results in reduced pulmonary blood flow with pulmonary vascular remodeling. Pulmonary hypoplasia secondary to CDH or due to oligohydramnios (prolonged leakage of fluid or reduced production due to renal compromise) causes alveolar and vascular hypoplasia and PPHN. The right subclavian artery (and blood flowing to the right upper extremity) is always preductal. The left subclavian artery may be preductal, juxtaductal or postductal. Hence, preductal oxygen saturations should be obtained from the right upper extremity. *Abbreviations:* PA, pulmonary artery; RV, right ventricle; LV, left ventricle; TR, tricuspid regurgitation; RA, right atrium; LA, left atrium; PDA, patent ductus arteriosus; PFO, patent foramen ovale.

*Source:* Nair J, Lakshminrusimha S. Update on PPHN: mechanisms and treatment. *Semin Perinatol.* 2014;38:78-91. Reproduced with Permission from Elsevier.

- **Underdevelopment** This occurs in setting of underdeveloped lungs resulting in hypoplastic pulmonary vasculature. Here, the cross-sectional area of the pulmonary vasculature is reduced, resulting in a relatively fixed elevation of PVR. Only small degree of postnatal pulmonary vasodilation can occur resulting in high risk of mortality. This pathology occurs in pulmonary hypoplasia which may be seen as an isolated anomaly or in association with CDH, oligohydramnios syndrome or renal agenesis.

Few patients with CDH also have associated left ventricular (LV) hypoplasia or dysfunction. LV dysfunction results in pulmonary venous hypertension, which in turn increases pulmonary arterial hypertension. This results in severe PPHN unresponsive to conventional management.



**BOX 1 Mechanism of persistent pulmonary hypertension of the newborn***Underdevelopment/hypoplastic pulmonary vasculature*

- Congenital diaphragmatic hernia
- Pulmonary hypoplasia

*Maldevelopment/vascular remodeling*

- Idiopathic PPHN
- NSAID intake during pregnancy

*Maladaptation*

- Meconium aspiration syndrome
- Perinatal asphyxia
- Sepsis
- Pneumonia
- Respiratory distress syndrome
- Transient tachypnea of newborn

Abbreviations: PPHN, persistent pulmonary hypertension of the newborn; NSAID, nonsteroidal anti-inflammatory drug.

- **Maldevelopment or vascular remodeling** Here the pulmonary vessels are normal in number along with the normally developed lungs. However, abnormal muscularization of normally nonmuscular intra-acinar arteries, increased smooth muscle thickness of pulmonary arterioles and excessive extracellular matrix surrounding these vessels results in pulmonary vascular remodeling which leads to elevation of PVR. One possible stimulus leading to vascular remodeling is fetal hypoxemia. It causes release of humoral growth factors from hypoxia-damaged endothelial cells resulting in overgrowth of smooth muscle cells in pulmonary vasculature. Excessive perfusion of fetal pulmonary vasculature due to premature closure of ductus arteriosus by NSAID intake during pregnancy also results in pulmonary vascular remodeling. Vascular remodeling is classically seen in idiopathic (or black lung) PPHN.
- **Maladaptation** Here the structure and number of pulmonary vessels is normal; however, increased levels of pulmonary vasoconstrictors along with low production of endogenous vasodilators causes active pulmonary vasoconstriction. This is the likely mechanism in PPHN secondary to perinatal asphyxia, sepsis, MAS and other pulmonary parenchymal diseases. Patients with MAS have ventilation-perfusion (V/Q) mismatch due to meconium plugging, surfactant inactivation and lung inflammation. Similarly, alveolar collapse leads to impairment of oxygenation in various other pulmonary parenchymal diseases too. Resulting hypoxia along with hypercapnia and acidosis leads to increase in PVR. LV dysfunction along with acidosis also contributes to increase in PVR in perinatal asphyxia and sepsis. Polycythemia also results in PPHN by increasing blood viscosity.

## PULMONARY HYPERTENSION IN PREMATURE INFANTS

Although PPHN is a disease of late preterm and term infants, it is increasingly being recognized in preterm infants, especially with BPD. A prospective study of 765 infants of less than or equal to 32 weeks gestation found echocardiographic proven PPHN in 2.2% cases. There was prolonged premature rupture of membranes in all infants who developed PPHN. Intrauterine growth restriction, fetal inflammation and ventilator induced lung injury (VILI) result in impaired angiogenesis and abnormal lung development in infants with BPD. Around one-third of these infants develop

pulmonary hypertension later on during the hospital stay or after discharge from neonatal unit.

## CLINICAL FEATURES

Infants with PPHN generally present with respiratory distress and marked central cyanosis usually within first few hours after birth. There may be associated signs of perinatal asphyxia or meconium staining. Appearance of labile saturation or disproportionate hypoxemia, especially in patients being treated for primary lung diseases, also points towards development of secondary PPHN. Cardiac examination may reveal prominent precordial impulse, a single or narrowly split and accentuated S<sub>2</sub> and sometimes a systolic murmur due to tricuspid regurgitation.

Presence of right to left shunt across ductus arteriosus results in differential cyanosis. This is detected by a gradient in the preductal (right extremity) and postductal (any of the lower limbs) arterial oxygenation. Difference of more than 20 mm Hg in PaO<sub>2</sub> or more than 10% in saturation between preductal and postductal values suggests PPHN. However, its absence does not rule it out as a subset of patients have shunting only across foramen ovale resulting in no gradient. A similar gradient between preductal and postductal arterial oxygenation can also be present in duct-dependent systemic blood flow lesions including hypoplastic left heart syndrome, critical aortic stenosis, coarctation of aorta and interrupted aortic arch.

## DIFFERENTIAL DIAGNOSIS

Congenital heart disease (CHD), severe uncomplicated pulmonary parenchymal disease and sepsis are the most common differential diagnoses in a case of PPHN. Presence of differential pulse volume between upper and lower extremities, generalized weak pulse, grade 3+ murmur, pulmonary edema and cardiomegaly favors CHD. Rapid improvement with supplemental oxygen and/or mechanical ventilation suggests primary lung disease. However, this may not be obvious with severe parenchymal disease. Moreover, most infants with PPHN have transient improvement with supplemental oxygen and/or mechanical ventilation, making it difficult to differentiate these two entities on clinical ground.

## APPROACH TO DIAGNOSIS

Chest radiograph (CXR) and arterial blood gas (ABG) are two foremost investigations done in a case of suspected PPHN. CXR shows variable findings depending on the underlying diagnosis such as RDS and MAS. In general, the degree of hypoxemia is disproportionate to the radiographic findings and it is more so in a case of idiopathic PPHN, where there are no parenchymal infiltrates with oligemic lung fields. Cardiac silhouette is normal with normal to low pulmonary blood flow. ABG reveals hypoxemia (PaO<sub>2</sub> < 50 mm Hg). Because PPHN is a labile disease, documentation of normal arterial PaO<sub>2</sub> at some point during the course of disease does help in excluding cyanotic CHD. Similarly, many infants with PPHN have at least one measurement of PaO<sub>2</sub> more than 100 mm Hg on 100% FiO<sub>2</sub> early in the course of their illness, which helps in differentiating it from cyanotic CHD. Echocardiography (ECHO) is the gold standard test to diagnose PPHN. It not only rules out CHD but also determines the predominant direction of shunting at foramen ovale and/or ductus arteriosus and assesses LV function. Interventricular septal flattening or bowing towards left side and presence of tricuspid regurgitation suggests PPHN. However, the diagnosis of PPHN requires documentation of predominant right to left shunting at atrial and/or ductal level. Doppler velocity measurement of tricuspid regurgitation jet helps in assessing pulmonary arterial pressure.



The careful assessment of the direction of shunts provides invaluable information and helps in the management of PPHN. Predominant right to left shunting at ductal level along with left to right shunting at foramen ovale suggests LV dysfunction with pulmonary venous hypertension as seen in CDH. Pulmonary vasodilation alone without improving LV dysfunction will result in pulmonary edema in such a situation. Duct-dependent systemic blood flow lesions also have similar shunt pattern. Predominant left to right shunting at ductal level and right to left shunt at atrial level suggest duct-dependent pulmonary blood flow lesions such as critical pulmonary stenosis.

## MANAGEMENT

Our aim is to reverse abnormally increased PVR and to maintain adequate oxygenation till it normalizes. This can be achieved by preventing factors which aggravates pulmonary arterial hypertension, optimizing lung volume, maintaining systemic circulation, treating underlying disease and using pulmonary vasodilators (**Box 2**). Once stabilization is achieved, supportive measures should be gradually tapered to prevent rebound pulmonary hypertension.

### General Supportive Care

It is important to maintain euthermia and to correct metabolic abnormalities, such as hypoglycemia and hypocalcemia as these can impair cardiac contractility. Hemoglobin should be normalized to optimize oxygen delivery. Polycythemia needs to be corrected. Activities should be clustered to minimize handling. Auditory and visual disturbance should also be minimized by covering eyes and decreasing environmental noise level respectively.

### Sedation/Analgesia and Skeletal Muscle Relaxant

Dyssynchronous breathing in patients on mechanical ventilation causes agitation resulting in catecholamine release which may increase PVR. So, fentanyl 1 hour (1–5 µg/kg/h) or morphine (loading dose: 100–150 µg/kg over 1 hour, followed by 10–20 µg/kg/h, IV) is generally used to facilitate ventilation and to minimize fluctuations in PVR. However, there is no randomized controlled trial (RCT) to support this practice. Pancuronium, a skeletal muscle relaxant, is occasionally used to achieve full synchronization. However, its use is associated with various adverse effects including hypotension edema and deterioration in lung function. Moreover, it has resulted in increased incidence of subsequent hearing loss. Therefore, its use should be strictly restricted.

### Hyperventilation and Alkali Therapy

Low pH causes pulmonary vasoconstriction. Both hyperventilation and alkali therapy (sodium bicarbonate) result in transient improvement by making the pH alkaline. However, prolonged alkalosis paradoxically increases pulmonary tone and permeability. Alkali therapy has been associated with increased use of extracorporeal membrane oxygenation (ECMO) and increased need of oxygen at day 28 of life. Cerebral vasoconstriction due to alkalosis has resulted in increased incidence of sensorineural hearing loss (SNHL) in survivors of PPHN. High tidal volume used to achieve hyperventilation causes lung injury resulting in increased incidence of BPD. Thus, in the absence of any sustained benefit and with availability of iNO, therapeutic alkalosis is no longer recommended. However, sodium bicarbonate infusion is still being practiced in many centers primarily to correct severe metabolic acidosis. This practice is controversial in the absence of any RCT. Careful attention should be paid to excess sodium load and increasing PaCO<sub>2</sub> levels while instituting this therapy.

### Systemic Circulation

Persistent pulmonary hypertension is often complicated by systemic hypotension because of multiple reasons including

## BOX 2 Treatment of persistent pulmonary hypertension of the newborn

### General supportive care

- Maintain normal temperature
- Correct metabolic abnormalities
  - Hypoglycemia, hypocalcemia, electrolyte imbalance, anemia and polycythemia
- Ensure minimal stimulation
  - Minimize handling
  - Cluster activities
  - Minimize auditory and visual disturbance

### Adequate sedation and analgesia

- Fentanyl, morphine sulfate

### Skeletal muscle relaxant (rarely required)

- Pancuronium

### Maintenance of systemic circulation

- Volume expander
  - Normal saline
- Cardiotonic agents
  - Dobutamine
  - Dopamine
  - Epinephrine

### Specific treatment of underlying disorder

- Surfactant
- Antimicrobial agents

### Supplemental oxygen

#### Mechanical ventilation (emphasis on 'gentle ventilation' to achieve 'optimal' lung inflation)

- Conventional ventilation
- High frequency ventilation

### Pulmonary vasodilators

- Selective pulmonary vasodilator
  - Inhaled nitric oxide (FDA approved)
- Nonselective pulmonary vasodilator
  - Phosphodiesterase 3 inhibitor—Sildenafil
  - Phosphodiesterase 5 inhibitor—Milrinone
  - Prostacyclin analogues—Iloprost
  - Endothelin receptor antagonist—Bosentan
  - Nonspecific—magnesium sulfate

### Extracorporeal membrane oxygenation

#### Newer therapies

- Free radical scavenger
- Nicotinamide-adenine dinucleotide phosphate oxidase inhibitor
- Recombinant human superoxide dismutase
- Soluble guanylate cyclase (sGC) stimulator

myocardial depression due to asphyxia, decreased venous return due to high mean airway pressure and by the disease (sepsis or pneumonia) per se. Systemic hypotension may further impair oxygen delivery by aggravating right to left shunt. So, it is important to maintain adequate cardiac output to optimize tissue perfusion. Functional ECHO helps in assessing cardiac output but is not universally available. Trend of vitals, especially blood pressure, urine output and lactic acidosis helps in assessing systemic perfusion. In case of hypotension, fluid bolus with 0.9% normal saline (10 mL/kg over 30 min) is used to replenish intravascular volume. If hypotension still persists despite volume replacement, cardiotonic agents like dobutamine, dopamine and epinephrine are indicated. However, administration of dopamine and epinephrine in higher doses can itself lead to pulmonary vasoconstriction by stimulating pulmonary alpha adrenergic receptors. Moreover, overzealous use

of inotropes for increasing systemic blood pressure to reverse the right to left shunt can actually worsen the LV function by increasing its afterload.

## Oxygen

Oxygen is a potent pulmonary vasodilator and an important natural mediator resulting in decrease in PVR at birth. Therefore, supplemental oxygen is the foremost therapy in PPHN. However, animal studies have shown that hyperoxemia ( $\text{PaO}_2 > 80$  mm Hg) does not result in additional pulmonary vasodilation and even brief exposure to 100% oxygen results in increased contractility of pulmonary arteries and decreased response to NO. There are no clinical trials to guide optimal  $\text{PaO}_2$  or  $\text{SpO}_2$  targets in infants with PPHN. Maintaining preductal saturation in the range of 90–97% was associated with lowest PVR in newborn lambs with PPHN. Therefore, most units target preductal saturation and  $\text{PaO}_2$  between 90% and 97% and 50–80 mm Hg respectively in these patients.

## Mechanical Ventilation

Mechanical ventilation helps in recruitment of atelectatic alveoli which reduces V/Q mismatch and facilitates iNO delivery. Goal is to achieve target parameters (ABG—pH: 7.30–7.40,  $\text{PaO}_2$ : 50–70 mm Hg,  $\text{PaCO}_2$ : 40–50 mm Hg) by practicing *gentle ventilation* strategies including optimal positive end expiratory pressure (PEEP) and relatively low peak inspiratory pressure. There is no role of hyperventilation due to the increased risk of VILI and long-term neurodevelopmental impairments. Optimal lung is very crucial in overall management. This is because PVR is minimal when lung is inflated at its functional residual capacity. Care should be taken to avoid over distension as it increases PVR, impedes venous return and cause lung injury. Presence of 7–8 posterior intercostal spaces on CXR suggests optimal lung inflation and is achieved by instituting adequate PEEP and/or mean airway pressure. Conventional or high frequency ventilation (HFV) are the available modes of mechanical ventilation; however neither mode has shown to be more effective in preventing ECMO in infants with PPHN. Treatment with HFV plus iNO has resulted in greater improvement in oxygenation as compared to treatment with HFV or iNO alone in severe PPHN secondary to pulmonary parenchymal disease.

## Surfactant

Use of surfactant in treatment of PPHN secondary to lung diseases has increased over the last one decade. Surfactant causes alveolar expansion in parenchymal lung diseases. This reduces V/Q mismatch and facilitates iNO delivery. Cochrane systematic review (2 RCTs,  $n = 208$ ) has shown that the administration of surfactant reduces the need of ECMO in term infants with MAS (RR 0.64, 95% CI 0.46–0.91); however, it has no effect on mortality. A multicentric trial ( $n = 34$ ) conducted among term infants with severe respiratory failure due to parenchymal lung diseases and at risk for requiring ECMO treatment found that need for ECMO therapy was significantly less in the surfactant group as compared to placebo group ( $p = 0.038$ ). The benefit was greatest for infants with relatively mild disease [i.e. neonates with {oxygenation index (OI) of 15–22}]. However, there was no effect on infants with idiopathic PPHN.

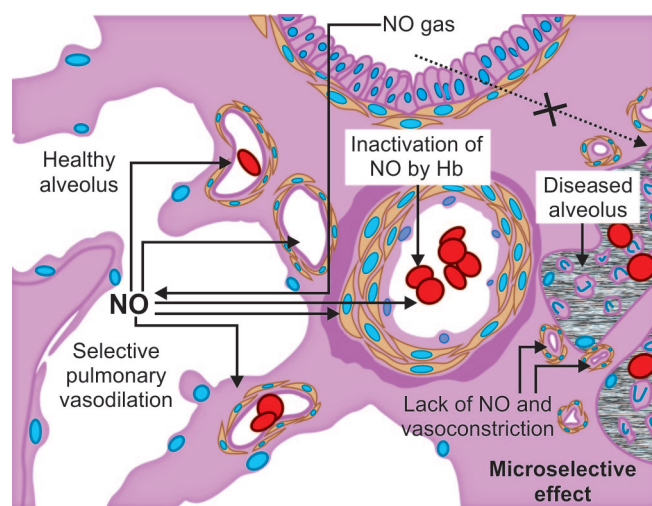
## Inhaled Nitric Oxide

Inhaled nitric oxide is a selective pulmonary vasodilator unlike other pulmonary vasodilators and its response appears within minutes of starting therapy. It stimulates sGC activity resulting in increased cGMP levels (Fig. 1). It combines with hemoglobin after entering into pulmonary vessels and is rapidly converted

to methemoglobin and nitrate. As a result, there is little effect—systemic blood pressure (selective action) (Fig. 3). iNO enters only ventilated alveoli and dilates adjacent pulmonary arterioles. This results in redirection of pulmonary blood flow to well ventilated parts of lung, thus reducing V/Q mismatch (Fig. 3).

Inhaled nitric oxide was approved by FDA in 1999 for near-term and term infants with PPHN. Evidence of its use comes from large RCTs where iNO therapy has shown to decrease the need of ECMO without any effect on mortality, length of hospitalization or risk of neurodevelopmental impairment. The cochrane systematic review (6 RCTs,  $n = 753$ ) comparing iNO with placebo or standard care in late preterm and term infants with PPHN concluded that use of iNO was associated with significant reduction in death or need for ECMO (RR 0.65, 95% CI 0.55–0.76). This difference was entirely due to reduction in need for ECMO without any effect on mortality. Overall 50% of the infants responded to iNO therapy in these trials. However, the benefit did not extend to infants with CDH. In fact, the final outcome was slightly worse in this subgroup. Current evidence does not support the use of iNO in infants with CDH however; transient improvement with initiation of iNO in a subset of CDH patients suggests that this intervention might be useful in achieving partial stabilization before starting ECMO. Available evidence also does not support the use of iNO in infants less than 34 weeks gestation.

Oxygenation index [ $\text{OI} = (\text{mean airway pressure} \times \text{FiO}_2 \div \text{PaO}_2) \times 100$ ] is used to assess the severity of hypoxemia in PPHN. iNO is generally started once OI is more than or equal to 25. Early initiation of iNO at an OI of 15–25 has not reduced the need for ECMO while an OI of 40 is generally accepted as an indication for ECMO. Adequate alveolar recruitment should be ensured and CHD should be ruled out before initiating iNO therapy. ECHO is



**Figure 3** Effect of iNO on the pulmonary circulation. iNO reaches healthy alveoli, shown on the left, and diffuses to the adjacent pulmonary arteries to cause vasodilation. As NO reaches the lumen of the pulmonary artery, it is inactivated by Hb, limiting its effect to the pulmonary circulation. NO does not reach the atelectatic alveoli, shown on the right, maintaining constriction of the adjacent pulmonary arteries. Increased perfusion of the ventilated segments of the lung improves the V/Q match and oxygenation in parenchymal lung disease.

Source: Konduri GG, Kim UO. Advances in the diagnosis and management of persistent pulmonary hypertension of the newborn. *Pediatr Clin North Am.* 2009;56:579–600. Reproduced with permission from Elsevier.

not mandatory but highly desirable before initiating iNO. However, it must be performed whenever there is clinical suspicion of underlying CHD.

Most RCTs support starting dose of 20 ppm. This was also the dose at which peak improvement in the pulmonary-to-systemic arterial pressure ratio was found among neonates with PPHN. Higher doses up to 80 ppm have been studied; however, found to be associated with more adverse effect (methemoglobinemia) with nonsignificant increase in response rate. Increase in  $\text{PaO}_2$  by more than 20 mm Hg or decrease in OI by 20% suggests clinical response and usually occurs within few minutes after starting iNO therapy. The potential adverse effects associated with iNO use are platelet dysfunction, methemoglobinemia and production of nitrates ( $\text{NO}_2$ ). Therefore, levels of these toxic metabolites should be monitored while patient is on iNO therapy. Once oxygenation improves, weaning should be gradually done to prevent rebound pulmonary hypertension. Tapering should be started once  $\text{FiO}_2$  is less than 60% and done at the rate of 5 ppm every 2–4 hourly. Once iNO dose is 5 ppm, gradual weaning at the rate of 1 ppm q 4–6 hourly is done.

Around 40% infants with PPHN do not respond or maintain a sustained response to iNO therapy. One should carefully analyze the relative role of parenchymal lung disease, pulmonary vascular disease and cardiac dysfunction in nonresponders. Optimization of lung volume with use of surfactant and HFV in parenchymal lung diseases improves response rate to iNO therapy. Cardiac performance should be optimized in presence of LV dysfunction. Repeat ECHO should be done to rule out underlying CHD. Formation of ROS and nitrogen species can contribute to ill sustained response to iNO. ACD and presence of severe lung hypoplasia may also result in failure of iNO therapy.

### Sildenafil

High failure rate, occurrence of rebound pulmonary hypertension after stopping iNO and high cost has led to the search for other pulmonary vasodilators. PDE inhibitors are a group of drugs which results in increased levels of cAMP or cGMP (**Fig. 1**). This in turn causes pulmonary muscle cell relaxation. Sildenafil, a phosphodiesterase type 5 inhibitor is available in both oral (0.25–0.5 mg/kg/dose up to a maximum of 2 mg/kg/dose q 6 h) and intravenous (loading dose is 0.4 mg/kg/dose IV over 3 h followed by a continuous infusion of 0.07 mg/kg/hour for up to 7 days) preparation. The Cochrane review (3 RCTs,  $n = 77$ ) comparing oral sildenafil with placebo in term newborns with PPHN concluded that the use of sildenafil was associated with significant reduction in mortality (RR 0.20, 95% CI 0.07–0.57). However, all RCTs were conducted in resource limited settings where iNO and HFV facilities were not available. An open label dose-escalation trial ( $n = 36$ ) of intravenous sildenafil in patients with and without prior exposure to iNO found it to be effective in improving oxygenation. Though the use of sildenafil in neonatal population has not been approved by FDA, it is often used off-label in settings where iNO is unavailable. It is also used for augmenting iNO response in partial responders, in treating rebound pulmonary hypertension and in BPD patients with pulmonary hypertension. The concern with systemic vasodilators like sildenafil is its potential to cause systemic hypotension.

### Milrinone

Milrinone is an inodilator and inhibits PDE-3 enzyme (**Fig. 1**). It has shown to decrease pulmonary artery pressure in various

animal models. It acts synergistically with iNO and may decrease rebound pulmonary hypertension. Infants with PPHN refractory to iNO therapy have responded to milrinone in few case series. However, RCTs comparing milrinone with iNO are lacking. Its use can lead to systemic hypotension.

### Magnesium Sulfate ( $\text{MgSO}_4$ )

Magnesium inhibits depolarization of smooth muscle cells by modulating uptake and binding of calcium, thus promoting vasodilatation. Evidence of its use primarily comes from few case series where intravenous infusion of  $\text{MgSO}_4$  has been used due to nonavailability of iNO. One RCT ( $n = 25$ ) has compared intravenous  $\text{MgSO}_4$  with iNO in term infants with PPHN. There was no difference in the proportion of infants who responded primarily to either therapy. However, more number of infants responded to iNO after failing initial  $\text{MgSO}_4$  therapy as compared to those who were administered  $\text{MgSO}_4$  following a failed iNO therapy ( $p = 0.03$ ).

### Bosentan

Bosentan is ET-1 receptor blocker and has been used in adults with PPHN. Few case reports suggest that bosentan can improve oxygenation in infants with PPHN. There is only one published RCT in neonates with PPHN ( $n = 47$ ,  $\geq 34$  weeks and  $< 7$  days old) where oral bosentan (1 mg/kg/dose q 12 hours) has been compared with placebo in the setting where iNO facility was not available. Bosentan was found to be superior with overall favorable response in 87.5% cases in contrast to 20% in placebo group ( $p < 0.0001$ ). The main concern with its use is hepatotoxicity.

### Prostacyclin

Prostacyclin activates adenylate cyclase which in turn increases cAMP concentration. This triggers smooth muscle cell relaxation leading to vasodilation. Intravenous  $\text{PGI}_2$  have been used in adults in treatment of pulmonary hypertension. In a retrospective review, oral  $\text{PGI}_2$  analog has been shown to cause significant improvement in oxygenation in five neonates with PPHN who were refractory to HFV. However, the disadvantage of systemic therapy is its potential to cause hypotension. Therefore, inhaled form of  $\text{PGI}_2$  (iloprost) is being used which produces selective pulmonary vasodilatation. Infants with PPHN who were refractory to iNO therapy have shown improvement in oxygenation with the use of inhaled  $\text{PGI}_2$  in few case reports. However, clinical trials are lacking resulting in their limited use.

### Extracorporeal Membrane Oxygenation

Approximately 40% of infants with PPHN do not respond to conventional therapy and require ECMO. ECMO is a life-supporting therapy which involves diversion of blood from a major systemic vessel through a gas exchange device and back to a major vessel. It maintains tissue oxygenation and gives time for the lungs and heart to recover. Increasing use of HFV, surfactant and iNO has led to reduction in the need of ECMO. The Cochrane review (4 RCTs,  $n = 244$ ) that compared ECMO with conventional management in newborns with severe respiratory failure concluded that use of ECMO was associated with significant decreases in the mortality (RR 0.44; 95% CI 0.31–0.61). This effect was even more significant in infants without CDH (RR 0.33, 95% CI 0.21–0.53). However, this therapy is costly and labor-intensive with limited availability.

Most units start ECMO when OI is consistently more than or equal to 40. ECMO is restricted to infants who are more than



35 weeks and have potentially reversible lung condition with no significant intracranial injury or coagulopathy. Patients who do not improve on ECMO are likely to have irreversible lung conditions such as ACD or severe pulmonary hypoplasia.

### Newer Therapies

Elevated concentration of ROS due to increased activity of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase or diminished activity of endogenous superoxide dismutase promotes vasoconstriction. Preliminary data suggests attenuation of vasoconstriction and improvement in oxygenation with administration of NADPH oxidase inhibitors and recombinant human superoxide dismutase. Decreased activity cGMP in remodeled pulmonary vessels causes diminished response to both endogenous and exogenous NO. A new molecule that directly stimulates sGC at an NO-independent site may have a promising role.

### OUTCOME

The advent of iNO and ECMO therapy has markedly improved the survival (85–90%) of PPHN infants in the developed world. However, mortality is still quite high in developing countries due to scarcity of resources and delayed referral. Survivors of PPHN are at risk for SNHL and various other neurodevelopmental disabilities irrespective of the use of iNO or ECMO. Around one-third of the survivors of Neonatal Research Network trial of iNO had at least one disability in the form of either SNHL (14%) or cerebral palsy (11%) or mental developmental index less than 70 (23%) or psychomotor developmental index less than 70 (14%) at 18–24 months of chronological age. Five percent had visual impairment and 2% had blindness. Infants with CDH were more prone with almost 50% developing SNHL. Various other studies have found behavioral problems (26%) and IQ score less than 70 (9%) at 1–4 years and at school age respectively. These infants are also more prone for rehospitalization especially within 1 year after discharge and have increased requirement of bronchodilator therapy at 5–11 years of age.

### PREVENTION

Good antenatal care, timely referral, optimum delivery practices (avoiding late preterm, early term and post-term deliveries, good intrapartum fetal monitoring) and adequate resuscitation along with high index of suspicion, immediate attention and timely management of predisposing conditions can prevent PPHN to some extent.

### IN A NUTSHELL

1. Failure to achieve or sustain the normal decrease in PVR at birth results in PPHN.
2. Diverse set of disorders causing vascular dysfunction and remodeling results in PPHN.
3. PPHN primarily affects infants more than or equal to 34 weeks gestation.
4. It should always be suspected in the presence of underlying risk factors or in a newborn with central cyanosis. Disproportionate ventilator requirement and labile saturation points towards development of PPHN.
5. Difference of more than 20 mm Hg in PaO<sub>2</sub> or more than 10% in saturation between preductal and postductal values in absence of CHD suggest PPHN but its absence does not rule it out.
6. ECHO is the gold standard test to diagnose PPHN and to rule out CHD.
7. Clinical management requires holistic care including optimization of ventilation and systemic circulation for achieving successful outcome.
8. The only FDA-approved selective pulmonary vasodilator for infants more than 34 weeks gestation is iNO which works very well in combination with HFV.
9. There is a potential role of sildenafil and milrinone in resource limited setups. However, more evidence is required.
10. Neurodevelopmental impairment and pulmonary sequelae occur in around one-fourth of survivors, thus highlighting the need of intense multidisciplinary follow-up of these infants.

### MORE ON THIS TOPIC

- Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. *Cochrane Database Syst Rev*. 2006;4:CD000399.
- Inhaled nitric oxide in term and near-term infants: neurodevelopmental follow-up of the neonatal inhaled nitric oxide study group (NINOS). *J Pediatr*. 2000;136:611-7.
- Konduri GG, Kim UO. Advances in the diagnosis and management of persistent pulmonary hypertension of the newborn. *Pediatr Clin North Am*. 2009;56:579-600.
- Lakshminrusimha S. The pulmonary circulation in neonatal respiratory failure. *Clin Perinatol*. 2012;39:655-83.
- Nair J, Lakshminrusimha S. Update on PPHN: mechanisms and treatment. *Semin Perinatol*. 2014;38:78-91.
- Porta NF, Steinhorn RH. Pulmonary vasodilator therapy in the NICU: inhaled nitric oxide, sildenafil, and other pulmonary vasodilating agents. *Clin Perinatol*. 2012;39:149-64.
- Steinhorn RH. Diagnosis and treatment of pulmonary hypertension in infancy. *Early Hum Dev*. 2013;89:865-74.
- Steinhorn RH. Neonatal pulmonary hypertension. *Pediatr Crit Care Med*. 2010;11:S79-84.
- Walsh-Sukys MC, Tyson JE, Wright LL, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. *Pediatrics*. 2000;105:14-20.



## Chapter 17.9

# Pulmonary Hemorrhage

Emily F Fishman, Rakesh Rao

Pulmonary hemorrhage (PH), described as early as in 1855 in preterm and term infants, is associated with high mortality and significant morbidity in survivors. It may manifest as minor bleeding in the endotracheal tubes in intubated patients, or as a life-threatening event with rapid deterioration resulting in respiratory compromise, cardiorespiratory collapse and even death. PH may remain occult and requires a high index of suspicion for rapid diagnosis and appropriate treatment.

## EPIDEMIOLOGY

Pulmonary hemorrhage varies inversely with gestational age with the highest incidence in infants at the limit of viability. The incidence of PH is reported between 1 and 11 per 1,000 livebirths and may be as high as 50 per 1,000 livebirths in high-risk population, such as infants with intrauterine or fetal growth restriction. PH is reported in 0.5–11.0% of very low birth weight infants (VLBW, < 1,500 g). The true incidence may vary according to the definition used.

With improving perinatal care and survival of VLBW infants, recent data from developing countries (Asia including India) suggest that PH may affect 8–32% of VLBW infants. Of importance, mortality with PH was reported in 50–82% of all preterm infants and in approximately 17–23% in term infants. PH was associated with near seven-fold higher risk of mortality in preterm infants less than 32 weeks gestation in one study.

## ETIOLOGY

A distinct bimodal distribution is seen with infants less than 35 weeks gestation developing PH within 72 hours of birth compared to a median age of 6 hours in infants more than 35 weeks gestation. However, the etiologies of PH in preterm and term infants vary with several factors predisposing VLBW infants and the more immature infants at higher risk (**Box 1**). Infants born at less than 26 weeks gestation, extremely low birthweight (ELBW, < 1,000 grams), lower Apgar scores at 1 and 5 minutes of age, and infants with more severe respiratory distress syndrome (RDS) are at higher risk for developing PH. The use of mechanical ventilation (associated with alveolar overdistension) is associated with a four-fold increased risk. Antenatal steroids used for fetal lung maturation are associated with a *decreased* risk of PH. Maternal cocaine use, multiple gestation, maternal antibiotic use and previous pregnancy loss have been associated with PH. However, other maternal factors, such as preeclampsia, cord prolapse, abruption and placenta previa have *not* been clearly identified as risk factors for PH after birth.

Fetal growth restriction [intrauterine growth restriction (IUGR)] and small for gestational infants are at particular risk for PH, an association that appears to be independent of other factors. A three-fold higher risk of PH has been reported in this population with one study noting near 100% mortality in preterm IUGR infants who developed PH.

Neonates with severe RDS are also at risk for pulmonary interstitial emphysema or pneumothorax. These complications may precede PH. Some believe that PH is a continuum of the severity of underlying lung disease.

PH is associated with surfactant use (described later). In vitro studies show that surfactant impairs coagulation, and paradoxically, blood and blood products cause surfactant inactivation.

### BOX 1 Risk factors associated with pulmonary hemorrhage

- *Maternal factors*
  - *Presurfactant era*: Breech delivery, multiple gestation
  - *Postsurfactant era*: Cesarean section, maternal antibiotic therapy, chorioamnionitis
- *Preterm infants*
  - Prematurity
  - Male gender
  - IUGR, small for gestation
  - Perinatal depression
  - Surfactant therapy
  - Patent ductus arteriosus
  - Metabolic acidosis
  - Hypothermia
  - Coagulopathy
  - Respiratory distress syndrome (severe)
  - *Air leak syndromes*: Pneumothorax, pulmonary interstitial emphysema
  - Mechanical ventilation
  - Septicemia
- *Term infants*
  - Meconium aspiration
  - Perinatal hypoxia/depression
  - Hypotension
  - Mechanical ventilation
  - Coagulopathy
  - Septicemia
- *Urea cycle disorders*
- *Rare*
  - Listeriosis, *H. influenzae*
  - Congenital CMV
  - Fungal infections

Abbreviations: IUGR, intrauterine growth restriction; CMV, cytomegalovirus

Patent ductus arteriosus (PDA) is a frequent complication of preterm birth. Presence of a hemodynamically significant PDA (hsPDA) increases risk of PH due to pulmonary overcirculation, left ventricular failure and elevated pulmonary capillary transmural pressure (see section on pathophysiology later). Preventing hsPDA could therefore decrease PH. A trial of prophylactic indomethacin showed a near 50% decrease in the incidence of PDA in the indomethacin compared to the placebo-treated group. *Post hoc* analyses from this study, however, showed a 35% decrease in PH in the prophylactic indomethacin arm only during the first week of life attributable to closure of PDA.

Rapid volume expansion (causing an increase in pulmonary blood flow and opening of the PDA) and use of blood and blood products (albumin) have been associated with PH in the more immature infants. Other factors associated with PH in preterm infants include histological chorioamnionitis, multiple births, breech presentation and cesarean section.

Metabolic acidosis is often associated with PH. Metabolic acidosis in preterm infants is associated with hypothermia (core temperature < 36°C), hypoglycemia, septicemia and disseminated intravascular coagulation, and often precedes PH. Perinatal depression necessitating aggressive resuscitation and hypoxia also lead to metabolic acidosis. Infants with PH develop secondary hypoxemia with respiratory and metabolic acidosis.

In the developing world, hypothermia in the delivery room or soon after birth is a significant complication attributable to varying delivery practices. Term infants can drop their core body temperature by 0.1–0.3°C per minute without intervention; preterm infants are at an even higher risk of hypothermia. Hypothermia leads to cold stress and secondary hypoglycemia, hypoxia, metabolic acidosis and coagulation defects. In vitro experiments

show that cold injury causes platelet aggregation which can lead to functional thrombocytopenia and potentially contribute to PH.

Any coagulopathy increases the risk for PH including inherited coagulation disorders. von Willebrand disease has been identified in infants that died from idiopathic PH. In a study of infants less than 34 weeks gestation, thrombocytopenia with platelet count of less than  $100,000 \times 10^6/\text{liter}$  was associated with four-fold increased risk of PH. PH has, however, rarely been reported in infants with hemorrhagic disease of newborn or hemophilia.

PH in late preterm and term infants are often related to antenatal and perinatal factors. PH is associated with intrauterine and perinatal hypoxia/depression, meconium aspiration syndrome (associated with surfactant inactivation and air leaks) and mechanical ventilation, and occurs within the first 6–12 hours of life. PH can follow airway trauma during endotracheal intubation. In addition, infants that require extracorporeal membrane oxygenation (ECMO) are at risk for PH since ECMO therapy requires systemic anticoagulation.

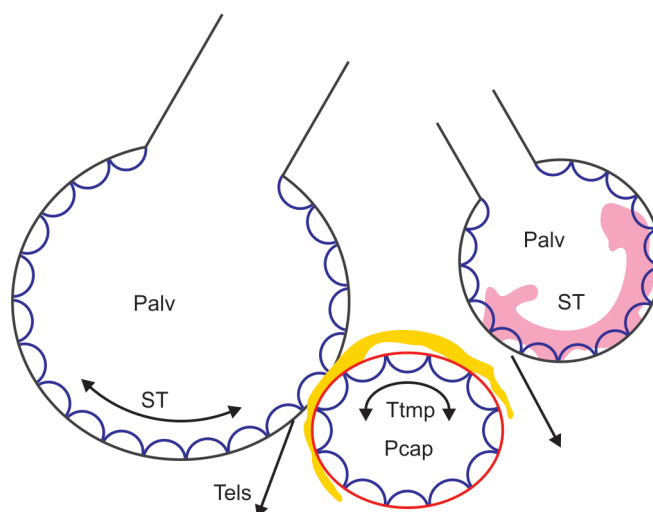
Rarely, PH has also been attributed to bacterial, viral and fungal infections [*Listeria*, *H. influenzae* and congenital cytomegalovirus (CMV), congenital heart diseases (aortopulmonary window)] and diffuse pulmonary embolism with drug/lipid micro-aggregates. Urea cycle defects such as ornithine transcarbamylase (OTC) deficiency can present with respiratory distress and PH usually after first day of life. Lastly, PH may be idiopathic in nature.

## PATHOPHYSIOLOGY

Initially believed to be frank bleeding into the lungs and airways, PH fluid composition studies revealed the contents to be more consistent with bloody pulmonary edema. PH lung effluents show presence of smaller molecular weight plasma proteins and lower hematocrit (15–20% lower) in comparison to a peripheral blood sample. Frank blood is more likely to be seen with aspirated blood or trauma after intubation.

Although the exact pathophysiology has not been fully elucidated, *stress failure* of the pulmonary capillaries is believed to be a primary mechanism of PH (Fig. 1). The pulmonary gas exchange unit (PGU) consists of the alveolus lined by the thin-walled epithelium and the pulmonary capillary lined by the endothelium; the two are separated by the extracellular matrix (ECM) composed of the basement membranes of the two cell layers. The presence of type IV collagen in the ECM with its high tensile strength allows the PGU to adapt to the changes in pulmonary capillary pressure. Three forces govern the strength of the PGU, viz. (1) circumferential or hoop stress in the capillary wall that is related to the capillary *transmural* pressure (pressure difference between inside and outside the capillary) and alveolar radius; (2) longitudinal tension in the tissue elements of the alveolar wall due to lung inflation; and (3) surface tension in the alveolus that counteracts the increase in capillary transmural pressure. The disruption of the pulmonary capillary endothelium/alveolar epithelium, referred to as *stress failure*, due to elevated pulmonary capillary pressure (as with congestive failure), loss of surface tension or overdistension of the alveolus results in leakage of hemorrhagic fluid into the interstitium and the alveolus.

In preterm infants, PH is often associated with hspDA. In utero, placental blood bypasses the pulmonary circulation with two-thirds of blood flow being directed via the PDA into the systemic circulation. After birth and as pulmonary vascular resistance begins to fall (and after administration of surfactant), pulmonary blood flow increases and can exceed systemic circulation in the presence of hspDA. Kluckow et al. noted that in preterm infants less than 30 weeks gestational age, the presence of a large PDA (> 1.5 mm) as early as 6 hours after birth was associated with nearly one and half times as much median pulmonary blood flow prior to developing



**Figure 1** Pathogenesis of pulmonary hemorrhage. Alveolar air exchange unit with pulmonary alveoli (Palv) and adjacent capillary (Pcap). Two types of alveoli are shown, one well aerated (left) and one with presence of hyaline membranes (pink, right). The alveolar basement membrane (black) and epithelium (blue) is tightly opposed to the capillary basement membrane (red) and endothelium (blue) with the extracellular matrix in the interstitium (yellow). Three forces act to prevent capillary stress failure (see text for details) (Abbreviations: Ttmp, circumferential or hoop tension due to capillary transmural pressure; Tels, longitudinal alveolar wall tension due to lung inflation; ST, surface tension in the alveoli) Figure was adapted from West JB, Mathieu-Costello O. *Ann Rev Physiol.* 1999;61:543-72.

PH (328 mL/kg/min vs 238 mL/kg/min). Infants received less antenatal steroids but more often received surfactant prior to PH. The increase in pulmonary blood flow as the PDA becomes clinically significant causes *stress failure* of the pulmonary capillaries. This may also support why the majority of PH in the preterm population generally occurs between days 2 and 4 of life.

Overall surfactant use does not increase risk of PH. However, use of prophylactic surfactant versus rescue surfactant [relative risk (RR), 95% confidence interval (CI) = 3.28, 1.5–9.2], mode of administration (endotracheal vs. nebulized in fetal lamb studies), and the type of surfactant used—animal derived (bovine or porcine) versus synthetic surfactant (such as Exosurf) (RR, 95% CI = 0.73, 0.51–1.06)—influence PH. The decrease in surface tension following surfactant administration causes increased pulmonary blood flow and decreasing vascular resistance leading to increased *stress failure* of the pulmonary capillaries. Of note, in infants with RDS who *do not* receive surfactant, PH is most often noted when pulmonary compliance and blood flow improve following resolution of RDS.

Neonates with perinatal depression often develop myocardial dysfunction with resultant increase in left atrial and pulmonary venous pressures and elevated pulmonary capillary transmural pressure. Hyperoxia has also been reported as a cause of pulmonary capillary *stress failure*.

Histopathological evaluation of lungs in neonates with PH may show a range of pathology. On gross macroscopic examination, lung weight is usually increased often with obliteration of the lobar borders and presence of frank blood in the airways. Microscopically, scattered red blood cells in the interstitium, intra-alveolar or intraparenchymal spaces to frank blood in the airways may be seen in the absence of significant inflammation. In infants treated with surfactant, PH is present in the alveoli, whereas in infants without surfactant treatment, there is more hemorrhage present in the interstitial spaces.

## CLINICAL FEATURES

Although the commonly accepted definition of PH is the presence of hemorrhagic fluid in the lungs and airways, particularly in mechanically ventilated neonates, PH may remain occult when hemorrhage is limited to the interstitium and does not extend into the alveolar space. Others consider PH as the presence of endotracheal blood accompanied by respiratory decompensation requiring increased support [increase in oxygen requirement by at least 10%, need for increased peak inspiratory pressure (PIP) or positive end expiratory pressure (PEEP)] or need for intubation within 60 minutes of the event. Tracheal secretions can vary from being frothy, pink or blood tinged effluent can be frankly bloody. The hallmark of presentation is characterized by rapid deterioration of the neonate; but PH can have a more subtle clinical presentation.

The onset of symptoms can be acute or can manifest over several hours (**Table 1**). In nonintubated neonates, PH may be manifested as apnea, intermittent hypoxemia with desaturations and bradycardia, and increasing oxygen requirements. Additional physical examination findings may include tachypnea, respiratory distress with retractions, and decreased or coarse breath sounds. In neonates on mechanical ventilation, decreases in pulmonary compliance, increased airway resistance and ventilatory support to deliver adequate tidal volume may be noted. The presence of frothy, pink tinged to frank bloody secretions is usually indicative of PH. Blood gas measurements will reflect elevated  $p\text{CO}_2$ , low  $\text{PaO}_2$  and an increase in alveolar to arterial (A-a) gradient. In cases of massive PH, neonates may develop rapid signs of shock secondary to hypovolemia and anemia including changes in heart rate (tachycardia followed by bradycardia with rapid deterioration), hypotension and impaired perfusion (mottled skin appearance and prolonged capillary refill).

Since PDA is a known risk factor for PH, signs and symptoms of PDA such as tachycardia, widened pulse pressure, respiratory and metabolic acidosis, presence of a cardiac murmur and cardiomegaly on X-ray may also be present.

## DIFFERENTIAL DIAGNOSIS

The diagnosis of PH is usually clinical and should be strongly suspected in preterm and term neonates with risk factors identified previously. The timing of presentation in preterm (between days 2 and 4) and term (on day 1) infants remains of importance.

In the absence of bloody effluent in the airways, the diagnosis of PH is often difficult to make in preterm (ventilated and nonventilated) infants as the clinical symptoms and signs may be subtle and can often be attributed to other reasons. For example, increased work of breathing, changes in oxygenation and ventilation may be secondary to worsening underlying lung disease, development of air leak syndromes such as pneumothorax, pulmonary hypertension or due to opening of PDA. Apnea and bradycardia may be secondary to prematurity itself. In addition, PH may often be a harbinger of other problem in the preterm neonate such as infection or sepsis.

Infants that present with massive PH (respiratory decompensation requiring intubation or escalation of ventilator support secondary to hemorrhagic secretions) are more likely to have evidence of hemorrhage as a primary sign. Similar to infants with more insidious presentation, the differential diagnosis should include infection or sepsis, patent ductus arteriosus, air leak syndrome including pneumothorax, chronic lung disease (in chronically ventilated infants), trauma and pulmonary hypertension. In addition, one should also consider inherited coagulopathic disorders and hemolytic disease of the newborn.

**Table 1** Symptoms and signs of pulmonary hemorrhage

<i>Symptoms of pulmonary hemorrhage</i>	<i>Signs of pulmonary hemorrhage</i>
Nonspecific clinical change in a previously well infant	Increased secretions Frothy pink secretions Frankly bloody secretions
Respiratory distress, increased work of breathing Apnea Bradycardia and desaturations Increasing oxygen requirements	Change in pulmonary compliance Increased pressures with mechanical ventilation Increasing airway resistance
Bleeding from other sites	Signs of shock Bradycardia, tachycardia Hypotension, decrease in cardiac output Hypovolemic shock including change in heart rate, prolonged capillary refill Patent ductus arteriosus Wide pulse pressure, tachycardia
Symptoms of patent ductus arteriosus	Pallor/Anemia Decreases in hematocrit may not occur initially
Shock or acute cardiovascular collapse	<i>Laboratory tests:</i> • Blood gas – Hypoxia: Increased A-a gradient – Hypercarbia – Metabolic acidosis • <i>White cell counts:</i> Bandemia, leukopenia, leukocytosis, thrombocytopenia, elevated D-dimer, decreased fibrinogen, prolonged PT • <i>X-ray:</i> White out, new infiltrates • <i>Head sonogram:</i> Intraventricular hemorrhage • <i>Echocardiogram:</i> Patent ductus arteriosus, left ventricular failure

Abbreviation: PT, prothrombin time.

In term infants who were previously healthy, metabolic disorders such as urea cycle disorders should be considered. It is important to recognize that systemic to pulmonary shunting of blood can lead to pulmonary edema and hemorrhage. Therefore, infants should be evaluated for congenital heart disease including left to right cardiac shunts, left-sided obstructive cardiac lesions and congenital mitral stenosis, evidence of pulmonary venous hypertension or, rarely, cerebral arteriovenous malformations.

Other causes include direct trauma to airways with endotracheal intubation, vigorous suctioning and lung injury during placement of chest tube. Aspiration of maternal blood can be ruled out using Apt test.

## APPROACH TO DIAGNOSIS

Preterm infants with PH typically present with sudden respiratory deterioration with bloody secretions in the airways. As mentioned earlier, infants may become apneic or develop respiratory distress, develop bradycardia or become hypotensive and go into cardiac failure or shock. Initial assessment of the infant should include a full clinical examination to evaluate for the underlying reason for the clinical deterioration including signs of bleeding from other sites.

Laboratory investigation should include a chest radiograph. While it has a low sensitivity and specificity with no defined diagnostic features for PH, it can be useful to distinguish PH



from other causes such as pneumothorax. Other radiograph findings include diffuse or fluffy opacities, scattered haziness, focal consolidation and features of underlying lung disease. Cardiomegaly and evidence of pulmonary edema may also be present (**Figs 2A and B**).

Signs of PDA such as widened pulse pressure with decreased diastolic blood pressure or hyperdynamic precordium may be apparent. Measuring simultaneous pre- and postductal oxygen saturations (pulse oximeter probes on the infant's right hand/wrist and a second probe on either feet or toes) can identify right to left shunting via the PDA. This may also serve as a basic screening test for congenital heart disease in term infants. An echocardiogram can confirm presence of hsPDA, other congenital heart disease or pulmonary hypertension.

Additional evaluation for degree of bleeding should include serial hemoglobin and hematocrit to evaluate changes secondary to hemorrhage. Complete and differential white cell count for infection, blood gas to evaluate oxygenation and metabolic status, and coagulation profile including prothrombin time, platelet count, fibrinogen and D-dimers should be checked to evaluate for disseminated coagulation. Bacterial, viral or fungal cultures should be considered.

In term infants, ammonia levels should be checked to rule out urea cycle defect. In preterm infants, a head sonogram should be obtained as intraventricular hemorrhage is also often noted following PH.

## MANAGEMENT

### Stabilization

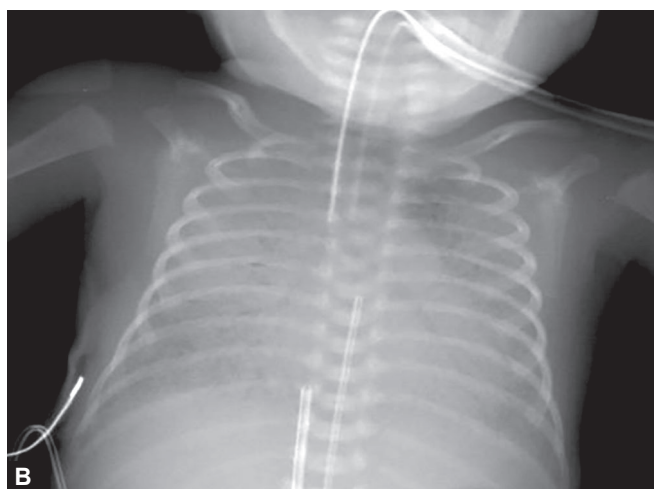
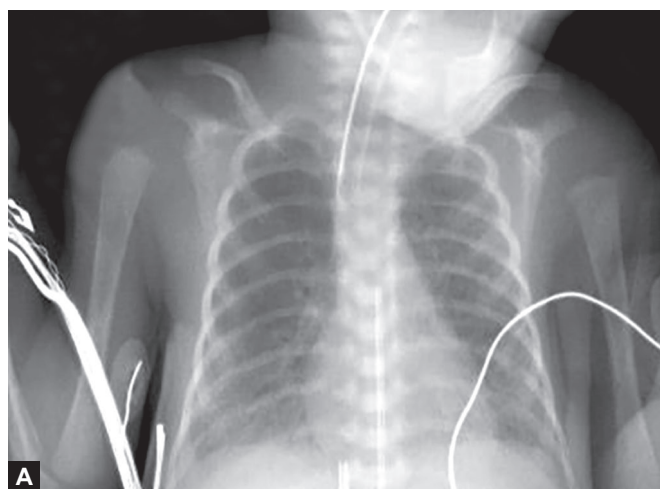
The initial management (**Box 2**) should be aimed at stabilization of vital signs via standard neonatal resuscitation (airway, breathing and circulation) and optimization of gas exchange. Airway management, particularly in the presence of visible blood in the airways, should include endotracheal intubation and placement on mechanical ventilation. If the neonate presents acutely with apnea and bradycardia or sudden cardiopulmonary collapse, control of airway with cardiac compressions and medications per standard resuscitation guidelines may be required. Noninvasive respiratory support such as continuous positive airway pressure (CPAP) may not be optimal in this situation. Further, suctioning the airway should be done as blood in the airways and alveoli decrease respiratory

compliance and increase airway resistance. Once intubated (or if PH develops in an intubated infant), the PEEP should be increased to 6–8 cm to provide tamponade effect. Caution should be exercised in raising PEEP further particularly in the more preterm infants as high PEEP may itself cause alveolar rupture, result in hypercarbia, impair venous return and decrease cardiac output. Oxygenation can further be optimized by increasing the concentration of inspired oxygen, increasing PIP and mean airway pressure (MAP). If increasing PEEP and MAP on conventional ventilator is not adequate, high frequency oscillatory ventilation (HFOV) can be used successfully to slow or reverse hemorrhagic edema, improve oxygenation and ventilation. HFOV has been successfully used to treat massive PH with improved survival compared to conventional ventilation.

### BOX 2 Management of acute pulmonary hemorrhage

- Consider intubation
- Mechanical ventilation
  - Increase PEEP to 6–8 cm
  - Consider high frequency ventilation
- Endotracheal epinephrine or adrenaline
  - 1:10,000 dilution
  - 0.1–1.0 mL/kg
    - Instill close to carina
    - Repeat until bleeding stops
- Consider\*
  - Recombinant activated factor VII (rFVIIa) 50 µg/kg twice a day for 2–3 days
  - Hemocoagulase 0.5 KU q 4–6 hours
- *Laboratory tests:* CBC with differential counts, coagulation profile (PT, PTT, fibrinogen, D-dimer), blood gas, ammonia, blood cultures
- Chest X-ray
- Echocardiogram
- Head ultrasound
- Serial chest X-rays, blood gas and metabolic monitoring
- Antibiotics
- Transfuse blood and blood products
- Consider surfactant once bleeding stops

\* Not sufficient data available to recommend as primary management.  
*Abbreviations:* CBC, complete blood count; PEEP, positive end expiratory pressure; PT, prothrombin time; PTT, partial thromboplastin time.



**Figures 2A and B** (A) 25-week gestation male (day of life: 1) with fine ground-glass opacities bilaterally consistent with hyaline membrane disease (postsurfactant); (B) Same infant (day of life: 2) following pulmonary hemorrhage. Note the extensive areas of new infiltrates, consolidation and air bronchograms. Also note the increase in the size of the cardiac silhouette and elevated left bronchus



## Maintenance of Circulation

Massive PH is associated with rapid exsanguination and may result in circulatory collapse. Fluid resuscitation with packed red blood cell transfusion or normal saline may be required for volume expansion to support circulation. Additionally, blood products such as platelets (for platelet dysfunction or thrombocytopenia) and fresh frozen plasma (for disseminated intravascular coagulation) may be warranted. Caution should be exercised as aggressive volume resuscitation may result in reopening of a PDA or precipitate cardiac failure and pulmonary edema.

## Drug Therapy

Evidence is limited regarding pharmacological treatment of PH, given the lack of randomized controlled trials. Endotracheal epinephrine or adrenaline (1:10,000 concentration or 0.1 mg per mL) in a range for dose of 0.1–1.0 mL/kg has been used most frequently to control the acute bleeding due to its vasoconstrictive and inotropic effects. Epinephrine should be instilled using a 6.5F or an 8F catheter (after suctioning) placed in the endotracheal tube as rapidly and as close to the carina (not beyond) as possible. Repeated doses may be necessary to control bleeding. Nebulized epinephrine has also been used with some success. A 4% cocaine solution instilled via the endotracheal tube has been used in the past, although this is no longer available.

Blood in the airways and alveoli increase airway resistance, decreases lung compliance and inactivates endogenous surfactant activity. Once bleeding is controlled (wait at least an hour after bleeding stops), repeat surfactant administration has been shown to improve pulmonary compliance, improve oxygenation and decrease the oxygenation index.

Activated recombinant factor VII (rFVIIa, a vitamin K-dependent glycoprotein that activates the extrinsic pathway), at a dose of 50 µg/kg twice daily for 2–3 days, has been shown in small clinical studies to be effective in controlling bleeding. It is more effective when coadministered with platelets. However, cerebral venous thrombosis has been reported as side effect in adults but not in neonates, hence caution should be exercised with its use.

Hemocoagulase (a purified enzyme mixture derived from the venom of South American viper, *Bothrops atrox*) converts prothrombin to thrombin and fibrinogen to fibrin, thereby decreasing bleeding time. Two small studies in neonates show that endotracheal administration of hemocoagulase [(0.5 KU (Klobusitzky unit) every 4–6 hours] may be effective in preventing and treating PH without significant adverse events. However, additional studies and availability of these drugs are needed to establish dose, frequency of administration and consistency of response before being recommended for routine use.

## Supportive Therapy

### Patent Ductus Arteriosus

As PDA is often antecedent to PH in the preterm population, it may be necessary to address closure of PDA once infant is stabilized. Medical treatment with indomethacin or ibuprofen may be attempted; ligation may be considered in the more critically sick neonate.

### Antibiotics

Infection and sepsis are often causes of PH as well as confounding factors in infants with acute decompensation. Broad spectrum

antibiotics based on the unit's bacteriological profile should be started while awaiting blood culture results.

### Others

Additional supportive care should include serial chest X-rays to evaluate pulmonary status; blood gas monitoring and correction of hypoxia and metabolic acid-base status, blood counts and coagulation profile (prothrombin time, platelet count, fibrinogen and D-dimers) for correction of disseminated coagulation. Fresh frozen plasma and other blood products may be needed. In term infants, if elevated ammonia levels suggest urea cycle disorder, intravenous dextrose and lipids along with sodium benzoate and sodium phenylacetate should be provided. Vitamin K may be administered if hemorrhagic disease of the newborn is suspected.

## OUTCOMES/PROGNOSTIC FACTORS

Despite advances in neonatal care, PH is a relative frequent complication and has high fatality in the most immature gestational age groups. PH in the developing countries has been identified a major cause of mortality in both term and preterm infants. Mortality rates over 50% have been noted in preterm infants but are lower in term infants. Majority of the mortality is acute and related to the severity of bleeding and severity of RDS in preterm infants; and to perinatal hypoxic injury and meconium aspiration in term infants.

In the short term, in one study in ELBW infants, those with PH who survived had higher rates of oxygen dependence at 28 days (RR 3.4), PDA (RR 3.1), seizures (RR 8.9) and periventricular leukomalacia (RR 2.2). Limited data on long-term neurodevelopment at 20 months in this cohort showed lower, but not statistically significant, psychomotor developmental scores than controls. Another study associated lower brain volume with preterm survivors with PH at term. However, similar data from the developing countries are currently lacking.

## PREVENTION

Existing literature suggests that maternal conditions are not significant contributors to PH after birth. However, obstetrical practices aimed at prevention of preterm birth—the population at highest risk of PH, are most likely to decrease the incidence of PH. Antenatal glucocorticoids improve pulmonary maturity and are associated with decreased incidence of PH, improve survival and decrease complications of prematurity.

After preterm birth, prophylactic indomethacin decreases the incidence of PH in the first week of life attributable to closure of PDA. Attention to fluid balance, limiting blood product use in the VLBW and ELBW infants in the first few days after birth is critical in minimizing pulmonary overcirculation with the resulting pulmonary edema and hemorrhage. Prompt attention should also be paid in treatment of a symptomatic PDA before PH can occur.

Trends towards decrease in PH have been noted with use of primary HFOV to treat RDS compared to conventional ventilation. In infants who develop PH, HFOV may be used to limit bleeding and improve ventilation and oxygenation.

### IN A NUTSHELL

1. Pulmonary hemorrhage (PH) is a complication seen in both preterm and term neonates. Incidence is inversely related to gestational age.
2. Antenatal administration of glucocorticoids decreases the risk of PH.
3. Fetal growth restriction/chronic intrauterine hypoxia or perinatal depression/hypoxia in both preterm and term infants increases the risk of PH.
4. PH in infants less than 35 weeks gestation occurs commonly between days 2 and 4 and is often associated with PDA and intraventricular hemorrhage. Hypothermia, metabolic acidosis, coagulopathy and prophylactic surfactant use increase the risk.
5. In near term and term infants, PH occurs within a few hours of birth and associated with meconium aspiration and hypoxia.
6. PH may present with subtle symptoms or with massive bleeding (into the lungs and airways) with acute decompensation requiring increased oxygen, increased ventilation, need for intubation or shock.
7. Management should include airway stabilization (intubation), endotracheal epinephrine and mechanical or high frequency oscillatory ventilation.
8. Evaluation should include underlying cardiac disease (such as patent ductus), initiation of broad spectrum antibiotics and assessment for infection, and close cardiorespiratory and metabolic monitoring.
9. Mortality in preterm infants with PH may be over 50%. Survivors are at higher risk for developing chronic lung disease and at a higher risk for neurodevelopmental impairment.

### MORE ON THIS TOPIC

- Abou Zahr R, Ashfaq A, Marron-Corwin M. Neonatal pulmonary hemorrhage. *NeoReviews*. 2012;13:e302-6.
- Alfaleh K, Smyth JA, Roberts RS, et al. Trial of indomethacin prophylaxis in preterm investigators. Prevention and 18-month outcomes of serious pulmonary hemorrhage in extremely low birth weight infants: results from the trial of indomethacin prophylaxis in preterms. *Pediatrics*. 2008;121(2):e233-8.
- Berger TM, Allred EN, Van Marter LJ. Antecedents of clinically significant pulmonary hemorrhage among newborn infants. *J Perinatol*. 2000;5:295-300.
- Kluckow M, Evans N. Ductal shunting, high pulmonary flow, and pulmonary hemorrhage. *J Pediatr*. 2000;137:68-72.
- Mukhopadhyay K, Louis D, Mahajan R, Kumar P. Predictors of mortality and major morbidities in extremely low birth weight neonates. *Indian Pediatr*. 2013;50:1119-23.
- Tagare A, Chaudhari S, Kadam S, et al. Mortality and morbidity in extremely low birth weight (ELBW) infants in a neonatal care unit. *Indian J Pediatr*. 2013;80:16-20.
- Thakur N, Saili A, Kumar A, Kumar V. Predictors of mortality of extremely low birth weight babies in a tertiary care center of a developing country. *Postgrad Med J*. 2013;89:679-84.
- Tomaszewska M, Stork E, Minich NM, et al. Pulmonary hemorrhage. Clinical course and outcomes in very low birth weight infants. *Arch Pediatr Adolesc Med*. 1999;153:715-21.

## Chapter 17.10

# Bronchopulmonary Dysplasia in Newborn

Samir Gupta, Sunil K Sinha

Improvement in neonatal intensive care has led to increasing survival of very immature babies, but a significant proportion of them also suffer from long-term morbidity including chronic lung disease (CLD), the severest form of which is called bronchopulmonary dysplasia (BPD). This is a multisystem disease and has important implications in terms of health resource utilization. Follow-up studies of these babies have demonstrated that BPD infants require frequent readmissions to the hospital in the first 2 years of life because of respiratory infections, asthma, and related problems, and they have persistent lung function abnormalities even as adolescents and young adults.

## EVOLUTION OF UNDERSTANDING OF BPD

The term bronchopulmonary dysplasia (BPD) was first coined by Northway et al. in 1967 and in its original description, this was seen in relatively mature babies, who were ventilated at high pressures, with high fractional concentration of inspired oxygen, resulting in lung overinflation with areas of atelectasis, cystic emphysema, and fibrosis as a result of significant interstitial and airway changes in the lungs. In contrast, BPD nowadays is seen primarily in very preterm newborns weighing less than 1000 g, who are born at 24–28 weeks of gestation. The histopathologic abnormalities of the *old* BPD have now been replaced by a *new* BPD with the large, simplified alveolar structures, variable interstitial cellularity and/or fibroproliferation. The clinical picture is also different. Today's premature babies developing BPD initially seem to have modest ventilatory and oxygen requirement and demonstrate a different radiographic picture, which shows diffuse haziness and a fine, lacy pattern. This difference between *Old* and *New* BPD can be better understood if one realizes that the lungs of infants born at 24–26 weeks gestation are in the early phases of lung development (canalicular and saccular stages) and, the alveolar and capillary development is further inhibited (developmental arrest) following exposure to the noxious effects of mechanical ventilation, oxygen exposure, and inflammation. In *new* BPD, airway and microvascular growth are also affected and this impaired angiogenesis was shown to be associated with decreased levels of vascular endothelial growth factor (VEGF) and angiogenic receptors, which are important components for normal structural development.

## DEFINITION

In the original form as described by Northway, definition of BPD was based on severity of respiratory illness associated with abnormality of chest X-ray appearance. Since then, however, this has changed and currently BPD is defined more on the basis of clinical severity and dependence on ambient oxygen and/or mechanical respiratory support at certain points in their clinical course, such as 28 days and 36 weeks postmenstrual age. Although oxygen supplementation has routinely been used as a surrogate for assessing the severity of underlying lung problem, this is subjective. It is not surprising that the prevalence of BPD varies significantly, depending on individual unit's clinical protocol and clinician's habit. To rectify this, Walsh et al. introduced the concept of *physiologic definition* of BPD in which infants, receiving less than 30% supplemental oxygen, were subjected to a stepwise 2%

reduction in supplemental oxygen until they were breathing in room air. The outcome of tests was defined as no BPD if oxygen saturation remained more than 88% for 60 minutes in room air or *BPD*, if saturation fell below 88% during this observation period. Throughout this period, these babies undergoing oxygen challenge were monitored for apnea, bradycardia and increased oxygen use. If any of these events occurred and required treatment, such babies were deemed to have failed and categorized as having *BPD*. Although still not perfect, at least this method does provide an objective assessment of the presence and severity of underlying lung problems. Most of the current studies have used this definition to compare outcome measures in clinical trials studying effect of any intervention related to prevention of BPD. This definition may still change in light of recent findings from large clinical trials suggesting that the optimal oxygen saturation range in preterm babies should be between 90 and 95%, and above 95% in those reaching *term gestation*. This recommendation is based on the findings from these large studies that lower concentration below 88% may be associated with increased mortality and adverse neurological outcome. NICHD—National Heart, Lung and Blood Institute further classified the BPD into Mild, Moderate or Severe on the duration and amount of oxygen required and the degree of respiratory support.

Arterial oxygenation is only one crude measure of lung function and it is very likely that in order to assess the full lung function, we may have to combine a number of tests measuring different aspects of lung function. This, however, may not be feasible in neonatal period as these tests are complex and practically difficult at such young age group. Until appropriate devices become available, clinicians will have to rely on simple markers to define populations at risk and predict later pulmonary outcomes.

## RISK FACTORS

A number of epidemiological studies have identified clinical risk factors which can modify the prevalence or severity of BPD. These include endogenous factors such as gestational immaturity, birth weight, male sex and family history of asthma. Genetic predisposition is another important factor which modifies the risk of BPD. Paucity of maternal glucocorticoids and endogenous surfactant certainly increases the risk of respiratory distress syndrome (RDS) and BPD. Administration of glucocorticoids clearly has advantages as this improves survival even amongst the tiniest of babies, but they do not seem to reduce the incidence of BPD. Recent studies have also indicated that prenatal factors including maternal smoking, pre-eclampsia, chorioamnionitis and intrauterine growth restriction are important risk factors for BPD.

Early neonatal pattern of lung disease, as assessed both clinically and radiologically, can identify babies at higher risk of BPD. The type of artificial respiratory support and its duration along with complications commonly seen in these babies including ventilator associated pneumonias (VAP), patent ductus arteriosus (PDA) and pulmonary interstitial emphysema (PIE) are known clinical risk factors as they exacerbate or prolong the respiratory illness and their ventilator dependence.

## ETIOPATHOGENESIS

Bronchopulmonary dysplasia (BPD) is multifactorial and an understanding of the *pulmonary injury sequence* may enable the development of strategies to interrupt this cascade. Essentially here are two main pathways leading to BPD. The first is intrinsic and is related to a *developmental arrest* of the lung resulting in diminished alveolarization. This results in inadequate surface area for gas exchange and impaired lung function, requiring the initiation of chronic ventilation and subsequent ventilator-induced

lung injury (VILI). Other factors include surfactant deficiency and the need to deal with a very compliant chest wall. Extrinsic factors also inhibit alveolarization and lung growth, and they include intrauterine cytokine exposure, antenatal and postnatal glucocorticoid treatment, insufficient nutrition, lung and systemic infections, and exposure to high concentrations of oxygen.

### Ventilator-induced Lung Injury (VILI)

Although a key component in the pulmonary injury sequence, VILI itself is multifactorial and mostly iatrogenic. The term *volutrauma* refers to injury related to overdistension or excessive stretching of the lung units (alveoli and smaller airways) by delivering too much gas (tidal volume). *Atelectotrauma*, in contrast, refers to the damage caused by insufficient tidal volumes (recruitment and de-recruitment of alveoli) associated with repetitive opening and closing of lung units. *Biotrauma* is a collective term to describe the adverse effects of infection and inflammation. *Rheotrauma* refers to damage caused by inappropriate airway flow. If the flow is excessive, it may cause inadvertent positive end expiratory pressure (PEEP), turbulence and ineffective gas exchange, and lung overinflation. On the other hand, if the flow is inadequate, it may lead to air hunger (flow starvation) and increased work of breathing. An understanding of the pathophysiology of VILI helps formulating ventilatory strategies aimed at reducing or preventing BPD in very small infants.

### Noninvasive Forms of Respiratory Support

Despite mechanical ventilation being the *standard* treatment for respiratory failure in newborns, there has been a recent upsurge in the use of *noninvasive* respiratory support, using single level support, such as continuous positive airway pressure (CPAP) and high flow nasal cannula (HFNC) or nasal intermittent positive pressure ventilation (NIPPV). CPAP is a form of distending pressure provided through a nasal interface. NIPPV provides intermittent positive pressure ventilation in addition to continuous distending pressure. The proponents of noninvasive ventilation claim that the absence of an endotracheal tube reduces the risk of trauma to the airways, reduces the risk of infection, and causes less acute and chronic lung damage, and thus prevents BPD. This, however, is not supported by the findings of large clinical trials. Yet, most neonatal units use noninvasive form of ventilation as it is simple to use and looks patient-friendly. Although long-term data regarding their safety is still not available, in short-term they at least appear to be safe. The choice of which type of respiratory support to use very much depends on individual unit's choice and personal experience.

### Continuous Positive Airway Pressure

Continuous Positive Airway Pressure supports the breathing of premature infants in a number of ways and can be delivered by a variety of devices and interfaces. CPAP devices can be categorized by the flow characteristics into *continuous flow systems*, such as bubble CPAP and ventilator-derived CPAP, and *variable flow system*, such as the infant flow driver and Benveniste (gas jet) valve CPAP. The meta-analysis of randomized trials comparing intubation and mechanical ventilation versus noninvasive respiratory support at birth reported a trend in favor of nasal CPAP in reducing BPD at 36 weeks (RR 0.91, 95% CI—0.07–0.01). Although statistically significant, its clinical significance remains unclear because the number needed to treat (NNT) to benefit from CPAP was 1 in 25.

### Volume-targeted Ventilation

Volume-targeted modalities of ventilation are relatively new to neonatal intensive care and represent a departure from traditional

time-cycled pressure limited ventilation (TCPLV) by focusing on tidal volume delivery to the lungs and allowing pressure to vary. Although there are only a few published randomized controlled clinical trials, thus far the evidence is highly encouraging. The consistency of tidal volume delivery during volume controlled ventilation (VCV) in the face of varying lung compliance and the auto-weaning of airway pressure may be clinically advantageous, especially in conditions in which lung compliance can change rapidly, such as after surfactant administration. A meta-analysis of volume-targeted ventilation reported a reduction in the total duration of ventilation, severe intraventricular hemorrhage and pneumothorax, and a strong trend toward a reduction in the incidence of BPD. Stability of tidal volume delivery may account for this, especially in extremely low birthweight infants, who are most at risk for sustaining complications associated with mechanical ventilation.

### High-frequency Ventilation

High-frequency ventilation (HFV), in contrast to conventional mechanical ventilation (CMV), uses extremely small tidal volumes delivered at rapid rates to affect gas exchange at lower alveolar pressures than CMV. There are two primary forms of HFV, high-frequency jet ventilation (HFJV), and high-frequency oscillatory ventilation (HFOV), as well as hybrid forms.

HFOV differs from HFJV in that even smaller tidal volumes are used at rates of 8–15 Hz. Mean airway pressure is used as a continuous distending pressure to inflate the lung to a static volume, and oscillations around this mean are used to affect gas exchange. Adjustments for oxygenation (via mean airway pressure) and ventilation (via amplitude) can be done independently of one another. Moreover, HFOV uses active exhalation, whereby gas is actively withdrawn from the lung during expiration.

A number of clinical studies of high frequency ventilation have reported long-term outcomes, although BPD was not the primary objective in most cases. Keszler et al. reported a reduced incidence of BPD and the need for home oxygen in infants treated with HFJV compared to CMV for uncomplicated RDS. A number of recent clinical trials compared HFOV to CMV in preterm infants with RDS. Two recently completed trials found differing results. The HIFI trial of Courtney et al. found a very slight reduction in BPD in babies receiving HFOV, although this could have reflected the fact that the control group was managed in synchronized intermittent mandatory ventilation (SIMV), which is not the ideal mode for acutely ill infants. The UKOS study found no difference in the incidence of BPD among infants receiving HFOV or conventional ventilation. Currently, there is insufficient evidence to recommend HFOV to reduce BPD.

### Permissive Hypercapnia

The rationale for using permissive hypercapnia, or in other words, *gentler ventilation*, using a low lung volume strategy, is that it may decrease volutrauma and lung injury, lessen the duration of mechanical ventilation, reduce alveolar ventilation and the complications of hypocapnia (especially reduced cerebral blood flow), and increase oxygen unloading at the tissue level (Bohr effect). The strategy of ventilating infants at a higher PaCO<sub>2</sub> level, termed permissive hypercapnia, is based upon the retrospective observation of Kraybill et al. in 1989. In a multicentric analysis of 235 preterm infants, these investigators demonstrated a higher incidence of BPD in those infants, who had lowest PaCO<sub>2</sub> on the second and fourth postnatal days, implying that they were *over ventilated*. Two prospective, randomized, controlled trials of permissive hypercapnia have been conducted. Although both studies demonstrated a statistically significant reduction in the duration of ventilation and other secondary outcome measures, the incidence of BPD did not differ.



## CLINICAL FEATURES AND DIAGNOSIS

Diagnosis of CLD and BPD is made on the composite of (a) background clinical information of prematurity, needing mechanical ventilation or other form of artificial respiratory support and oxygen therapy; (b) continuing respiratory distress at 21 days or 36 weeks postmenstrual age, and requiring oxygen and/or any form of mechanical respiratory support such as CPAP or HFNC; and (c) X-ray appearance showing features of atelectasis/over inflation or simply ground glass appearance (**Figs 1A and B**).

Severe cases of BPD may progress to develop pulmonary hypertension and cor pulmonale with features of right sided heart failure requiring cardiac and hemodynamic assessment. The underlying lung abnormality, in severe cases, may persist in later childhood showing features of atelectasis and obstructive airways disease, presenting as persistent cough, shortness of breath and need for inhaled bronchodilators. Such children also end up with frequent lower respiratory tract infection requiring hospitalization or visit to their doctor. Children with BPD often exhibit motor and cognitive developmental delay requiring specialist therapists.

## TREATMENT

### Ventilatory Strategies

The management of infants who have already developed BPD has not been studied fully and there is no clear strategy developed to deal with such babies. A suggested guideline for dealing with different lung issues is shown in **Table 1**. The infant with ventilator-dependent BPD presents many challenges to the clinician. Chronic respiratory insufficiency may result in aberrant gas exchange, manifest by severe hypercarbia, with marked renal compensation. The inexperienced clinician often attempts to make the baby conform to *physiologic* blood gases, and in doing so, may inadvertently overventilate the baby and unwittingly contribute to VILI. It is perhaps wiser to view the chest radiograph in the context of *What can I expect from these lungs?* and adjust one's expectations of blood gases accordingly.

Alteration in lung mechanics is another key feature of BPD. Reactive airways may result in increased pulmonary resistance. This may be treated empirically by adjustments in ventilator strategy, such as increasing PEEP and/or airway flow, or by using a modality with *variable* inspiratory flow, such as pressure control or pressure support compared to traditional *fixed* flow TCPLV. Lung compliance may also be abnormal. Ventilating the lung at an appropriate functional residual capacity, where incremental changes in pressure

recruit the most lung volume, is often a challenge. Assessing compliance at different levels of PEEP may be helpful in this regard. Alterations in resistance and compliance will alter the respiratory time constant, and sufficient expiratory time to avoid gas trapping and inadvertent PEEP must be provided. Decisions about the best mode or modality to ventilate a baby with BPD are best made on an individual basis. Theoretically, if lung disease is homogeneous, a modality such as pressure control might be advantageous, whereas heterogeneous lung disease should respond better to VCV because peak pressure and peak volume delivery occur at the end of inspiration, helping to make gas delivery more uniform throughout the lung. This will require clinical investigation.

Periodic assessment of cardiac function, looking for evidence of pulmonary hypertension, may also guide one's use of supplemental oxygen and establishment of appropriate ranges for  $\text{SaO}_2$ , although the optimal limits are yet to be established. All changes in strategy should be objectively assessed for response.

### Pharmacological Adjunctive Therapies

Once BPD is established, treatment is only supportive and aimed to alleviate the symptoms. Many such therapies, however, are based on *habit* rather than scientific evidence, and one should be aware of the usefulness and limitations of such therapies as they can be associated with adverse side effects. Commonly used therapeutic adjuncts in babies with BPD include steroids, diuretics, caffeine and Vitamin A. There are other adjuncts such as nitric oxide which have been tested in over 5000 babies with limited preventative or therapeutic benefits.

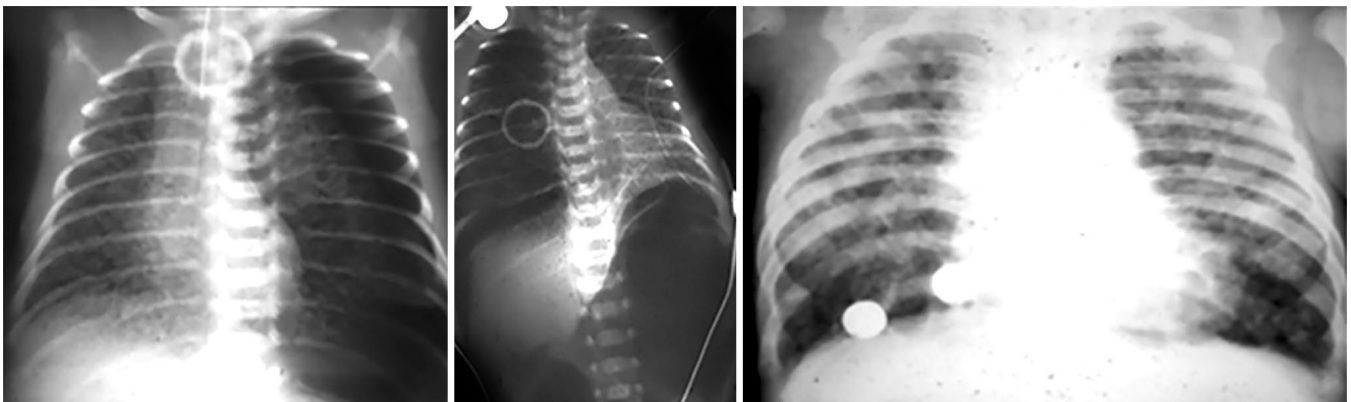
#### Antenatal Glucocorticoids

Because RDS results from surfactant deficiency, it only makes sense that efforts be made to induce endogenous surfactant production. Glucocorticoids are known to induce maturity of the lungs and this forms the rationale for using one course of glucocorticoids (usually betamethasone, given in two dosage at 12–24 hours, to mothers with imminent premature delivery). This does improve survival and severity of RDS, but there is no evidence that it reduces infant's pulmonary outcome or reduces the incidence of BPD.

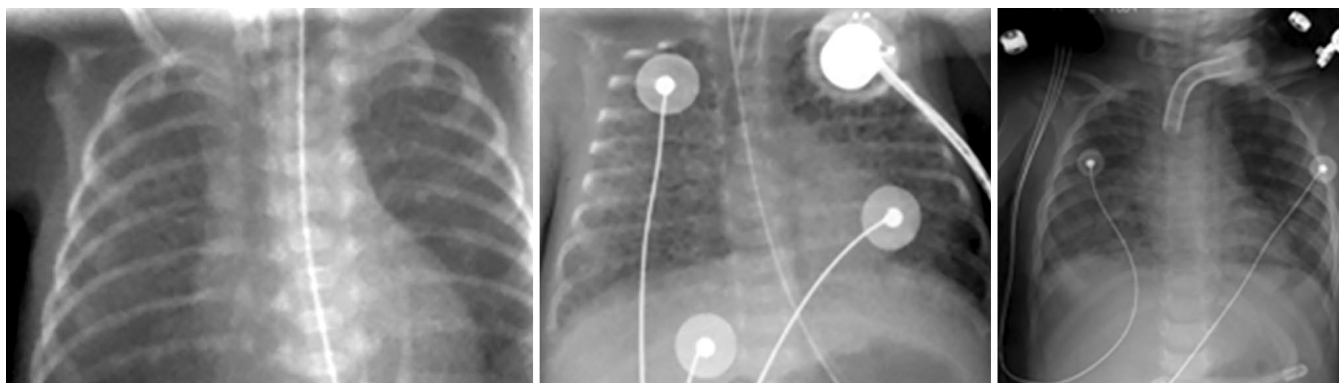
The only other lung maturation strategy is a combination of corticosteroids and thyrotropin-releasing hormone (TRH). They are known to act synergistically, but ultimately there is no evidence that this combined therapy is of any use in preventing RDS or BPD. In fact they have toxic effects and, therefore, not used.

#### Postnatal Dexamethasone

Corticosteroids are anti-inflammatory and help in facilitating extubation in babies who are chronically ventilatory dependent.



**Figure 1A** Areas of hyperlucency in both lungs indicative of hyperinflation mixed with areas of distinct opacities suggestive of interstitial lung disease as characteristically seen in the severe form of BPD



**Figure 1B** Mild haziness covering both lungs as seen in early stages of RDS in a 3-week-old baby with no evidence of hyperinflation characteristic of new BPD

**Table 1** Respiratory management options for BPD

Issue	Strategy	Comments
Increased resistance	Variable inspiratory flow (pressure control or pressure support ventilation) Consider using higher PEEP to stent collapsing airways. Use largest comfortable endotracheal tube	Seen with airway injury and hyper-reactivity
Decreased compliance	Use higher PIP/PEEP. Consider high frequency ventilation. Avoid hyperinflation. Monitor tidal volumes	Reflects parenchymal lung injury
Heterogenous lung disease	Consider volume-targeted ventilation	Pressure-targeted flow patterns may contribute to ventilation/perfusion mismatch
Pulmonary hypertension	Consider pharmacotherapy. Liberalization of arterial oxygen tension	Limited evidence; follow echocardiogram
Hypercapnia	Re-evaluate gas exchange capability; allow higher carbon dioxide tension if pH is not deranged	Do not attempt to achieve <i>normal</i> gas exchange
Nutrition	Try to optimize caloric and fluid intake, but avoid excess carbohydrate or fat	Non-nitrogen calories will contribute to carbon dioxide production and respiratory load

Abbreviations: PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure.

However, there have been concerns that excessive or prolonged use of dexamethasone could be associated with cerebral palsy and adverse neurodevelopmental outcome. In view of this, it only makes sense to adopt a cautious approach and use corticosteroids only in very select group of babies, who are still ventilatory dependent and unlikely to come off the ventilator. In such cases, dexamethasone can be used at the lowest dose for the shortest course possible with some beneficial effect. Considering the efficacy and associated systemic side effects of dexamethasone, studies have looked into the feasibility of giving steroids in a nebulized form. This, however, does not show any benefit either in terms of survival or incidence of BPD.

### Diuretics

Infants with RDS and BPD have a tendency to retain excess body fluids. This can lead to a deterioration in pulmonary function and need for further respiratory support, which in turn causes BPD (pulmonary injury sequence). In such cases use of diuretics along with fluid restriction might be theoretically beneficial. The commonly used diuretics in babies with RDS and BPD include: (a) combination of chlorothiazide and spironolactone; (b) furosemide; and (c) bumetanide.

Despite their widespread use, there are relatively few data assessing the meaningful value of diuretic therapy in BPD. Of all the adjunctive therapies used in preterm infants with BPD, diuretics therapy is one of the most commonly used or abused drugs without evidence of substantive benefit. Moreover, they can cause significant complications such as hypercalciuria and nephrocalcinosis leading to secondary complications. This, however, mostly resolves after cessation of diuretic therapy.

### Vitamin A Supplementation

Vitamin A is one of the few drugs which is known to have beneficial effect on growing tissue such as lungs. Babies born prematurely are deficient in vitamin A and this has been shown to be associated with BPD. A large randomized controlled trial among infants weighing less than 1000 g at birth showed a significant beneficial effect of intramuscular Vitamin A given at birth. Despite this, vitamin A is still not used regularly on most neonatal units probably because it requires intramuscular injection. Another trial of oral vitamin A therapy daily for four weeks in a similar population of infants failed to detect any beneficial effect. A meta-analysis involving a number of randomized controlled trials has suggested that vitamin A supplementation reduces risk of BPD at 36 weeks postmenstrual age (RR 0.87, 95% CI 0.77–0.98).

### Caffeine Therapy

Caffeine has traditionally been used for treatment of *apnea of prematurity*. It also facilitates extubation from mechanical ventilation. However, there were concerns that caffeine may be associated with adverse cerebral and intestinal blood flow velocity, thus increasing the risk of cerebral palsy and necrotizing enterocolitis (NEC). A large international trial showed caffeine therapy to significantly reduce risk of BPD (OR 0.63, 95% CI 0.52–0.76;  $p < 0.001$ ). Interestingly, BPD was not a primary outcome measure of this trial and, therefore, it is believed that the beneficial effect of Caffeine amongst ventilated babies came because of earlier extubation and shortened duration of ventilatory dependency. A subsequent analysis of data from this large study also confirmed

that caffeine when given early amongst babies who were receiving mechanical respiratory support was associated with better outcome compared to those in whom caffeine was administered either late or for other indications.

### IN A NUTSHELL

1. Bronchopulmonary dysplasia is a recognized sequel of preterm birth. With improving survival of infants at lower gestational ages, the prevalence is on the rise.
2. Pathological features of BPD include alveolar maldevelopment, with or without areas of pulmonary fibrosis. Assisted ventilation, infection/inflammation, oxygen administration and fluid overload are major identified risk factors in the evolution of BPD.
3. The prevention of BPD needs a multifocal approach by decreasing VILI through utilization of newer ventilatory strategies such as volume-controlled ventilation and the use of non-invasive forms of respiratory support in selected preterm babies. Many other therapies are still investigational and potentially dangerous and need further evidence before they can be routinely recommended. Determining the optimal strategy for infants with ventilator-dependent BPD is a work in progress, but a very necessary one in view of the number of affected infants.
4. Once established, BPD is associated with a number of adverse health consequences requiring input from a number of specialists including respiratory pediatrician, cardiologists, neurodevelopmental pediatrician, clinical psychologists and specialist therapists, such as physiotherapist, occupational therapists and dietician. Therefore, efforts should be aimed at preventing BPD rather than trying to cure it when it has already established.

### MORE ON THIS TOPIC

- Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. *J Pediatr*. 1979;95(5 Pt 2):819-23.
- Brion LP, Primhak RA, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease. *Cochrane Database Syst Rev*. 2002;1:CD001817.
- Doyle LW, Davis PG, Morley CJ, et al. Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter, international, randomised, controlled trial. *Pediatrics*. 2006;117:75-83.
- Ehrenkranz RA, Walsh MC, Vohr BR, et al. Institutes of Child Health and Human Development Neonatal Research Network. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics*. 2005;116:1353-60.
- Groneck P, Speer CP. Inflammatory mediators and bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonatal Ed*. 1995;73:F1-3.
- Johnson AH, Peacock JL, Greenough A, et al. High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. *N Engl J Med*. 2002;347:633-42.
- Kang JL, Park W, Pack IS, et al. Inhaled nitric oxide attenuates acute lung injury via inhibition of nuclear factor-kappa B and inflammation. *J Appl Physiol*. 2002;92:795-801.
- Kraybill EN, Runyan DK, Bose CL, Khan JH. Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams. *J Pediatr*. 1989;115:115-20.
- Ng GY, da Silva O, Ohlsson A. Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2001;3:CD003214.
- Peng W, Zhu H, Shi H, Liu E. Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 2014;99:F158-65.
- Schmölzer GM, Kumar M, Pichler G, et al. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. *BMJ*. 2013;347:f5980.
- Tin W, Gupta S. Optimum oxygen therapy in preterm babies. *Arch Dis Child Fetal Neonatal Ed*. 2007;92:F143-7.

# Section 18 NEONATAL MALFORMATIONS

**Section Editor** Siddarth Ramji

## Chapter 18.1

### Esophageal Atresia and Tracheoesophageal Fistula

*Yogesh Kumar Sarin, Shalini Sinha*

Esophageal atresia and tracheoesophageal fistula (EA-TEF) is one of the differential diagnoses for respiratory distress in the newborn. As the esophageal continuity is lacking, the baby is unable to feed and is likely to aspirate; literally drowning in its own saliva. In India, where many babies are born at home and may present late with severe respiratory distress, EA-TEF may be overlooked when the neonate presents with pneumonia. Missing this diagnosis can have grave implications.

#### EPIDEMIOLOGY

Esophageal atresia (EA) has an incidence of 1 in 3,000-4,500 births according to western literature. It is gradually declining, the reasons for which are not yet known. There is no data available citing the incidence of EA-TEF in India. Though the male-to-female ratio is equal in studies from the developed world, several reports from the Indian subcontinent reveal a falsified male preponderance ranging from 65% to 92%. The reason for this skewed ratio can only be attributed to negligence of the girl child by the local population.

#### ETIOPATHOGENESIS

Although a genetic etiology for EA-TEF has not been definitively established, EA-TEF has been known to occur in several generations of the same family with a 2% recurrence risk in the sibling. EA has been known to occur in sets of dizygotic twins. The etiology is most likely heterogeneous and multifactorial and involves multiple genes and complex gene-environmental interactions. The pathogenesis is equally obscure and many theories surround it:

- Esophageal occlusion and failure of recanalization
- Spontaneous deviation of tracheoesophageal septum
- Abnormal migration of putative tracheoesophageal septum
- Mechanical obstruction
- Component of cephalic neurocristopathy
- Defect in signaling pathway of the extracellular organ differentiation-promoting glycoprotein, sonic hedgehog (Shh).

#### ASSOCIATED ANOMALIES

Structural weakness of the membranous part of trachea is commonly associated with EA-TEF resulting in tracheomalacia. This causes the trachea to collapse at the end of expiration simulating stridor, which becomes more obvious when the baby cries. Associated congenital anomalies occur frequently with EA-TEF. Collectively, these anomalies are identified with the acronyms VATER or VACTERL syndrome (when three or more anomalies present), which is seen in 25% of patients with EA-TEF. The various components of VACTERL are as follows: Vertebral (hemivertebrae,

scoliosis, rib deformities); Anorectal malformations (8%); Cardiac defects [ventricular septal defects (VSD), tetralogy of Fallot (ToF), patent ductus arteriosus (PDA), atrial septal defect (ASD), auriculoventricular (AV) defects in 20-40%]; Tracheoesophageal fistula; Renal anomalies (renal agenesis, Potter syndrome, horseshoe kidney, polycystic kidney, urethral atresia, vesicoureteral reflux in 15%); and Limb and radial anomalies (absent radius, radial dysplasia, radial ray deformities, polydactyly, syndactyly and tibial deformities). Coarctation of aorta and single umbilical artery are also known to coexist with EA-TEF. Another acronym for associations is CHARGE that includes Coloboma, Heart defects, Atresia choanae, developmental Retardation, Genital hypoplasia and Ear deformities. Gastrointestinal (GI) tract anomalies (duodenal atresia, ileal atresia, malrotation, Meckel diverticulum), neural tube defects, undescended testes, hypospadias, ambiguous genitalia and trisomy of 13, 21, 18 are found to be associated with EA-TEF.

#### ANATOMIC CLASSIFICATION

The most common anatomic classification used for EA-TEF was suggested by Gross in 1953 and is depicted in **Figures 1A to E**. The most common type, EA with distal TEF (type C) occurs in 75-85% of the cases. The next most frequent is pure EA (type A) seen in 8%; this type is associated with higher incidence of duodenal atresia, Down syndrome and prematurity. Type E (TEF without EA) occurs in 5% cases and is named H-type TEF. Type D (EA with fistula between both proximal and distal ends of the esophagus and trachea) and type B (EA with TEF between proximal segments of esophagus and trachea) are rare.

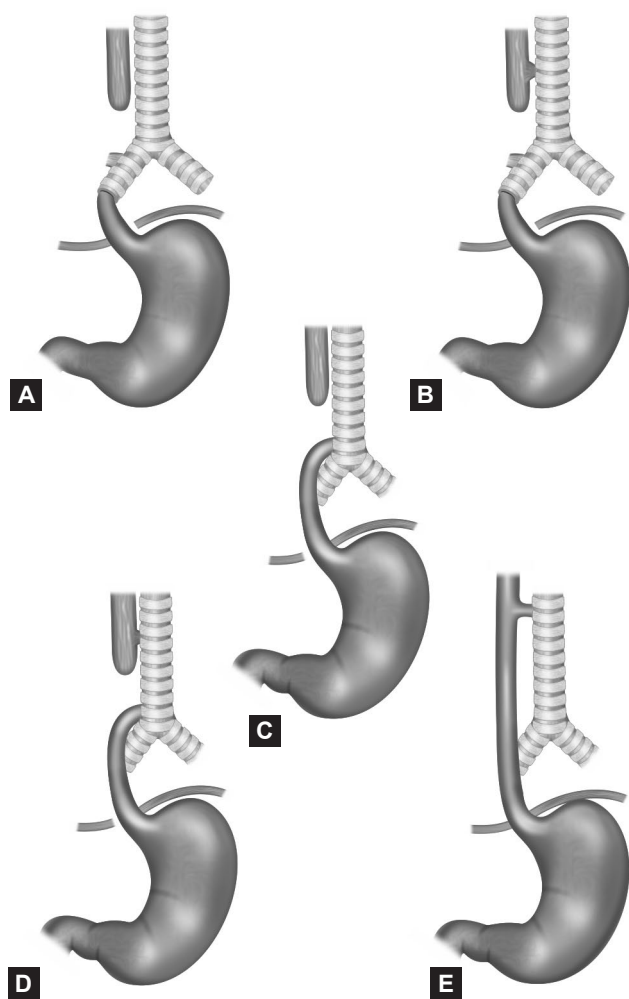
#### CLINICAL PRESENTATION

The clinical presentation of types A, B, C or D of EA is similar; the neonates present with excessive salivation and drooling. The neonates cough, choke, and get cyanosed when fed. In the presence of distal TEF (EA types C and D), air passes through the fistula into the stomach resulting in abdominal distention. This combined with the chemical pneumonitis that occurs due to regurgitated gastric juice through the distal TEF leads to severe respiratory distress. If EA type C or D is associated with duodenal atresia, the abdominal distention is extreme and occurs very early, mandating urgent surgical correction. In case of EA type A, no air passes into the stomach and the abdomen is rather scaphoid.

#### DIFFERENTIAL DIAGNOSIS

A nasopharyngeal perforation ensuing after traumatic insertion of a nasogastric or orogastric tube is the most important differential diagnosis. The baby has copious oral secretions and the orogastric tube cannot be passed in the stomach. In fact, the orogastric tube may track down through this perforation to varying distances outside the esophagus. This complication can ensue in neonates. It can also happen following a rough finger sweep to clean the neonate's mouth following home delivery conducted by an untrained birth attendant in the rural or suburban set-up. The oral secretions in such a case are blood stained, a feature not often seen





**Figures 1A to E** Anatomical variants of esophageal atresia with or without tracheoesophageal fistula

with a neonate of EA-TEF. In case of doubt, a contrast study could be performed.

## DIAGNOSIS

### Antenatal Diagnosis

Less than 50% of the cases can be diagnosed antenatally. The two often-mentioned signs on ultrasound—presence of polyhydramnios and absent or small stomach bubble—are at best indirect and nonspecific. The visualization of cervical or thoracic fluid image corresponding to the expansion of the bottom of upper esophageal (*pouch sign*) on antenatal ultrasound or MRI is more specific. Recently, amniotic fluid biochemical markers (a biochemical pattern characterized by high total protein,  $\gamma$ -glutamyl transpeptidase and normal L-leucine aminopeptidase) have been suggested to have 100% detection rate.

### Postnatal Diagnosis

An orogastric tube (10Fr red rubber catheter) cannot be passed into the stomach and arrests at 9–11 cm. The *pouch sign* may occasionally be seen on a plain chest radiograph. If a soft infant feeding tube is used, it will be seen coiled in the upper esophageal pouch.

### Plain Radiograph of Chest and Abdomen

The upper pouch can clearly be seen as a blind ending structure with the tube coiled in it. Besides, it is important to determine the

presence or absence of bowel gas in the abdomen as it indicates the nature of fistula, e.g., presence of abundant air shadows in the gastrointestinal tract depicts a distal TEF (**Fig. 2**), gasless abdomen is seen in pure EA (or rarely a tiny distal TEF blocked by a mucous plug) (**Fig. 3**), presence of a double bubble and paucity of distal gas in bowel in addition to EA imply a coexisting duodenal atresia, etc. In addition, there may be associated aspiration pneumonia (commonly seen as consolidation of right upper zone), especially when the baby presents late and is being fed since the diagnosis has been missed at birth. Associated anomalies such as hemivertebrae, cardiomegaly and extra ribs can also be visualized on the plain radiograph.

### Look for Associated Anomalies

*Echocardiography* is necessary to rule out associated anomalies of heart and great vessels. It will also reveal whether the aortic arch is left sided or right sided, which may influence the approach to surgical repair. Vertebral anomalies are evaluated by *plain radiography*; a spinal ultrasound may be done, if any is detected. Perineum must be carefully looked at to rule out associated anorectal malformation. Conversely, in all newborns with anorectal malformation, EA-TEF should be excluded by passing an orogastric red rubber catheter. An associated enlarged kidney (hydronephrosis or multicystic kidney) may be clinically



**Figure 2** Plain radiograph showing blind upper pouch, gas in bowel suggesting distal TEF



**Figure 3** Plain X-ray showing blind upper pouch and gasless abdomen suggestive of pure EA

palpated; this needed to be confirmed on *abdominal ultrasound*. The associated limb deformities, if any, are very obvious, the most common being radial aplasia or hypoplasia (**Fig. 4**). The relevant plain radiographs would confirm these. Rib anomalies may also be present. Presence of 13th rib on one or both sides suggests presence of longer gap between the upper and lower esophageal segments. Presence of a booming cough with or without inspiratory stridor may indicate concomitant tracheomalacia.

### Upper Gastrointestinal (GI) Contrast Study

Water soluble contrast study should be done with extreme caution to avoid aspiration pneumonitis, only when the diagnosis cannot be confirmed on clinical or plain radiological imaging, e.g., late presentation around 10 days of life, suspicion of cricopharyngeal perforation (**Fig. 5**).

## MANAGEMENT

### Initial Resuscitation

The initial resuscitation of neonates with EA-TEF includes initiation of warmed electrolyte solution, intravenous antibiotic therapy, decompression of the upper pouch and other maneuvers to improve the respiratory status. Two strategies are devised to

decrease the degree of aspiration of saliva pooling in the upper esophageal pouch: (i) to nurse in the anti-Trendelenburg position, (ii) a sump catheter (Replegle tube) is placed in the upper pouch on continuous suction. If Replegle tube is unavailable, frequent low pressure suctioning is mandated.

### Risk Stratification

There are several risk stratification systems described like Waterston and Spitz criteria, which are based on the birthweight, presence of and severity of pneumonia and presence and type of associated other congenital anomalies with special attention to congenital heart disease. Presence of life-threatening cardiac anomaly takes precedence over EA-TEF repair and presence of pneumonia may mandate few days of antibiotics and even ventilation before definitive surgical repair.

### Timing of Surgical Intervention

In a stable neonate, the definitive repair may be performed soon after the work-up for the associated anomalies is done. Definitive repair of the EA-TEF is rarely a surgical emergency to be performed in the middle of the night.

### Management in the Preterm Neonate

A premature neonate with EA-TEF has the following issues that deteriorate his pulmonary status associated hyaline membrane disease; recurrent aspiration through the fistula; increased abdominal distention, which leads to raised diaphragm, basal atelectasis and compromised lung expansion. Such a preterm neonate would be better off with high frequency oscillatory ventilation (HFOV). Severe gastric distention may mandate placement of a gastrostomy tube. However, once the gastrostomy tube is placed, the pulmonary status could paradoxically worsen as the ventilated gas preferentially may pass through the TEF and get lost through gastrostomy. To correct this problem, the gastrostomy tube may be placed under water seal. The definitive repair would be done only after alleviation of the pulmonary status of the neonate.

### Primary Esophageal Anastomosis

In a stable infant, division of TEF and primary esophageal repair is done. Preoperative bronchoscopy may be performed to determine the opening of the distal esophageal segment in trachea, carina or right bronchus. A retropleural approach is preferred over the transpleural approach for repair. A primary esophagoesophageal anastomosis is performed over a transanastomotic feeding tube. A chest tube drain is placed and the incision is closed. With the advent of minimally invasive surgery, thoracoscopic repair of EA-TEF is also being done in stable patients.

### Postoperative Management

Routine postoperative intubation and ventilation is undesirable as it may put pressure on the site of tracheal closure. However, postoperative ventilation would be mandatory in the presence of prematurity or pneumonia. Whenever, the anastomosis is performed under some tension, it is preferable to electively ventilate the neonate for 3–5 days even, if pulmonary status is satisfactory.

If a transanastomotic tube is placed, expressed breastmilk could be fed through it from the very early postoperative period. In case transanastomotic tube is not placed, then parenteral nutrition would need to be instituted through a central line. The chest tube drain should not drain more than few mL of serous fluid on 1st postoperative day in the normal course; presence of saliva in the tube indicates an anastomotic leak. A contrast swallow is obtained on 7–10th postoperative day to determine whether a leak is present and to rule out anastomotic stenosis, if any. If no



**Figure 4** Plain radiograph of a neonate with esophageal atresia (EA) type C with associated vertebral defects, scoliosis, radial aplasia and right upper zone consolidation



**Figure 5** Contrast study showing nasopharyngeal perforation that was clinically mimicking as EA-TEF



**Figure 6** Contrast dye study demonstrating recurrent TEF

leak is demonstrable, the chest tube and the nasogastric tube are removed and the breastfeeding is started.

## COMPLICATIONS

### Early Complications

These include an anastomotic leak (10–15%), anastomotic stricture (10–20%) and recurrent TEF (5–15%). All three complications may coexist in a particular patient. *Major anastomotic leaks* manifest within first few postoperative days with hydropneumothorax, mediastinitis and sepsis and necessitate immediate surgical exploration. *Minor anastomotic leak* is usually incidentally detected on the contrast swallow or may be seen in the form of small amount of saliva in the chest tube in a stable neonate. It invariably heals spontaneously.

*Strictures* may present with swallowing difficulties (dysphagia, vomiting, cough, poor or slow feeding), foreign body obstruction (including food bolus), recurrent respiratory tract infections and/or poor weight gain. Diagnosis is made on barium esophagography and esophagoscopy. Few dilations with Savary-Gilliard bougies are usually required. Rarely, resection of the stricture and repeat anastomosis are necessitated.

The diagnosis of *recurrent TEF* would warrant barium esophagography and bronchoscopy (**Fig. 6**). Reoperation would be indicated in most of the cases, though there are some reports of success with endoscopic use of laser, cautery, tissue adhesives or biological mesh.

### Late Complications

These include gastroesophageal reflux (GER), esophageal dysmotility and tracheomalacia. Varying degrees of *gastroesophageal reflux* occur in almost neonates after repair of EA-TEF. Nearly two-thirds of EA patients have some form of *dysphagia* in adulthood.

*Tracheomalacia* tends to improve with growth of the baby, but severe and persistent tracheomalacia may require aortopexy.

## SPECIAL CIRCUMSTANCES

Patients with type *E TEFs*, also called *H-type*, usually present beyond the newborn period. Recurrent chest infections and failure to thrive are the common presentations. The diagnosis of H-type TEF is often made on barium esophagography and is confirmed on bronchoscopy. Division of the H-type fistula is generally possible through a cervical approach; a thoracotomy is rarely necessitated. The outcome is invariably good. Neonates born with *EA-TEF and duodenal atresia* require an urgent surgical treatment owing to the closed obstruction of the stomach and proximal duodenum; any delay may lead to gastric perforation.

*Pure EA* (type A) represents a difficult entity to treat as primary esophageal anastomosis is usually not feasible owing to the fact that the upper and lower ends are too apart. Traditionally, the treatment approaches include performing a feeding gastrostomy tube at presentation, bouginage over weeks and months to lengthen the upper pouch and then doing delayed primary esophageal anastomosis. Reconstruction in the form of esophageal replacement is required using either a gastric pull-up or gastric tube or colon interposition. Foker's technique has been described for pure EA and other long-gap EA in recent years.

## OUTCOME AND PROGNOSTIC FACTORS

Many different risk stratification or prognostication systems have been used (**Table 1**). Antenatal diagnoses of EA have been known to be associated with a 75% mortality rate. In the low-risk neonates, the overall survival rates of greater than 90% have been achieved in the western world. In high-risk neonates (those having

**Table 1** Risk stratification systems for EA-TEF

Waterston (1962)		Montreal (1993)		Spitz (1994)	
<b>A</b> (mortality 0%)	Birthweight > 2,500 g, well	<b>I</b> (mortality 7.3%)	All other patients	<b>I</b> (mortality 3%)	Birthweight ≥ 1,500 g and no major cardiac anomaly
<b>B</b> (mortality 4%)	Birthweight 1,800–2,500 g and well Or Birthweight > 2,500 g and moderate pneumonia or congenital anomaly	<b>II</b> (mortality 69.2%)	Life-threatening anomalies  Both major anomalies and ventilator dependence	<b>II</b> (mortality 41%)	Birthweight < 1,500 g or major cardiac anomaly
<b>C</b> (mortality 11%)	Birthweight < 1,800 and well Or Birthweight > 2,500 g and severe pneumonia or congenital anomaly			<b>III</b> (mortality 78%)	Birthweight < 1,500 g and major cardiac anomaly

associated severe cardiac and chromosomal anomalies or extreme prematurity), the survival rates have been quoted in the range of 50%. Staged procedures have increased survival rates in these high-risk neonates. Despite such remarkable survival figures in these western centers, nearly half of the survivors have complications. Data from the Indian subcontinent show an overall survival rate of 40–55% with only 20–30% survival in high-risk groups, though there are no recent statistics available. Reports from Africa paint a much more dismal picture.

### IN A NUTSHELL

1. Esophageal atresia with or without fistula is not a surgical emergency.
2. Preoperative stabilization and assessment for associated anomalies should be done before surgical correction.
3. Prognostic risk stratification is helpful in decision making.
4. Native esophagus is the best esophagus; hence, all attempts should be made to achieve a primary anastomosis.
5. In high-risk patients with long gap or pure EA (without fistula), diversion in the form of cervical esophagostomy and gastrostomy is a feasible option.
6. Developing countries lag far behind in providing good survival rates for EA-TEF due to lack of infrastructure and neonatal supportive care.
7. Close follow-up for detecting early and/or late complications is advisable.

### MORE ON THIS TOPIC

- Agarwala S, Bhatnagar V, Bajpai M, et al. Factors contributing to poor results of treatment of esophageal atresia in developing countries. *Pediatr Surg Int*. 1996;11:312-5.
- Alshehri A, Lo A, Baird R. An analysis of early nonmortality outcome prediction in esophageal atresia. *J Pediatr Surg*. 2012;47:881-4.
- Gupta DK, Sharma S. Esophageal atresia: the total care in a high-risk population. *Semin Pediatr Surg*. 2008;17:236-43.
- Nwosu JN, Onyekwulu FA. Oesophageal atresia and tracheoesophageal fistula: a 12 years experience in a developing nation. *Niger J Med*. 2013;22:295-8.
- Poenaru D, Laberge JM, Neilson IR, Guttman FM. A new prognostic classification for esophageal atresia. *Surgery*. 1993;113:426-32.
- Rintala RJ, Sistonen S, Pakarinen MP. Outcome of esophageal atresia beyond childhood. *Semin Pediatr Surg*. 2009;18:50-6.
- Sharma AK, Shukla AK, Prabhakar G, et al. Esophageal atresia: tragedies and triumphs over two decades in a developing country. *Int Surg*. 1993;78:311-4.
- Spitz L, Kiely EM, Morecroft JA, Drake DP. Oesophageal atresia: at-risk groups for the 1990s. *J Pediatr Surg*. 1994;29:723-5.
- Spitz L. Oesophageal atresia. *Orphanet J Rare Dis*. 2007;2:24.
- Tandon RK, Sharma S, Sinha SK, et al. Esophageal atresia: factors influencing survival—experience at an Indian tertiary centre. *J Indian Assoc Pediatr Surg*. 2008;13:2-6.



## Chapter 18.2

# Diaphragmatic Hernia and Eventration

*Shalini Sinha, Yogesh Kumar Sarin*

Malformations of the diaphragm in the newborn include congenital diaphragmatic hernia (CDH) and eventration of diaphragm (ED). While CDH is a life-threatening anomaly that can easily be diagnosed prenatally, ED usually presents beyond the neonatal age and sometimes even in adulthood. The physiological derangements associated with CDH in the form of pulmonary hypoplasia and pulmonary hypertension [persistent pulmonary hypertension of the newborn (PPHN)] need expert management by skilled neonatologists both before and after surgery.

### EPIDEMIOLOGY

Congenital diaphragmatic hernia occurs in approximately 1 in every 2,000 to 4,000 newborns. There is no data available from developing countries. About one-third neonates may be stillborn and hence the calculation of its incidence is likely to be underestimated. In 80–85% patients, the CDH is left-sided. A hernial sac is seen in 10–15% of CDH cases.

### ETIOLOGY

The exact etiology of CDH is still unknown. It is believed to be multifactorial with interplay of genetic as well as environmental factors. The fetal diaphragm develops in 7–10th week of gestation by fusion of the pleuroperitoneal membranes with the septum transversum and dorsal mesentery of the esophagus thus closing the pleuroperitoneal canal. Any interference in this process results in CDH. The nitrofen model speculates that CDH is an embryopathy caused by toxin exposure in early gestation. The role of retinoic-acid-related target gene in the causation of CDH is also being studied.

### PATHOGENESIS

Herniation of abdominal viscera into the thoracic cavity in CDH hinders the growth of the ipsilateral lung. The heart and mediastinum are shifted to the opposite side thus compressing the contralateral lung. Diminished intrathoracic space affects the pseudoglandular phase of lung development during the first trimester and results in bilateral pulmonary hypoplasia, which is more severe on the ipsilateral side. There is inadequate surface area for gas exchange, decreased cross-sectional area of the pulmonary vascular tree, precocious muscularization of the pulmonary vessels and probable surfactant deficiency. Raised levels of circulating vasoactive mediators, along with an increased sensitivity to these mediators, further accentuate the pulmonary hypertension.

With the initiation of the newborn's first breath, fetal circulation is converted to the adult type due to fall in pulmonary vascular resistance. Failure of this process, as occurs in CDH patients, leads to persistent fetal circulation with increased right to left shunt, either at atrial or ductal level. This causes fall in the saturation of systemic blood circulation and hypoxia, which further increases the pulmonary vascular resistance. A vicious cycle develops which results in respiratory failure.

The abdominal viscera that herniate through the diaphragmatic defect on the left side include left lobe of liver, spleen, stomach, varying lengths of small and large intestine and rarely left kidney. There may be an obstruction at the level of gastroesophageal junction due to displacement of the stomach, thus resulting in

polyhydramnios. On the right side, the right lobe of liver along with intestines occupy the hemithorax. Abnormal drainage of the hepatic veins directly into the right atrium may cause difficulty in surgical repair. When a sac is present, it is formed by the parietal pleura and peritoneum.

### Anatomic Classification

Bochdalek hernia is a posterolateral defect in the embryogenesis of the diaphragm and is the most common type of CDH constituting 95% of cases. Morgagni hernia is a rare anterior defect in the diaphragm and forms 2% of CDH patients. Also known as parasternal or retrosternal hernia, the abdominal contents herniate through the foramen of Morgagni, which lies adjacent to the xiphoid process of the sternum.

### CLINICAL PRESENTATION

The presentation of a baby born with CDH depends on the degree of pulmonary hypoplasia and associated PPHN. The spectrum of severity includes an infant with severe pulmonary hypoplasia and hypoxemia refractory to conventional and innovative ventilation techniques to those with a much more benign course and minimal blood gas derangements. Most patients develop respiratory distress either at birth or within the first 24 hour of life. Milder forms may present by 5–7 days. In developing countries, where antenatal pick-up is poor and many babies are born at home, only the milder forms of CDH reach hospital in time for intervention. Since the pulmonary hypertension is less in those with delayed presentation, the salvage rates are better. Rarely, a small group of cases goes unrecognized into adulthood.

Other presentations of CDH in the newborn include antenatally diagnosed CDH; respiratory distress at birth associated with cyanosis, hypoxia, tachycardia; abnormal bulge of hemithorax on the affected side; mediastinal shift to opposite side as seen by abnormal position of the cardiac impulse; bowel sounds heard over the hemithorax instead of breath sounds or a scaphoid abdomen. A neonate with Morgagni hernia or right-sided Bochdalek hernia may not be symptomatic at birth and may present later with respiratory or gastrointestinal symptoms.

### Associated Anomalies

Other anomalies are present in about 40% cases, most commonly congenital heart disease. Nearly 20% are found to have genetic defects. The various anomalies associated with CDH include neural tube defects, cranial malformations, hypoplastic left heart syndrome, tetralogy of Fallot, and coarctation of aorta and skeletal anomalies. Nonrotation of gut is almost invariably present. Tracheobronchial tree anomalies—tracheal stenosis, trifurcation of trachea are seen in 18% cases. Stillborn infants with CDH have a very high incidence of associated lethal anomalies nearing 100%.

### DIFFERENTIAL DIAGNOSIS

Congenital cystic lesions of the lung may simulate the presentation of CDH. These babies may also have respiratory distress at birth and a macrocystic variety of congenital cystic adenomatoid malformation (CCAM) may mimic the X-ray picture of CDH. When in doubt, a simple method to differentiate the two entities is to repeat the X-ray after inserting a nasogastric tube. This will confirm the presence of the stomach in the hemithorax in CDH. In a stable neonate, computed tomography can help. Rarely, agenesis of lung can be confused with CDH. A Bochdalek hernia may have a similar picture on chest X-ray as Morgagni hernia or congenital hiatus hernia which can be differentiated on upper GI contrast study. The radiological picture of CDH with sac simulates that of ED. The latter can be confirmed by paradoxical movements of the diaphragm as seen on fluoroscopy.

## DIAGNOSIS

### Antenatal Diagnosis

#### Prenatal Ultrasonography

The presence of stomach bubble or fluid-filled intestinal loops in the fetal hemithorax at the same cross-sectional level as the heart is suggestive of CDH on antenatal sonography (**Fig. 1**). Mediastinal shift to the opposite side, absence of stomach bubble in the abdomen and presence of liver in the thorax may also help in diagnosing CDH prenatally. Associated polyhydramnios is seen in about 80% cases. These features may be evident around 18 weeks of gestation at the time of level II scan, however, the mean age of antenatal detection of CDH has been reported to be around 24 weeks with a diagnostic accuracy of 40–90% as per western literature. Other associated anomalies should also be looked for lung to head ratio (LHR) and lung-thoracic ratio (LTR) have been used as prognostic markers. **Table 1** summarizes the prenatal ultrasound findings in CDH.

#### Others

*Fetal echo* is done to confirm and evaluate the details of concurrent heart disease. *Three-dimensional ultrasound* has been used to confirm the antenatal diagnosis and accurately assess the perinatal outcome. *Fetal MRI* is increasingly being used for detailed quantitative assessment of complex congenital anomalies including CDH. It is also useful to calculate lung volumes and reliably assess the degree of liver herniation.

### Postnatal Diagnosis

*Plain radiograph of chest and abdomen* shows absence of diaphragmatic dome on the affected side with herniation of bowel loops into the hemithorax in addition to the mediastinal shift (**Fig. 2**). Postnatal echocardiography is indicated for associated heart anomalies and to detect PPHN. Measurement of *preductal arterial blood gas (ABG)* is a cornerstone for attempting to establish clinical predictive criteria in CDH. The newborn is considered stable, if the  $\text{PaO}_2$  is greater than 100 mm Hg and  $\text{PCO}_2$  is less than 50 mm Hg. The diagnosis of PPHN in CDH is usually made on the basis of a preductal or postductal saturation gradient. *Upper GI contrast study* may be useful in Morgagni hernia when there is intermittent herniation of bowel and a normal X-ray appearance.

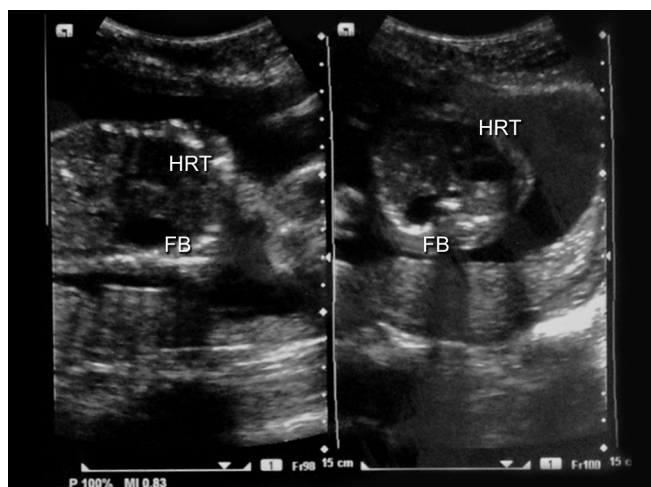
## MANAGEMENT

Medical therapy of CDH entails optimizing oxygenation while avoiding barotrauma, using gentle ventilation and permissive hypercarbia. Newer modalities such as high-frequency oscillatory ventilation (HFOV), intratracheal pulmonary ventilation (ITPV), inhaled nitric oxide (iNO) and extracorporeal membrane oxygenator (ECMO) can be used in severe cases; however, they have not been shown to clearly improve the outcome. The available evidence suggests that outcomes are better when infants with CDH are delivered at experienced centers, the surgical repair is delayed until hemodynamic and respiratory stability is achieved, and by the use of nonaggressive mechanical ventilation and permissive hypercapnia.

### Perinatal Stabilization

The indications for fetal stabilization are LTR of less than 0.2 in the absence of any severe associated anomalies in a near term fetus of at least 36 weeks gestation. The protocol for fetal stabilization includes:

- Monitoring of fetal respiratory movement and heart beat by ultrasonography
- Administration of morphine (20–30 mg) and diazepam (5 mg) to the mother



**Figure 1** Prenatal ultrasonogram at 24 weeks gestation and stomach fundic bubble (FB) at the same cross-sectional level as the heart (HRT) suggestive of congenital diaphragmatic hernia

**Table 1** Features described in literature on antenatal ultrasonography in fetus with congenital diaphragmatic hernia

1. Major mediastinal shift
2. Intrathoracic stomach/bowel/liver
3. Polyhydramnios
4. Reduced fetal abdominal circumference
5. Fetal pulmonary artery diameters on Doppler US
6. Fetal LHR (LHR of < 1.0 suggests bad prognosis)
7. LTR (LTR of < 0.2 suggests bad prognosis)
8. Nakata index: Right lung area/thorax area ratio (< 0.11 suggests bad prognosis)
9. Fetal lung volume on 3D US
10. Fetal nuchal translucency thickness (as a marker of intrathoracic compression-related pulmonary hypoplasia)
11. Associated anomalies

Abbreviations: LHR, lung-head ratio; LTR, lung-thoracic ratio.



**Figure 2** Chest radiograph showing herniation of bowel loops into the left hemithorax and mediastinal shift to right, suggestive of left-sided congenital diaphragmatic hernia

- Confirmation of any interruptions in fetal movement followed by a cesarean section
- Administration of muscle relaxant pancuronium (0.5 mg) through the umbilical vessels
- Intubation before clamping of the umbilical cord
- HFOV without bagging.
- Perinatal stabilization has been found to be effective in preventing PPHN, improving the survival rate of patients with severe CDH.

### Postnatal Resuscitation

A neonate with suspected or confirmed diagnosis of CDH must be delivered at a tertiary care center where facilities for HFOV, ITPV, iNO, ECMO, etc. are readily available and neonatal surgical expertise is at hand. Due to cardiorespiratory instability, transfer of these patients is extremely precarious and should be avoided. Delivery should be planned at term; a prenatal diagnosis of CDH alone is not an indication for cesarean section. Bag and mask ventilation is contraindicated during resuscitation of the neonate as it can distend the stomach and intestines with air and thus worsen the respiratory compromise. The newborn should be immediately intubated in the delivery room. Decompression of the stomach by placement of a nasogastric tube and aspiration is extremely helpful. The baby should then be shifted to the neonatal intensive care unit (NICU) for placement of arterial and venous access through the umbilicus, and baseline investigations including preductal ABG, chest X-ray, echocardiography should be sent. A transcutaneous saturation probe should be placed on the right upper limb to record the preductal saturation ( $\text{SpO}_2$ ). As for all neonates, meticulous attention should be paid to thermoregulation, glucose homeostasis and hemodynamic circulation. Avoidance of any stressful stimuli which can exacerbate PPHN is important. Different ventilator modalities should be tried to maintain a  $\text{PaO}_2$  of greater than 85 mm Hg. The surgeons should be informed about the admission of such a neonate in the NICU so that they can coordinate with the neonatologist regarding the optimal time for surgery.

### Timing of Surgery

Controversy still exists regarding the best time for surgical intervention in CDH. The possibilities are:

- In utero
- Emergent (within 2–4 hours after birth or arrival of the patient in our context)
- Urgent (within 24 hours of birth or arrival)
- Delayed (not related to any particular time cut-off; instead it is a delayed primary repair done after physiological stabilization of the neonate)

A Cochrane analysis published in 2002 could not delineate any substantial advantage of delayed repair over an urgent surgical correction of CDH.

*Fetal surgery* is promising as it may help to ameliorate the progression of PPHN in the fetus. However, it is plagued with a high incidence of preterm labor and fetal loss. In addition, it has not shown an improved outcome. The plug the lung until it grows (PLUG) and fetal endoscopic tracheal occlusion (FETENDO) techniques are minimally invasive alternatives to fetal surgery; however, even they have failed to show any improvement in outcome.

### Ventilatory Stabilization and Treatment of Persistent Pulmonary Hypertension of the Newborn

Modes of ventilation used in CDH are summarized in **Table 2**. Increased pulmonary vascular resistance is an almost universal

finding in CDH even when not clinically manifest by right-to-left shunting at the ductal level. The diagnosis of PPHN in CDH is usually made on the basis of a preductal or postductal saturation gradient. There are three distinct groups into which these very newborns with CDH can be categorized: (i) minimal pulmonary hypoplasia, (ii) unilateral hypoplasia and (iii) bilateral hypoplasia. The first group probably does not need pharmacologic support, while in the last, it probably does not help. Management of PPHN has been already discussed in a previous chapter.

Key aspects of management are outlined in **Box 1**.

#### BOX 1 Key aspects of management of CDH

- *In utero* referral of prenatally diagnosed CDH to experienced center with advanced neonatal intensive care facilities
- Planned delivery at term
- No bag and mask ventilation
- Immediate intubation of the newborn in the delivery room
- Nasogastric tube placement and frequent aspiration of gastric contents and air
- Shifting to the NICU for respiratory and hemodynamic stabilization after baseline investigations
- Gentle ventilation and permissive hypercapnia
- Delayed surgical intervention after physiological stabilization
- CDH is a physiological emergency and not a surgical emergency.

### The Operative Technique

#### Surgery

Details of surgical technique are beyond the purview of this chapter. Minimally invasive techniques such as laparoscopic or thoracoscopic repair of CDH are best suited for delayed presentation in stable neonates.

#### Postoperative Care

The preoperative and perioperative resuscitation measures are continued in the postoperative period. Enteral feedings are started when nasogastric aspirates decrease. Drain can be removed when it stops functioning and there is no hemo- or pneumothorax on chest X-ray.

#### Neonatal Lung Transplantation

One of the several innovative therapies that have been described for high-risk CDH include lung transplantation. This option is often discussed as a potential solution and has some experimental support. The clinical experience has been limited to few patients of CDH.

### COMPLICATIONS

Recurrence of CDH is seen in 10–50% of cases with agenesis of diaphragm requiring prosthetic patches and is difficult to manage surgically. Long-term complications such as failure to thrive, chronic pulmonary disease, neurodevelopmental delay, esophageal dysmotility and reflux are seen in half the patients ever since the survival of neonatal CDH has improved. Although alveolar growth is known to occur till 8 years of age, these children have emphysematous lungs and may develop a bronchopulmonary dysplasia like picture.

### OUTCOME AND PROGNOSTIC FACTORS

The mortality rate associated with CDH remains high all over the world (30–70%) despite great advancements in biotechnology. Survival is dismal in developing countries lacking infrastructure. In a recent study by diaphragmatic hernia research and



**Table 2** Different modes of ventilation used in congenital diaphragmatic hernia

Mode of ventilation	Characteristics	Advantages	Disadvantages
CMV	High PIP $\leq 25$ cm H <sub>2</sub> O, high rates, target PaO <sub>2</sub> of $>85\%$	Simple routine principles of ventilation, can be done in smaller set-ups	High PIP associated with VILI-barotrauma, pneumothorax and BPD
Permissive hypercapnia	Maintain PaCO <sub>2</sub> of 40–50 mm Hg	Less VILI	Respiratory acidosis
HFOV	Oscillations at a frequency of 3–15 Hz	Maintains PEEP without VILI	Needs specialized equipment
ITPV	Constant flow of humidified gas through reverse Venturi catheter kept at distal end of the endotracheal tube	Reduces physiological dead space, facilitates expiration and improves elimination of CO <sub>2</sub>	Needs specialized equipment
iNO	Used in conjunction with HFOV	Vasodilator for pulmonary vasculature	May not be available in smaller set-ups
Liquid ventilation	Perfluorocarbons-inert liquids with low surface tension and high solubility for respiratory gases (administered daily; total cumulative doses of $36 \pm 8$ mL/kg over 5–6 days)	Used in conjunction with HFOV, iNO	May not be available in smaller set-ups
ECMO	VA or VV bypass	Used when no response to all other modes	Hemorrhagic complications, provides short-term support
Surfactant	Not useful in CDH		

*Abbreviations:* CMV, conventional mechanical ventilation; HFOV, high frequency oscillatory ventilation; ITPV, intratracheal pulmonary ventilation; iNO, inhaled nitric oxide; ECMO, extracorporeal membrane oxygenation; PIP, peak inspiratory pressure; VILI, ventilator induced lung injury; VA, venoarterial; VV, venovenal; PEEP, positive end expiratory pressure; BPD, bronchopulmonary dysplasia.

exploration; advancing molecular science (DHREAMS) group, it was found that survivors of CDH had lower developmental scores at age of 2 years. Factors associated with developmental delays were need for ECMO, supplemental oxygen at 28 days of life, discharge on enteral tube feeds, need for readmission and lower socioeconomic status.

Poor prognostic factors for survival in CDH are listed in **Box 2**. PPHN is the most challenging factor that ultimately determines the final outcome. In a developing country like ours, an antenatal diagnosis may not be available in many and the neonate may arrive after few hours or days of birth with respiratory distress. There is a need for stratification of risk to decide the management strategy. These neonates can be broadly divided into three groups:

**Group 1** Neonates who present later than 6 hour of birth are relatively stable. They can be taken up for an urgent surgery after about 4 hour of arrival following confirmation of diagnosis and initial resuscitation and investigations. The survival rates are usually good.

**Group 2** Includes physiologically unstable patients as per criteria described in **Table 3**. They require postnatal resuscitation and

stabilization over few days before they can be taken up for surgical repair safely.

**Group 3** Those with very severe pulmonary hypoplasia who do not stabilize despite of all measures including ECMO. To decide timing about surgical repair in this group of patients is extremely difficult as they shall never stabilize. These patients may be either left alone or operated when the treating physicians believe that there is no further chance of improvement. Survival rates are poor.

### Honeymoon Period

Honeymoon period in the context of neonatal CDH refers to a transient stable interval during which adequate oxygenation (PaO<sub>2</sub>  $> 100$  mm Hg + PCO<sub>2</sub>  $< 50$  mm Hg) is maintained with maximal conventional ventilatory and supportive therapy. This phenomenon is usually seen in first 48 hours of life and has been

**Table 3** Postnatal predictors of outcome of CDH

X-ray assessment of contralateral lung
Blood gas derangement (initial blood gases and in relationship to maximal ventilatory settings)
Initial PaO <sub>2</sub> and PaCO <sub>2</sub> , pH, best postductal PaO <sub>2</sub> and worst: PaCO <sub>2</sub> after 6 hours of treatment, best PaCO <sub>2</sub> after 48 hours of treatment, $VI=RR \times MAP \times PaCO_2$ , $MVI=RR \times PIP \times PaCO_2/1,000$
Indices of cardiopulmonary stability/pulmonary hypertension: $V_t$ , pulmonary compliance/CRS, dynamic compliance, CO <sub>2</sub> index, A-aDO <sub>2</sub> , OI, Bohn's criteria (four quadrants), MGI (ratio between diameters of pulmonary arteries and descending aorta), MGI and birthweight. (four categories)
Other criteria: Prenatal diagnosis, associated anomalies especially, cardiac defects, prematurity, low birthweight, major air leak, Apgar scores at 1 and 5 min, lack of honeymoon period (continued low PaO <sub>2</sub> )

*Abbreviations:* VI, ventilation index; RR, respiratory rate; MVI, modified ventilation index; MAP, mean airway pressure; PIP, peak inspiratory pressure;  $V_t$ , initial tidal volume; CRS, compliance of respiratory system; A-aDO<sub>2</sub>, alveolar-arterial difference; OI, oxygenation index; MGI, McGoon index.

#### BOX 2 Poor prognostic factors for survival in CDH

- Prenatal diagnosis before 25 weeks of gestation
- Coexisting severe congenital heart disease or other major associated anomalies
- Fetal LHR less than 1.0
- Fetal LTR less than 0.2
- Nakata index: Right lung area/thorax area ratio less than 0.11
- Presence of polyhydramnios\*
- Diaphragmatic agenesis requiring prosthetic mesh
- Herniation of stomach into the hemithorax\*
- Right-sided CDH\*
- Severe pulmonary hypertension at 1 month of age
- Prematurity
- Low birthweight
- Need for ECMO.

\*Equivocal studies, hence role not confirmed.



known to last for about 24 hours after which the subjects deteriorate because of PPHN and left to right shunting. The honeymoon group of patients has a lesser degree of pulmonary hypoplasia and is known to have better outcome than the no-honeymoon group of neonates who have overwhelming pulmonary hypoplasia.

### FORAMEN OF MORGAGNI HERNIA

Morgagni hernia occurs through a diaphragmatic defect in the anteromedial part. It usually presents in older children with an acute gastrointestinal crisis due to strangulation of the herniated colon and small intestine through the narrow defect. Rarely, it can be seen in neonates as an incidental finding on chest radiograph—air-fluid levels or as a mediastinal mass. A sac is almost always present and there is no pulmonary hypoplasia or PPHN associated. There may be nonrotation of gut. Rarely, it is seen as a part of Cantrell's pentalogy with several other midline defects. A GI contrast study or computed tomography can confirm the diagnosis. Operative correction can be performed through the abdominal route by reducing the contents and repairing the defect. Thoracoscopic and laparoscopic approaches are also useful as these children are much older and usually stable.

### EVENTRATION OF DIAPHRAGM

Congenital ED may present analogous to neonatal CDH with sac. More commonly, infants with ED become symptomatic beyond the neonatal period with recurrent lower respiratory tract infections and episodic respiratory distress. The diaphragmatic muscle though completely present is atretic and fibrosed, hence remains elevated into the thorax. Acquired ED occurs due to phrenic nerve injury either during birth (Erb's palsy) or following surgical correction of congenital heart disease. Eventration can either be partial or complete, left sided or right sided.

The patient may be absolutely asymptomatic and the finding of elevated dome of diaphragm on X-ray may be incidental (**Fig. 3**). Diagnosis of ED is confirmed by visualization of paradoxical movements on fluoroscopy due to phrenic nerve paralysis. Computed tomography can also help when in doubt.

A small ED can be left alone in an asymptomatic patient unless there is atelectasis of the ipsilateral lung compromising its growth.



**Figure 3** Chest radiograph showing elevated left hemidiaphragm suggestive of eventration of diaphragm (ED)

A large ED or a symptomatic one needs surgical intervention in the form of plication with nonabsorbable sutures. Right-sided ED is better accessed by thoracotomy whereas left-sided repair of ED is preferred via abdominal route. In the neonate having respiratory distress, the differentiation between CDH with sac and ED is often made intraoperatively. Thoracoscopic and laparoscopic methods of plication can also be done in stable patients. The prognosis of infants with ED is much better than CDH.

### MORE ON THIS TOPIC

- Bhat YR, Kumar V, Rao A. Congenital diaphragmatic hernia in a developing country. *Singapore Med J*. 2008;49:715-8.
- Chiu P, Hedrick HL. Postnatal management and long-term outcome for survivors with congenital diaphragmatic hernia. *Prenat Diagn*. 2008;28:592-603.
- Logan JW, Cotten CM, Goldberg RN, Clark RH. Mechanical ventilation strategies in the management of congenital diaphragmatic hernia. *Semin Pediatr Surg*. 2007;16:115-25.
- Moyer V, Moya F, Tibboel R, et al. Late versus early surgical correction for congenital diaphragmatic hernia in newborn infants. *Cochrane Database Syst Rev*. 2002;1:CD001695.
- Sarin YK. Paradigm shift in management of congenital diaphragmatic hernia in newborn. *Pediatric Clinics of India*. 2008;43:364-84.
- Van Meurs KP, Rhine WD, Benitz WE, et al. Lobar lung transplantation as a treatment for congenital diaphragmatic hernia. *J Pediatr Surg*. 1994; 29:1557-60.
- Wynn J, Krishnan U, Aspelund G, et al. Outcomes of congenital diaphragmatic hernia in the modern era of management. *J Pediatr*. 2013;163:114-9.

### IN A NUTSHELL

1. CDH is a medical emergency and not a surgical emergency. Surgery should be done after physiological stabilization of the neonate.
2. PPHN associated with CDH need expert management by skilled neonatologists both before and after surgery.
3. Prenatal diagnosis can be made in 40–90% cases in the west, thus facilitating referral to specialized tertiary centers. Characteristic feature on ultrasonography is the detection of heart and stomach at the same cross-sectional level.
4. Respiratory distress at birth associated with abnormal bulge of hemithorax, mediastinal shift to opposite side and scaphoid abdomen are suggestive of a diagnosis of CDH.
5. Preductal ABG is the cornerstone for establishing clinical predictive criteria in CDH. The newborn is considered stable, if the PaO<sub>2</sub> greater than 100 mm Hg and PCO<sub>2</sub> less than 50 mm Hg.
6. Despite availability of advanced methods of ventilation and pharmacological support, the best mode of treatment and the ideal timing of surgery still remain elusive.
7. Medical therapy of CDH entails optimizing oxygenation while avoiding barotrauma, using gentle ventilation and permissive hypercarbia.
8. Prenatal diagnosis before 25 weeks of gestational, coexisting severe congenital heart disease and fetal LHR less than 1.0 on the antenatal ultrasound are some of the poor prognostic factors.
9. The mortality rate remains high all over the world (30–70%) despite all efforts. Survival is dismal in developing countries lacking in infrastructure.
10. Delayed presentation of milder forms of pulmonary hypoplasia has better outcomes.

## Chapter 18.3

# Gastrointestinal and Abdominal Malformations

Satish Kumar Aggarwal

### NEONATAL INTESTINAL OBSTRUCTION

Common gastrointestinal (GI) malformations relate to congenital mechanical obstruction, such as atresia or stenosis, functional obstruction such as Hirschsprung disease (HD) or abnormality of bowel rotation and fixation referred to as malrotation. The causes of neonatal intestinal obstruction are listed in **Box 1**.

#### BOX 1 Congenital intestinal malformations leading to neonatal intestinal obstruction

- Esophageal atresia
- Pyloric atresia (uncommon)
- Duodenal atresia
- Jejunal atresia
- Ileal atresia
- Colonic atresia
- Rectal atresia (uncommon)
- Anorectal malformations
- Meconium disease of infancy
  - Meconium ileus (simple meconium disease)
  - Meconium peritonitis (complicated meconium disease)
- Hirschsprung disease (functional obstruction)
- Congenital hypertrophic pyloric stenosis (onset at 3–4 weeks).

### General Clinical Aspects

Bile-stained vomiting and abdominal distension are the key features of neonatal intestinal obstruction. Timing and degree of abdominal distension vary depending on the level of obstruction. Abdominal distension is directly related to the amount of gas in the gut. At birth, there is no gas in the intestines. With the onset of breathing, some air gets ingested leading to normal distribution of bowel gas soon after birth. Proximal obstructions, such as duodenal and jejunal atresia, present with early vomiting but minimal distension. Distension at birth has limited differential diagnosis: congenital mass lesions (duplications, lymphangioma, retroperitoneal teratoma) and meconium disease of infancy especially giant cystic meconium peritonitis. Ileal and colonic atresia present with gradual distension over 1–2 days and late onset of vomiting.

Most babies born with congenital mechanical bowel obstruction are otherwise well and active. They also accept first few feeds well only to develop vomiting and abdominal distension later. A septic and ill child may develop paralytic intestinal obstruction but in that case the systemic signs will precede intestinal symptom. This may occur in a setting of meconium-stained liquor, premature rupture of membranes, maternal infections and prolonged labor. If a child has passed milk stools, it rules out intestinal atresia.

A baby, who was born normal and healthy and took feeds well but develops bilious vomiting on the 3rd or 4th day and becomes limp and pale suddenly, is most likely to have acute midgut volvulus because of malrotation. Examination will reveal shock and pallor with minimal abdominal signs. Plain abdominal film may show paucity of distal gas with few proximal loops. It may even be normal. This is the most feared entity and although an upper GI contrast study is indicated, there may not be enough time. It is

a fire brigade emergency, requires quick fluid resuscitation and a prompt laparotomy to de-twist the small bowel. Laparotomy may be a part of resuscitation. Failure to act quickly may result in ischemic loss of the entire small bowel with dreaded consequences of short bowel syndrome.

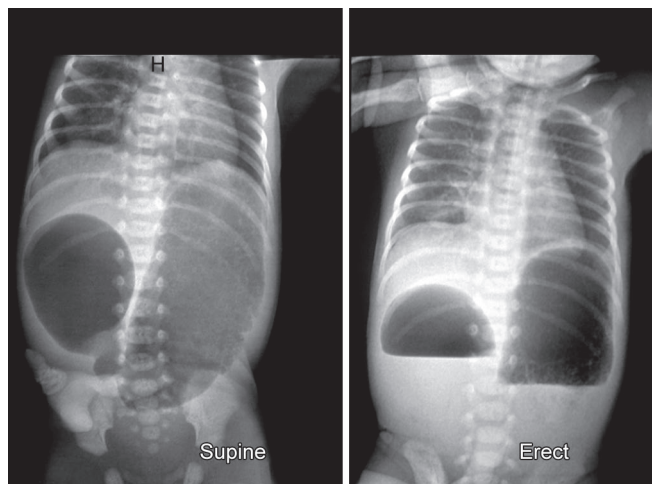
### Imaging

Plain X-ray of the abdomen is the most important imaging tool. An anteroposterior (AP) view should be taken in supine position. Erect view and invertogram are unnecessary and distressing to the neonate. Presence of gas in rectum rules out proximal atresia. Stenosis, however, still remains a possibility. Following diagnoses are possible on plain film:

- Only distended stomach and no distal gas: *Pyloric atresia*
- Distended stomach and proximal duodenum (double bubble) (**Fig. 1**): *Duodenal atresia*. The dimple in between two bubbles is because of the pyloric contraction.
- Proximal few bowel loops seen and no distal loops: *Jejunal atresia*.
- Many distended loops suggest distal obstruction:
  - Many distended loops. Step ladder pattern, many levels on lateral view: *Ileal atresia*
  - Dilated proximal loops, soap bubble appearance and paucity of distal gas: *Meconium ileus*
  - Too many dilated loops with distended abdomen and gas filled loops reaching the periphery: *Hirschsprung disease (HD) or colonic atresia*
  - Calcification on plain film *Meconium ileus (MI) with calcification*. An ultrasound should also be done to look for other causes of calcification such as adrenal calcification, neuroblastoma and teratomas.

### Free Gas on Supine Film

X-ray in an erect position is not necessary to diagnose free gas. Free gas on supine film is seen as *football sign*. The free gas collects in the central abdomen on either side of the falciform ligament, which shows as an oblique shadow in the center of a big blob of gas. Small amount of free gas may be missed on supine film. For this cross table, view in left lateral decubitus position is better. The child lies in lateral position on his left side, X-ray plate is kept against the back and the X-ray beam comes from the front. Small triangular pockets of free air are seen opposite the abdominal wall flanked by bowel loops. Free air may also be seen between the right edge of the liver and the right lateral abdominal wall.



**Figure 1** Plain X-ray in duodenal atresia showing double bubble

### Cross Table Lateral View in Prone Position

The child lies in prone position for 2–3 min with the pelvis elevated by 45° on a soft wedge. X-ray plate is kept along the left or right thigh perpendicular to the table; X-ray beam comes from across the table, centered over the greater trochanter. So, a dead lateral view is taken. This view is of importance in suspected HD and anorectal malformations. In the prone position with pelvis elevated, the gas rises in the rectum. If X-ray shows rectal gas, it almost rules out HD. In anorectal malformations, the distance between the rectal gas and the skin is measured. If it is less than 1 cm, then a primary perineal anoplasty operation can be done. If more than 1 cm, then colostomy should be done and definitive repair deferred for few weeks. The invertogram has become obsolete.

### Contrast Studies

Upper GI contrast studies help in diagnosing proximal bowel obstructions, such as malrotation and duodenal stenosis; lower GI contrast (enema) in lower GI obstructions such as HD and meconium disease. If there is too much gas on plain film, a contrast enema will be helpful and vice versa. Generally, the diagnostic study should be performed with nonionic water-soluble contrast.

### Upper Gastrointestinal Series

The most important and frequent indication is to confirm or exclude malrotation in a neonate presenting with bile-stained vomiting. Normal location of the duodenojejunal junction (DJ) is above and to the left of transpyloric plane. Any abnormality in the location of DJ means malrotation irrespective of other findings. Midgut volvulus may be evidenced by corkscrew appearance of proximal jejunal loops in addition to an abnormally located DJ. One more possible use of upper GI series is in partial upper small bowel obstruction such as duodenal or jejunal stenosis, band obstruction and internal herniation. In such cases, the presentation is usually not in the neonatal period but a few weeks after birth.

### Lower Gastrointestinal Study (Contrast Enema)

It is performed under antibiotic cover. Diagnosis is made with water soluble nonionic contrast. Dye is instilled per rectum till the dilated loops are filled in. If the dye reaches the dilated loops, it rules out atresia. In suspected meconium ileus, there will be microcolon (colonic diameter less than 1 cm). The differential diagnosis of microcolon includes MI and its variants, total colonic aganglionosis and distal ileal atresia.

Appearance of soap bubble appearance on plain film and microcolon in contrast enema calls for therapeutic enema with Gastrografin. Gastrografin contains surface active agents and will dissolve the thick tenacious meconium from the terminal ileum which will be passed per rectum relieving the obstruction. Enema may have to be repeated several times for the first few days to be clinically effective. Care should be taken to hydrate the patient well so that fluid shifts into the bowel lumen and does not cause intravascular dehydration and circulatory insufficiency.

### Ultrasound

It has limited role for evaluation of neonatal obstructions. In suspected malrotation, it is used to see the relationship of the superior mesenteric artery (SMA) and the superior mesenteric vein (SMV). Normally, the SMV is to the right of SMA (same as inferior vena cava and aorta). In malrotation, this is reversed. One can also see corkscrew appearance of jejunal loops in volvulus. Cystic and solid masses can be assessed with ultrasound. A child with distension at birth is a good indication for ultrasound. Rarely, neonatal appendicitis and intussusception can be picked up.

### Principles of Preoperative Management

Provide general neonatal care with monitoring of temperature and SpO<sub>2</sub>. Pass nasogastric (NG) tube and aspirate contents. Leave it on free drainage. Replace NG losses with normal saline every 6 hour. Establish IV access, draw samples for blood tests and start fluid resuscitation. Monitor serum Na and K, and urine output. Send blood sample for hematocrit, counts, urea, electrolytes. Start broad-spectrum antibiotics. A cephalosporin and metronidazole combination is sufficient in most cases. Once hemodynamically stable, obtain a plain abdominal film in AP view. Consult the surgical team and decide, if further contrast study is required. Surgical management will depend on the condition. **Table 1** gives a summary of the management of different conditions. Laparotomy should be planned only after adequate resuscitation and diagnostic work-up. However, there is one exception—malrotation with midgut volvulus, which can be a dire emergency. A description of this anomaly follows for better understanding of the pathophysiology and the nature of emergency.

### MALROTATION WITH MIDGUT VOLVULUS

This is a congenital abnormality that makes the midgut prone to twist in a clockwise manner around the superior mesenteric vessels due to a very narrow base of the mesentery (**Fig. 2**). It results from failure of rotation and fixation of the midgut during 8–12 week of intrauterine life. The DJ junction is abnormally located to the right of midline, the duodenum and cecum are juxtaposed close to each other, and a band (Ladd band) runs from the retroperitoneum across the cecum and duodenum.

Clinical features may be due to volvulus of the small bowel around SMA (most common and most dreaded) or chronic duodenal obstruction due to Ladd bands or due to an intrinsic duodenal stenosis. Volvulus of the midgut occurs most frequently within the first week of life with sudden onset of bile vomiting on 3–5th day. Rapid deterioration occurs because of gut ischemia and the child may present in shock. A quick resuscitation should be followed by an upper GI study, if the child is resuscitable. Many a time laparotomy is required urgently as part of resuscitation. The key to surgery is the root of the mesentery. The volved gut is untwisted, mesentery is widened and Ladd band is divided (**Fig. 3**).

### DUODENAL OBSTRUCTION

Congenital duodenal obstruction can occur because of atresia, stenosis, perforate or imperforate webs and extrinsic compression by bands or duplication cysts. Annular pancreas can cause a total or partial obstruction and may be indistinguishable from atresia. Duodenal atresia arises from failure of recanalization in utero.

Duodenal atresia, the most common cause of duodenal obstruction, occurs in 1 per 5,000 livebirths. 25% cases have associated Down syndrome. In 80% cases, the obstruction is distal to the ampulla of Vater resulting in bilious vomiting. In 20%, it is preampullary causing nonbilious vomiting. Antenatal ultrasound shows polyhydramnios and dilated stomach and duodenum. Duodenal atresia is the most frequent prenatal diagnosis amongst bowel obstructions. Since associated cardiac defects and Down syndrome are common, prenatal diagnosis becomes important to facilitate parental decision on medical termination of pregnancy. Therefore, detection of polyhydramnios with a dilated bowel loop on prenatal ultrasound is an indication of amniocentesis for chromosomal analysis to screen for Down syndrome.

Treatment is surgical. Duodenoduodenostomy is performed under general anesthetic. Postoperatively total parenteral nutrition (TPN) may be required for a few days till the duodenal motility is restored. Prognosis is good if Down syndrome is not associated.



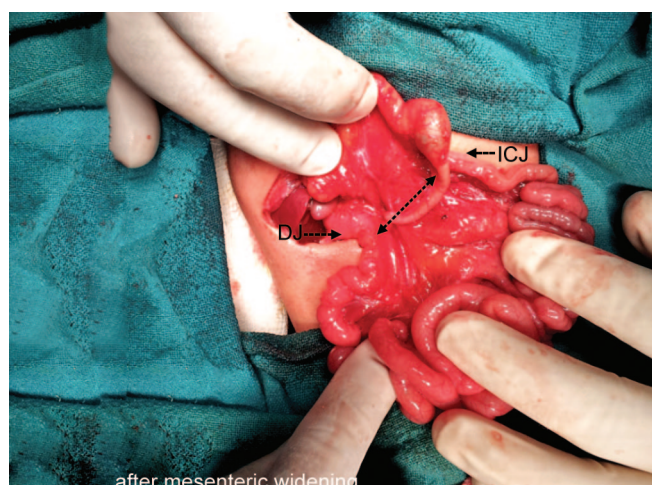
**Table 1** Summary of the management of neonatal intestinal obstruction according to the underlying condition

Condition	Clinical features	Imaging	Treatment	Remarks
Duodenal atresia	Within few hours after birth, bilious vomiting, no abdominal distension	Double bubble sign on plain X-ray	Duodenoduodenostomy	<b>Etiology:</b> <ul style="list-style-type: none"> <li>Failure of canalization</li> <li>Twenty-five percent have Down syndrome.</li> </ul> <b>Differential diagnosis:</b> <ul style="list-style-type: none"> <li>Annular pancreas, duodenal stenosis, duodenal diaphragm</li> <li>Prognosis good if no chromosomal abnormality</li> </ul>
Jejunal atresia	Within 24 hours, bilious vomiting, mild distension	<ul style="list-style-type: none"> <li>Few dilated bowel loops in upper abdomen</li> </ul>	Resection of atresia and end to end anastomosis	<b>Etiology:</b> <ul style="list-style-type: none"> <li>Intrauterine vascular accident</li> <li>Prognosis good</li> </ul>
Ileal atresia	Within 24–48 hours, progressive significant distension, late vomiting, may pass meconium	<ul style="list-style-type: none"> <li>Many dilated loops with air fluid levels on plain film</li> <li>Microcolon on contrast enema</li> </ul>	Resection of atresia and end to end anastomosis	Resect about 5 cm on either side of atresia (poor myoelectric property) and to eliminate lumen disparity.
Meconium ileus	Almost immediately after birth, distension and bilious vomiting, no meconium passed or very tenacious meconium	<ul style="list-style-type: none"> <li>Soap bubble appearance on plain film</li> <li>Microcolon on contrast enema</li> </ul>	<ul style="list-style-type: none"> <li>Gastrografin enema may be therapeutic</li> <li>Laparotomy may be required</li> </ul>	<ul style="list-style-type: none"> <li>Repeat Gastrografin enema may be required</li> <li>Investigate for cystic fibrosis</li> <li>Exclude HD by rectal biopsy</li> </ul>
Hirschsprung disease	No meconium in 24 hours, gradual soft distension, no vomiting despite massive distension (distension because of colonic dilatation)	<ul style="list-style-type: none"> <li>No rectal gas on cross table prone X-ray</li> <li>Transition zone on contrast enema</li> </ul>	<ul style="list-style-type: none"> <li>Rectal washouts for 6–8 weeks</li> <li>Primary pull through at 6–8 weeks</li> <li>May require urgent colostomy</li> </ul>	<ul style="list-style-type: none"> <li>Rectal biopsy is diagnostic</li> <li>Atypical presentation likely in total colonic aganglionosis</li> <li>May present as acute small bowel obstruction requiring colostomy</li> </ul>
Malrotation with midgut volvulus	Within 3–5 days, sudden onset bilious vomiting, rapid deterioration to shock	Plain film may be normal, abnormal location of DJ on upper GI contrast study	<ul style="list-style-type: none"> <li>Urgent Ladd's procedure</li> <li>No time for imaging</li> </ul>	<ul style="list-style-type: none"> <li>In 90% cases, volvulus occurs within the first month of life</li> <li>May also present with recurrent chronic duodenal obstruction.</li> </ul>

Abbreviations: HD, Hirschsprung disease; DJ, duodenojejunal junction; GI, gastrointestinal tract.



**Figure 2** Malrotation with midgut volvulus. Note the twisted bowel on narrow mesentery (double arrow)



**Figure 3** Malrotation. The bowel has been untwisted; mesentery has been widened (dotted line)

Abbreviations: ICJ, ileocaecal junction; DJ, duodenojejunal flexure.

### JEJUNOILEAL ATRESIA (FIGS 4 to 7)

Intestinal atresia refers to a congenital absence of bowel lumen resulting in total obstruction. Unlike duodenal atresia, Jejunoileal atresia is believed to be caused by an intrauterine mesenteric

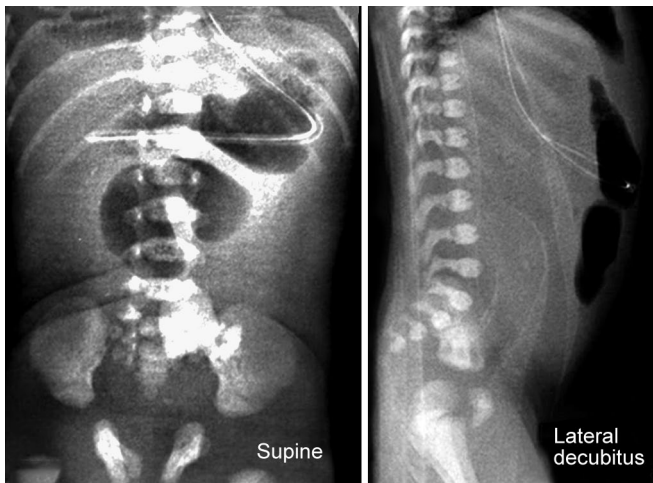
vascular accident. The most common type is type III wherein there is separation of the two ends with a V-shaped defect in the mesentery. Unlike duodenal atresia the incidence of associated malformations is very low.



Clinical symptoms in intestinal atresia depend upon the location of atresia. In proximal obstructions, such as duodenal and jejunal atresia, the abdomen is not distended or minimally distended; onset of bilious vomiting is early. Abdominal distension is much less and is limited to upper abdomen in proximal atresia. If there is proximal obstruction (duodenal or jejunal), the decision for surgery is simple and could be based on plain X-ray alone. The approach may be quite different for distal ileal or colonic obstruction because surgery may not always be required urgently (as in meconium ileus, HD). A contrast enema is required to differentiate ileal atresia from meconium ileus, HD and colonic atresia. In distal ileal atresia, the dye will not reach the dilated segment and there will be microcolon. In HD, a transition zone will be seen. In meconium ileus, the Gastrografin enema may be therapeutic. Treatment of intestinal atresia is by resection of the atresia and end to end anastomosis. Prognosis is good.

### HIRSCHSPRUNG DISEASE (HD) IN THE NEWBORN

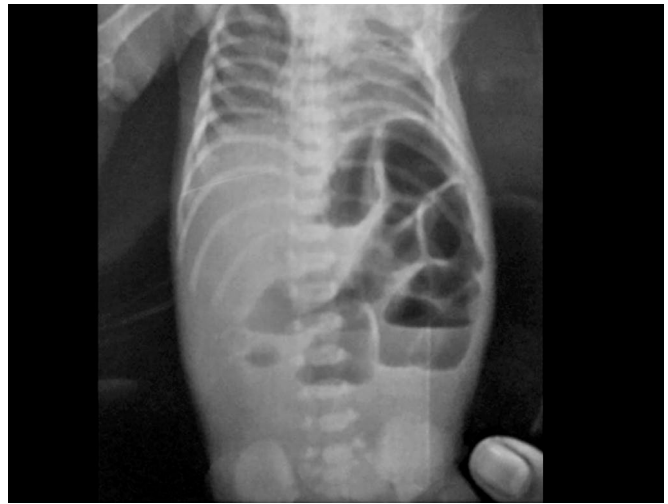
Hirschsprung disease can present in the neonatal period as failure to pass meconium within 24 hours of birth, or full blown small bowel obstruction.



**Figure 4** Jejunal atresia. Plain X-ray in supine and lateral decubitus views. Only proximal loops are dilated with no distal gas



**Figure 5** Operative picture of the same patient as in Figure 4. Note the type I atresia in the proximal jejunum. The proximal bowel is hugely dilated as compared to the distal bowel



**Figure 6** Mid-ileal atresia. Note many dilated bowel loops with air fluid levels



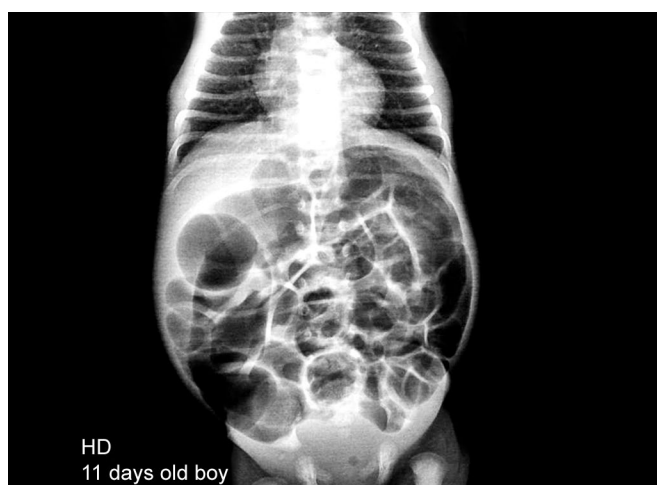
**Figure 7** Operative picture of the same patient as in Figure 6. Note the type III atresia and the difference in the lumen of proximal and distal bowel. This was an *Apple Peel* atresia

### Failure to Pass Meconium within 24 hours

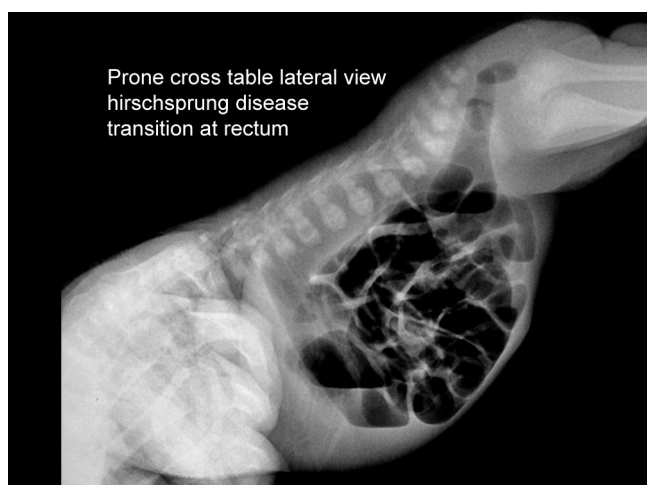
This is the most common presentation. Gradually, abdominal distension occurs. The child continues to accept feeds and there is no vomiting. Plain X-ray (**Fig. 8**) shows many gas filled loops all over the abdomen. Prone cross table lateral view (**Fig. 9**) shows no gas in the rectum. Diagnosis is made by contrast enema which shows typical transition zone (**Fig. 10**). Rectal biopsy provides the most definitive diagnosis. In the biopsy specimen, the acetylcholinesterase activity is raised, ganglion cells are absent and nerve bundles are hypertrophied.

### Management

The baby is put on rectal washouts with normal saline twice or thrice daily to help bowel decompression. Oral feeds are given. Child is sent home on daily rectal washouts. At 6–8 weeks, when the child has shown satisfactory growth, a definitive pull through operation is performed. The current trend is to perform open or laparoscopic primary pull through. If response to washouts is not good, a stoma may need to be created. At operation the transition zone is identified as shown in **Figure 11**.



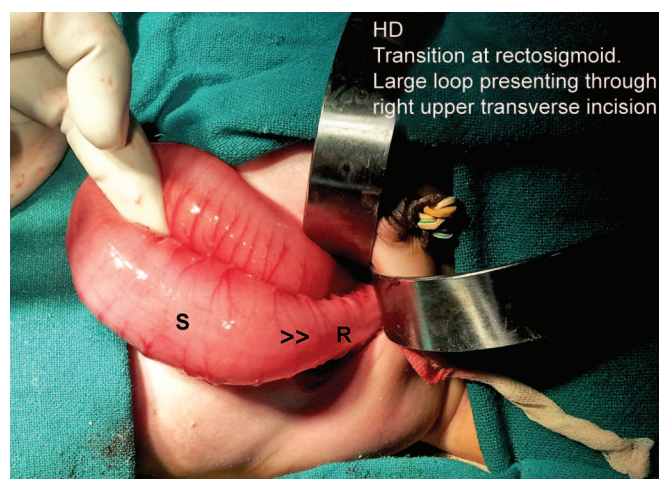
**Figure 8** Plain X-ray in Hirschsprung disease (HD). Note peripherally dilated loops suggestive of large bowel loops. Also the pelvic gas is deficient



**Figure 9** Prone cross table view in Hirschsprung disease (HD). Note the transition zone



**Figure 10** Contrast enema in the same patient as in Figures 8 and 9. Rectosigmoid transition is seen. Note that the same information is obtained on prone cross table lateral film



**Figure 11** Operative picture showing the transition zone (double arrow) in HD  
Abbreviations: R, rectum; S, sigmoid colon; HD, Hirschsprung disease.

### Full Blown Small Bowel Obstruction

Full blown small bowel obstruction with bilious vomiting, distension and failed passage of meconium is often difficult to differentiate from ileal atresia. This presentation is usually seen in total colonic aganglionosis. Contrast enema is helpful in diagnosis. It shows microcolon with a rounded splenic flexure. Proximally, there are several dilated loops of small bowel. An urgent laparotomy is required with creation of a stoma.

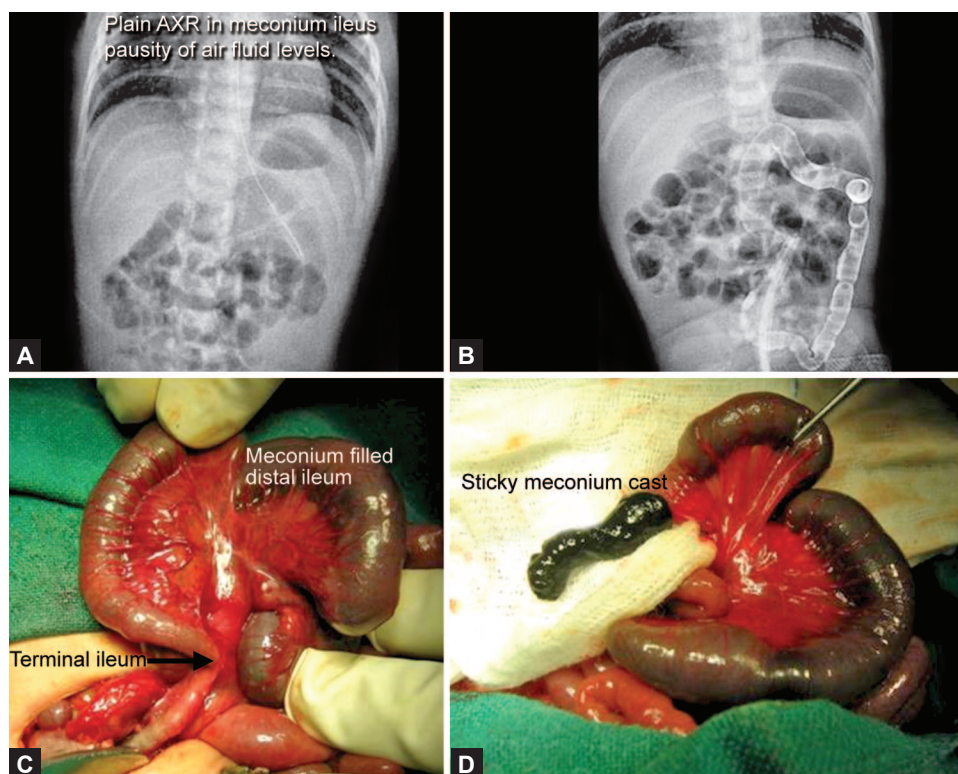
### MECONIUM ILEUS (MI)

It is characterized by retention of thick and tenacious meconium in the distal small bowel causing obstruction. Pancreatic deficiency and cystic fibrosis (CF) are known to be associated in about 80%. Seen in 15% cases of CF, MI is the earliest manifestation of CF. The meconium is rich in proteins making it thick and viscid. There is further contribution by decreased gut motility and defective secretory properties leading to increased mucin content in the meconium. Antenatally, this can be picked up on ultrasound as hyperechoic bowel contents. Suspicion of MI with a family history

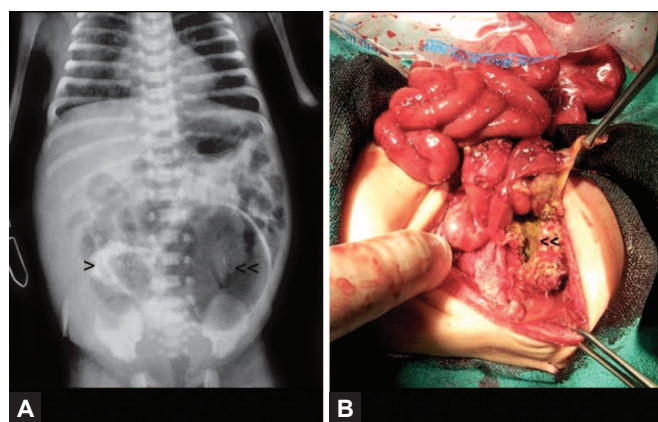
of CF should lead to amniocentesis for evaluation of delta F508 mutation on the CF gene and DNA polymorphism. If positive, the pregnancy should be terminated.

Postnatally, the presentation may be that of *simple MI* or *complicated MI*. Simple MI (**Figs 12A to D**) presents with abdominal distension at birth, bilious vomiting and failure to pass meconium. Distension gradually increases. The dilated bowel loops may be visible and may indent on pressure. Digital rectal examination is difficult as the small rectal caliber does not allow insertion of the finger. Complicated MI may have volvulus, atresia, perforation meconium peritonitis or giant cystic meconium peritonitis. At birth, severe abdominal distension is usually present with erythema of the wall. A palpable mass may be there suggesting a cyst formation. Perinatal perforation may also lead to tracking of meconium into the scrotum through a patent processus vaginalis. Plain X-ray in simple form shows a soap bubble appearance in the right lower abdomen due to mixing of air and meconium. Proximal loops are dilated but air fluid levels are not many. Complicated form may show calcification indicating antenatal bowel perforation (**Figs 13A and B**). A mass





**Figures 12A to D** Simple meconium ileus. (A) Plain X-ray showing few dilated small bowel loops but no air fluid levels; (B) Contrast enema showing microcolon; (C) Operative: distal ileum collapsed. Proximal ileum filled with thick meconium; (D) Dilated ileum opened to reveal thick tenacious viscid meconium



**Figures 13A and B** Complicated meconium disease. (A) Plain X-ray showing dilated loops and calcification (single arrow). The large blob of air in left iliac fossa is due to a perforation resulting in air filled meconium cyst (double arrow); (B) Operative: the cyst has been opened. Calcified area is also seen (double arrow)

effect may be seen due to cyst formation. Contrast enema shows microcolon. The dye refluxes into the ileum showing meconium pellets as filling defects. In simple MI, Gastrografin enema may be therapeutic as described earlier.

Nonoperative treatment with Gastrografin can be attempted when other surgical causes have been ruled out; the child is well hydrated and antibiotics have been given. Possible complications are rectal and small bowel perforation, hypovolemic shock and necrotizing enterocolitis (NEC). Success rate with this approach is about 50–60 % only. In the rest and in complicated variety of MI, a laparotomy is indicated.

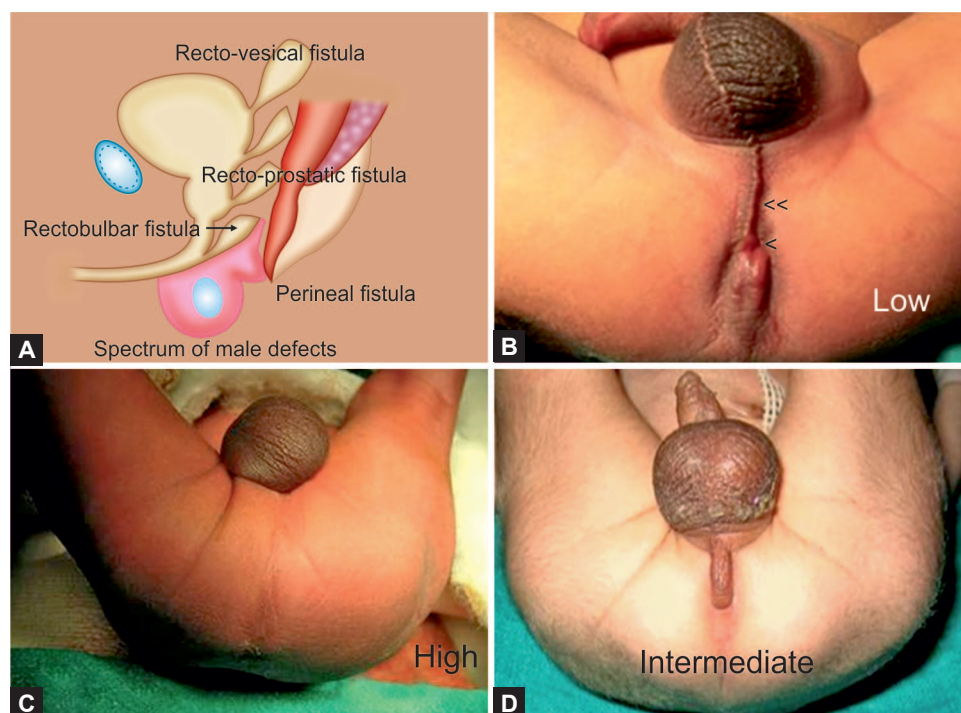
## ANORECTAL MALFORMATIONS

Anorectal malformation (imperforate anus) is a congenital defect in which the child is born without an anal orifice. It occurs in a spectrum and is described separately for boys and girls.

### Anorectal Malformation in Boys (Figs 14A to D)

The rectum terminates either above (*high malformation*) or below (*low malformation*) the levator ani. In high malformations the rectum terminates in the urinary tract through a rectourinary fistula, the level of which may vary from recto-bladder fistula to rectobulbar urethral fistula. Rectobulbar fistula is the commonest malformation. In low malformations, the rectum terminates within about a cm from the skin; there is no rectourinary communication and often the meconium shows up in the perineum through a small opening (perineal fistula) either at the site of normal anus or along the median raphe in the scrotum (anocutaneous fistula). The diagnosis should be made in the delivery room by inspecting the perineum—no anal opening is found. The next step is observing for meconuria—passage of meconium in urine. Meconuria with absence of anal opening in the perineum invariably indicates a high malformation which requires a colostomy in the newborn period. Low malformations do not become evident until 24 hours (which is the time taken for meconium to descend down the gut) when the meconium may show in the perineal fistula. These defects can be managed by a perineal anoplasty without a colostomy in the newborn period.

Associated malformations are seen in 50–60% cases, out of which nearly two-thirds are genitourinary, 25% vertebral, 20% cardiac and 10% GI. 15% have VACTERL or CHARGE association. High malformations have higher chances of associated malformations.



**Figures 14A to D** Spectrum of anorectal malformations in males. (A) Schematic diagram showing different levels at which the rectum can terminate either into the urinary tract or on the perineal surface; (B) Low malformation. Perineal fistula or anal stenosis (single arrow). Note the thin subepithelial tract along the midline scrotal raphe (double arrow); (C) Flat perineum with no anal dimple indicates high malformation; (D) Good perineum with pigmented anal dimple indicates intermediate anomaly probably rectobulbar urethral fistula

### Perineal Examination and Imaging

**Examine perineum** There is no anal opening. Look for gluteal fold, natal cleft and palpate spine or sacrum. Is it a flat bottom? Is there a dimple at the anal site with pigmentation? Is anocutaneous reflex present? Is there a fold of skin under which you can pass a probe (bucket-handle deformity)? Is there any mass? Can you see a thin white epithelial thickening in the median raphe—suggests anocutaneous fistula? Is there any speck of meconium in the perineum—perineal fistula? Is there any abnormality of the external genitalia—bifid scrotum, hypospadias and undescended testes? Look for evidence of meconuria—gas or meconium discharge per urethra.

**Prone cross table lateral shoot abdominal film (Fig. 15)** It is required if clinical information at 24 hours is insufficient to decide whether a colostomy is needed. The technique has been described under the general imaging section. The distance of rectal gas from the skin marker is measured. If less than 1 cm, a perineal anoplasty is performed; there is no need for a colostomy. If more than 1 cm, a colostomy is opened.

### Indicators of High Anomaly where a Colostomy is Indicated

No meconium in the perineum at 24 hours, flat bottom, absent anal dimple or pigmentation, absent anocutaneous reflex, sacral abnormality, meconium in urine (or gas in bladder on X-ray), suggestion of a pouch colon on plain abdominal film and associated bifid scrotum, proximal hypospadias or bilateral undescended testes.

### Indicators of Low Anomaly (Suitable for Primary Anoplasty)

Good perineum, pigmented dimple, anocutaneous reflex, visible fistula in the perineum, bucket-handle deformity—a bridge of skin

over the anal site under which an instrument can be passed and meconium can be seen under the skin.

When a colostomy is performed at birth, the definitive pull through operation is performed at few weeks. In the waiting period, the following investigations are carried out: echocardiography, renal ultrasound, sacral X-ray to determine sacral ratio, X-ray spine, and distal cologram. Primary pull through without a colostomy is also performed by some surgeons at birth. However, it requires a careful selection of patients (no cardiac malformation, good weight, no major distension and no meconuria). Miniature cystoscope is used to locate the site of rectourinary fistula.

### Anorectal Malformation in Girls

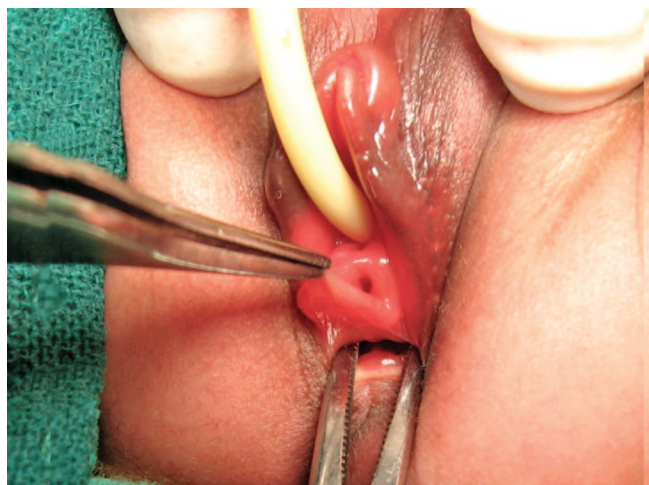
Most anomalies in girls are low and the hindgut opens within the vestibule through a small opening referred to as *anovestibular fistula* (Fig. 16). This is the commonest anorectal malformation in females. Bowel is decompressed but not adequately. The opening is very small often hidden in the posterior fourchette behind the vagina and it requires diligent examination in good light to identify the anovestibular fistula. At times the opening is easily seen, is wider, and has anal folds visible—this is called *vestibular anus* (Fig. 17). The bowel decompression is better. The number of openings in the vulva gives a good guide for diagnosis of anorectal malformations in females (Figs 18A to D):

- **Three openings:** Anovestibular fistula (commonest), rectovestibular fistula, perineal fistula, anterior ectopic anus
- **Two openings:** Rectovaginal fistula (rarely vestibular fistula with vaginal atresia)
- **One opening (Cloaca):** The vulva is small. The child passes urine and stools through the common opening. The vagina may be distended (hydrocolpos) and present as a lower abdominal mass. Urinary system may be obstructed.





**Figure 15** Prone cross table view in a case of rectobulbar urethral fistula. This is the commonest anomaly in males. The distance between the skin marker (\*) and the rectal gas is shown by dotted line. The rectal gas has descended beyond the coccyx. The perineal appearance is as shown in Figure 14D



**Figure 16** Anovestibular fistula: the commonest anorectal malformations (ARM) in females. Note the small opening behind the vagina in which an instrument has been passed to visualize it. There is a catheter in the urethra



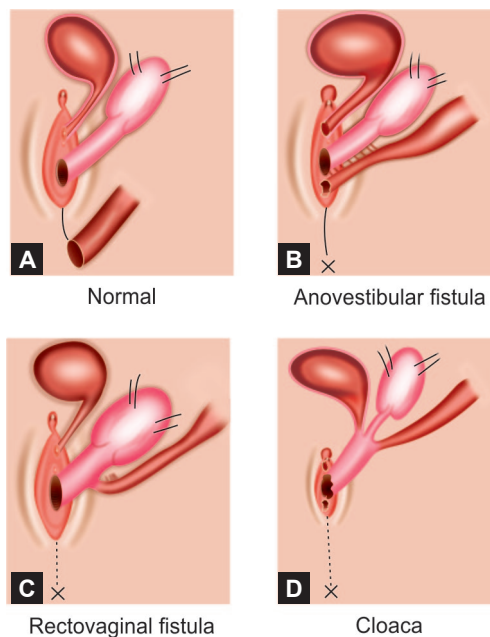
**Figure 17** Vestibular anus. Note the anal folds and a larger easily identifiable opening. There are three openings in the vulva  
Abbreviations: U, urethra; V, vagina.

### Management

- **Anovestibular fistula:** Aim of immediate neonatal management is to ensure gut decompression. This may require gentle dilatation of the anovestibular fistula with or without saline rectal washouts. Elective repair is undertaken at few weeks of age. Usually no colostomy is required.
- **Cloaca:** Urgent investigations are done to assess urinary tract and vagina. Usually a transverse colostomy is performed at birth. If there is hydrocolpos, a vaginostomy is also carried out.
- **Rectovaginal fistula:** It is a rare malformation. It requires a colostomy at birth. Mayer-Rokitansky syndrome should be excluded.

### UMBILICAL AND ABDOMINAL WALL MALFORMATIONS

During the 3rd week of gestation, three embryological folds (cephalic, lateral and caudal) determine the formation of anterior abdominal wall. They have splanchnic and somatic components.



**Figures 18A to D** Spectrum of anorectal malformations (ARM) in females. Perineal examination and number of openings in the vulva is the key to diagnosis. (A) Normal anatomy; (B) Three openings, anovestibular fistula (commonest); (C) Two openings, rectovaginal fistula; (D) Single opening (cloaca)

Splanchnic components are the embryonic foregut, midgut and hindgut respectively. Somatic components form the abdominal wall. Abnormal folding may result in a variety of defects:

- **Cephalic fold defect:** Epigastric omphalocele, diaphragmatic defects, chest wall defects, Cantrell's pentalogy.
- **Lateral fold defect:** Omphalocele or exomphalos, hernia of umbilical cord. Normal folding results in the formation of umbilical ring which closes after the return of midgut from the extra embryonic coelom. Abnormal folding and delayed return of the midgut cause failed closure of umbilical ring allowing herniation of gut or liver through the wide ring. With folding process, the yolk sac is also displaced by the amniotic cavity and the connection between the yolk sac and the

midgut, omphalomesenteric duct, obliterates. This leads to the formation of cord like body stalk which contracts to form the umbilical cicatrix.

- *Caudal fold defect:* Hypogastric omphalocele, exstrophy bladder, cloacal exstrophy.

### Exomphalos and Hernia of Umbilical Cord (Fig.19)

Exomphalos or omphalocele is a herniation of intra-abdominal viscera through a wide umbilical ring into the base of the umbilical cord. There is a three layered covering membrane comprising of parietal peritoneum, Wharton jelly and amnion. When the width of the ring is more than 4 cm, it is termed as exomphalos. If it is less than 4 cm, it is called hernia of the umbilical cord. Large

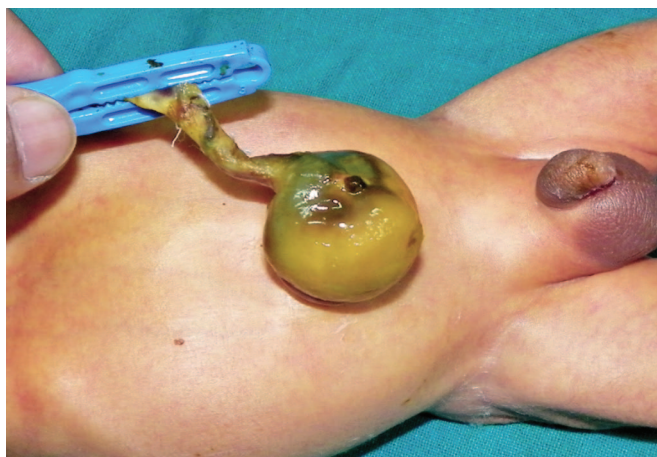


Figure 19 Exomphalos

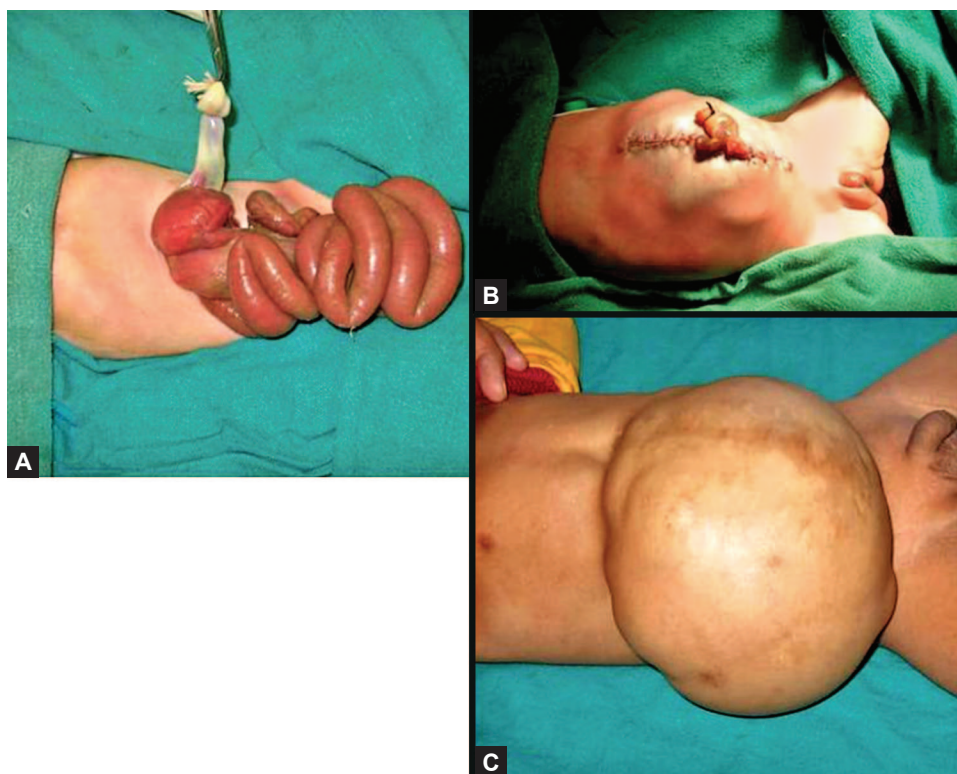
defects cause liver herniation also. Hernia of the umbilical cord never contains the liver. Associated malformations are frequent and determine survival and outcome. On antenatal ultrasound, the condition can be differentiated from physiological state of gut evisceration by identifying the liver as content. Liver is never a part of physiological herniation. Decision for termination of pregnancy should be taken only if the diagnosis has been confirmed and amniocentesis shows abnormal karyotype or there is associated cardiac defect.

If pregnancy is continued, the mother should be referred to a higher center for an elective Cesarean section at term. Postnatal management should aim at prevention of traumatic rupture of the sac, prevention of sepsis and assessment for associated cardiac malformations. The baby should be nursed supine with the sac supported on both sides. Dilute povidone iodine or Mercurochrome (0.5% in alcohol) may be applied on the surface to facilitate epithelialization. The resulting skin covered ventral hernia can be closed at 6 months or later. Urgent surgery may be required if the sac ruptures or there is intestinal obstruction. Primary closure should be done if possible. Often a silo pouch is needed.

### Gastroschisis (Figs 20A to C)

During development of the abdominal wall, the right umbilical vein disappears, leaving a relatively weak area to the right of umbilical ring. Due to a possible vascular insult if this weak area gives way, it leads to evisceration of the bowel, referred to as gastroschisis. Since there is no peritoneal sac, the gut is exposed to urea rich amniotic fluid leading to edema, thickening and at times stenosis. The differences between gastroschisis and exomphalos are shown in the Table 2.

The delivery should occur by an elective cesarean section at term in a tertiary care center. The eviscerated gut should be immediately



**Figures 20A to C** Gastroschisis. (A) The defect is to the right of umbilicus. The gut has no covering membrane; (B) The gut has been covered by skin alone as the fascial covering was not possible due to less space in the abdomen; (C) Resultant ventral hernia after few months. This will be closed in stages



**Table 2** Differences between exomphalos and gastroschisis

Criterion	Exomphalos	Gastroschisis
Embryology	Insult in formation of lateral embryonic fold. Umbilical ring remains wide allowing herniation	Weakness to the right of umbilicus due to regression of right umbilical vein. Umbilical cord normal
Timing	Early in 3rd week	Late second trimester or perinatal. Late event associated with less bowel problems—less exposure to amniotic fluid
Covering	Peritoneum, Wharton jelly and amnion	None
Contents	Gut and liver. Gut is healthy and normal	Gut. It is edematous, may have stenosis or atresia
Associations	Forty percent Cardiac, trisomy 18, Beckwith–Wiedemann syndrome. Less intestinal malformations	Uncommon. Intestinal stenosis and atresia more frequent due to exposure to amniotic fluid
Other associations	Multifactorial etiology	Young mothers, intrauterine growth restriction (IUGR), drug abuse
Treatment	Conservative or surgical	Surgical. Primary closure, skin closure, silo
Prognosis	Bad. Related to associated malformations	Good if gut healthy. Problem related to bowel dysfunction. Needs parenteral nutrition

covered by a cling film to prevent fluid and heat loss. The baby is nursed supine to prevent drag on the mesentery. A quick survey should be made for other anomalies. Intravenous access should be obtained and a fluid bolus given. Surgery should be performed promptly within few hours of birth. Primary fascial closure is the best treatment but may not be possible due to less space in the abdominal cavity and edematous bowel. In that case only skin closure may be obtained and the resultant ventral hernia repaired after few months. In very severe cases, a silo pouch needs to be made. The silo is tightened every day to aim at formal wall closure by 6th or 7th day.

### Meckel's Diverticulum and Related Malformations

Vitelointestinal duct, which normally disappears after the formation of umbilical cicatrix, may persist to cause a spectrum of abnormalities:

- *Meckel's diverticulum*: Persistence of duct at intestinal end
- *Meckel's band*: Fibrous remnant of the duct and its blood supply
- *Umbilical sinus*: Patent distal end of the duct
- *Patent vitelointestinal duct (PVID)*: A completely patent duct causing communication of intestinal lumen to the surface
- *Umbilical polyp*: Proliferation of tissue at the distal end with a persistent Meckel's band running from the umbilicus to midgut and umbilical cyst.

PVID is very evident at birth because it leads to bilious discharge from the umbilicus. Urinary discharge may be due to persistent lumen in the urachus—a remnant of allantois. Meckel's diverticulum may present as an emergency due to inflammation and perforation, bleeding from ectopic gastric mucosa or intestinal obstruction by volvulus around the Meckel's band.

### Umbilical Granuloma

It is a proliferation of granulation tissue during the process of falling off of the umbilical cord in immediate neonatal period. Generally presents as pinkish growth with serous- or blood-stained discharge. It responds to chemical cautery by silver nitrate. Large granulation may require electrical cauterization. They should be distinguished from umbilical polyp which results from persistence of a portion of vitelointestinal duct, which is present at birth, contains mucosal lining, discharges mucus and does not respond to cauterization.

### Umbilical Hernia

It is different from hernia of the umbilical cord. The umbilical cicatrix is largely formed well but is weak leading to herniation of

bowel in the first few days to weeks after birth, the overlying skin is normal and one can feel the small defect in the umbilical cicatrix through the skin. The hernia becomes more prominent when the child cries. Often the parents blame the hernia for crying (although it is the reverse). Most of these hernias resolve spontaneously within the first 2 years of life. Strapping over coins, although frequently practiced should not be done, as it may lead to skin maceration and allergies. Surgery should be offered to persistent hernias beyond 2–3 years. Complications in the form of obstruction, strangulation and perforation are rare.

### IN A NUTSHELL

1. A baby, who was born normal and healthy and took feeds well but develops bilious vomiting on the 3rd or 4th day and becomes limp and pale suddenly, is most likely to have acute midgut volvulus because of malrotation. Quick fluid resuscitation and urgent laparotomy, as part of continuing resuscitation, may be lifesaving.
2. Intestinal atresia and Hirschsprung disease (HD) are the most common causes of neonatal intestinal obstruction.
3. Bile-stained vomiting and abdominal distension are cardinal signs of neonatal intestinal obstruction.
4. Plain X-ray abdomen is the single most important diagnostic investigation for neonatal intestinal obstruction.
5. Failure to pass meconium within 24 hours of birth should alert for HD. Eighty percent of all cases of HD are diagnosed at birth. They should be managed by rectal washouts initially followed by early definitive pull through without colostomy.
6. Contrast enema using Gastrografin may be therapeutic for simple meconium ileus.
7. Most anorectal malformations in males are high type with rectourinary communication. They usually require a colostomy at birth. Most anorectal malformations in females are low type which can be managed without a colostomy at few weeks of age.
8. Invertogram is obsolete. Prone cross table lateral film gives useful information about the level of the malformation.
9. Omphalocele is associated with systemic malformations of other systems, such as cardiac defects, while gastroschisis is associated more with intestinal obstruction due to local factors.
10. Omphalocele with intact sac may be managed conservatively, but gastroschisis should be repaired within few hours after birth.

**MORE ON THIS TOPIC**

- Ashcraft KW, Murphy JP, Sharp RJ, et al. *Pediatric Surgery*. 3rd ed. Philadelphia: WB Saunders Company; 2001.
- Choudhury P, Bagga A, Chugh K, et al. *Principles of Pediatric and Neonatal Emergencies*. 3rd ed. New Delhi: Jaypee; 2011.
- Mathur MK, Aggarwal SK, Ratan SK, Sinha S. Laparoscopic-assisted transanal pull-through for Hirschsprung's disease: comparison between partial and near total laparoscopic mobilization of rectum. *J Indian Assoc Pediatr Surg*. 2014;19:70-5.
- Najmaldin A, Rothenberg S, Crabbe D, Beasley S. *Operative Endoscopy and Endoscopic Surgery in Infants and Children*. London: Hodder Arnold; 2005.
- Pant Nitin, Aggarwal SK, Ratan SK. Laparoscopic repair of hernia in children: comparison between ligation and nonligation of sac. *J Indian Assoc Pediatr Surg*. 2014;19:76-9.
- Spitz L, Coran AG. *Operative Pediatric Surgery*. 6th ed. London: Hodder Arnold; 2006.
- Ziegler MM, Azizkhan RG, Weber TR. *Operative Pediatric Surgery*. International ed. New York: McGraw-Hill; 2003.



## Chapter 18.4

# Genitourinary Malformations

Satish Kumar Aggarwal

Genitourinary malformations (GUM) account for 50% of all malformations detected on antenatal ultrasound scan. Nearly two-thirds of them are hydronephrosis. Antenatal ultrasound has made a huge impact on diagnosis and management of these malformations by providing insight into their pathogenesis and natural history. Fetal magnetic resonance imaging (MRI) and other modalities have helped in confirming diagnosis and decision making regarding medical termination of pregnancy in select cases of multiple or life-threatening malformations. In most cases, the pregnancy can be continued till term and delivery can take place in a tertiary care center where better neonatal facilities including surgical care are available. Parental counseling is also an important aspect of the care. A small subset of patients may be candidates for in utero interventions, but their results have been disappointing. Stem cell technology and advances in regenerative medicine is the key to future postnatal management of some of these malformations, e.g., laboratory manufactured bladder from stem cells may be the future treatment of bladder exstrophy.

## EMBRYOLOGICAL BASIS

A working knowledge of embryology is essential to understand the genesis, morphology and functional implications of GUM. Organogenesis occurs during 3–10 weeks of gestation. Maturation, growth and development continue until term. In the embryonic disc, at an early stage, the mesoderm is arranged in three areas: paraxial, intermediate and lateral plate mesoderm. The genitourinary system originates from the intermediate mesoderm. The cervical portion of the mesoderm (pronephros) disappears, the middle portion (mesonephros) develops into the gonads and the distal portion (metanephros) becomes the kidney. Migration of primordial germ cells from the yolk sac to the mesoderm initiates formation of gonads and the genital ducts. Mesonephric (wolffian) duct communicates with the primitive cloaca which separates into the urinary tract anteriorly and the hind gut posteriorly by ingrowth of urorectal septum. The mesonephric duct develops into the epididymis, vas and seminal vesicles and its communication with the urinary system stays intact as it drains into the urethra as ejaculatory duct. The ureteric bud originates from the mesonephric duct at 4–5 weeks and as it grows outward, it hits the metanephros to initiate nephrogenesis at 6 weeks. The glomeruli of the kidney originate from the metanephros and the collecting system including the pelvicalyceal system and the ureter originate from the ureteric bud. The kidney is formed lower than the gonad but later the kidneys ascend upward and the gonads descend downward. While the kidney derives its blood supply sequentially at different levels, the gonads carry their blood supply with them from the site of origin. Fetal urine production, which starts at 10–12 weeks, contributes for 90% of the amniotic fluid volume. By 14–16 weeks, the genitourinary system is developed nearly completely and antenatal ultrasound can pick up congenital malformations.

In females the paramesonephric (müllerian) ducts develop lateral to the mesonephric (Wolffian duct). Absence of testosterone leads to regression of mesonephric ducts after the ureteric bud has originated for renal and ureteric development at about 6 weeks. The proximal part of paired paramesonephric ducts gives origin to the fallopian tubes while the distal portion, which crosses over to midline and fuses together (uterovaginal canal), gives rise to

uterus and proximal vagina. The distal vagina develops from the urogenital sinus. Therefore, a blind stump of vagina is seen to persist in conditions such as androgen insensitivity syndrome and vaginal (Müllerian) atresia.

Differentiation of external genitalia occurs during 12–16 weeks. Clitoris and phallus develop from genital tubercles, urethra and labia minora from genital folds and the scrotum and labia majora from genital swellings.

## Ureteric Bud Theory

The site of origin of the ureteric bud from the mesonephric duct determines the fate of future kidney and ureters. Normal renal development requires origin of ureteric bud at the normal site on the mesonephric duct. Ureteric bud abnormalities are responsible for a number of anomalies: lateral ureteral ectopia (caudal origin of ureteric bud), duplex system with ureterocele (two ureteric buds), renal dysplasia (off the mark origin of ureteric bud), etc. In complete duplication anomalies of ureteric bud, the upper moiety ureter always opens on the bladder distal and medial to the lower moiety ureter (Weigert-Meyer Law). The upper moiety is also more likely to be dysplastic as the ureteric bud for this moiety does not hit the normal metanephric blastema.

Since embryogenesis progresses simultaneously in several organ systems, an insult to the process is likely to produce multiple malformations—a fact responsible for associations like VACTERL (vertebral, anorectal, cardiac, tracheoesophageal, renal and limb). Renal agenesis on one side is often associated with absent vas or Müllerian agenesis on the ipsilateral side. Similarly 30% cases of high anorectal malformations have associated GUM. Complex embryological processes are involved in rare duplication anomalies with congenital masses. Duplication anomalies may be a spectrum of caudal duplication syndrome with bizarre clinical appearances coupled with varying degrees of internal organ duplications (Fig. 1).

## RENAL MALFORMATIONS

### Renal Agenesis

Unilateral renal agenesis is usually a silent condition, incidentally detected on ultrasound. It may reflect an intrinsic defect of the embryonic mesenchyme, hence association with absent vas and Müllerian agenesis on the ipsilateral side. While operating for hernia in a child if vas is found to be absent, this finding should be



**Figure 1** Caudal duplication. Note two phallus and scrotal sacs. The child also has a presacral mass and anorectal malformation. Internally the bladder and rectum were duplicated

recorded and ultrasound carried out to check for renal agenesis. Bilateral renal agenesis is incompatible with life.

### Renal Dysplasia

Abnormal ureteric bud and/or severe embryonic urinary tract obstruction may lead to renal dysplasia characterized by small lobulated kidney with distorted primitive tubules and presence of cartilage and fibromuscular tissue. In cases of posterior urethral valves (PUV), varying degree of dysplasia occurs depending upon the severity and the timing of onset of fetal urinary obstruction. Most of this is genetically determined and is unlikely to benefit much from relief of urinary obstruction. Similarly, severe reflux is also associated with genetically determined renal dysplasia.

### Cystic Renal Malformations

The spectrum of cystic renal malformations in order of frequency is: multicystic dysplastic kidney (MCDK), autosomal recessive polycystic disease (ARPD), cystic renal neoplasms, and simple renal cysts. These disorders will be discussed separately in Section 41 on diseases of the kidneys.

### Horseshoe Kidney and Duplex Kidneys

A horseshoe kidney is characterized by fused lower poles of the two kidneys. Usually, it is an incidental diagnosis but occasionally obstruction at pelviureteric junction (PUJ) can occur in one or the other kidney. Diagnosis is confirmed on ultrasound. Magnetic resonance (MR) urogram gives good information about the anatomy as well as function (**Fig. 2**).

*Duplication anomalies* arise due to duplication of ureteric bud which may be complete or partial. Two ureteric buds originating separately on both sides culminate into bilateral duplex system. The upper moieties are usually dysplastic but normal function in all four moieties is also possible. Rarely, one of the moieties can have pelviureteric junction obstruction (PUJO) (**Fig. 3**). The ureters share a common vascular sheath but open at different sites in the bladder as per Weigert-Meyer law. Incomplete duplications causing Y-shaped ureters or split pelvis are largely inconsequential.

*Ureterocele* is a dilatation of the lower end of ureter. Usually, it is associated with duplex system with the upper moiety ureter terminating into an ureterocele. When large it may produce bladder neck obstruction in addition to ureteric obstruction. On imaging, such as intravenous urogram (IVU) and micturating cystourethrogram (MCUG), it appears as a filling defect in the bladder (**Fig. 4**). Often it requires emergency endoscopic deroofing soon after birth in order to relieve obstruction.

### Abdominal Mass at Birth

Kidney is the most common organ giving rise to an abdominal mass at birth. The most common is a giant hydronephrotic kidney caused by PUJ obstruction. Other cystic masses may be retroperitoneal lymphangioma, large ovarian cyst, omental or mesenteric cysts, distended vagina (hydrocolpos) and distended bladder. Solid masses could be congenital Wilms tumor (**Fig. 5**), neuroblastoma and retroperitoneal teratoma. Ultrasound and computed tomography (CT) should give a diagnosis. Giant hydronephrosis is usually associated with poor renal cortex and poor function. It should be managed by initial percutaneous nephrostomy. Renal function should be assessed after few weeks of drainage. If significant function recovers, pyeloplasty should be done. If not, a nephrectomy is indicated. Decision for nephrectomy should be taken carefully and when dimercaptosuccinic acid (DMSA) scan shows very poor (<10%) function. Some surgeons prefer a primary pyeloplasty. The opposite kidney should be assessed for concomitant pathology. Neonatal renal solid masses should undergo nephrectomy.

## EPISPADIAS-EXSTROPHY COMPLEX AND CLOACAL EXSTROPHY

A defect in the cloacal membrane during early embryogenesis may lead to exposure of the inner lining of the common cloaca on the surface there being no body wall in front. Depending on the timing of the embryonic insult, it can result in a spectrum of anomalies:

### Epispadias (Fig. 6)

The bladder is closed, but the urethra is exposed. The phallus has a dorsal chordee. The child may be continent or incontinent depending on the level to which the urethral plate is open. Treatment is surgical. It is carried out at the age of 1 year. In incontinent epispadias, bladder neck reconstruction is also required.

### Epispadias-Exstrophy Complex (Fig. 7)

In this classical form, the child is born with an exposed inner lining of the bladder and the urethra in its entire length. The ureteric orifices are exposed on the surface. The surrounding paraexstrophy skin is thin and shiny. The anus is anteriorly placed. In the male, the penis is short and dorsally curved with separation of corporal bodies. In the female, the clitoris is bifid. Vaginal stenosis and duplication may occur. The pubic bones are set wide apart (pubic diastasis). The anomaly looks gross but the child is otherwise normal, accepts feeds and there is no urinary obstruction. The upper tracts are usually normal. Prenatal diagnosis is suggested by absence of a normal bladder, anterior abdominal wall mass and low set umbilicus.

### Management in the Newborn

- Ligate umbilical cord with a long thread rather than clamp (clamp may traumatize the delicate bladder)
- Cover the exposed bladder by thin clear plastic sheet such as cling film. Gauge cotton may adhere and damage the epithelium. Avoid petroleum jelly or saline soaked gauge on the bladder. Put diapers over the cling film.
- Obtain a renal ultrasound to exclude upper tract anomalies such as duplex system.
- Surgical closure should be performed within 24–72 hours once the parents have been counseled and consented.

The initial surgery is closure of the bladder. Further surgery consists of bladder neck repair and epispadias correction. Many surgeons prefer a single stage total correction. The results regarding cosmesis and continence are variable. Many patients ultimately require bladder augmentation. Stem cell technology and tissue engineering have enabled bladders to be grown in the laboratory for transplantation. It is going to be the future of these malformations.

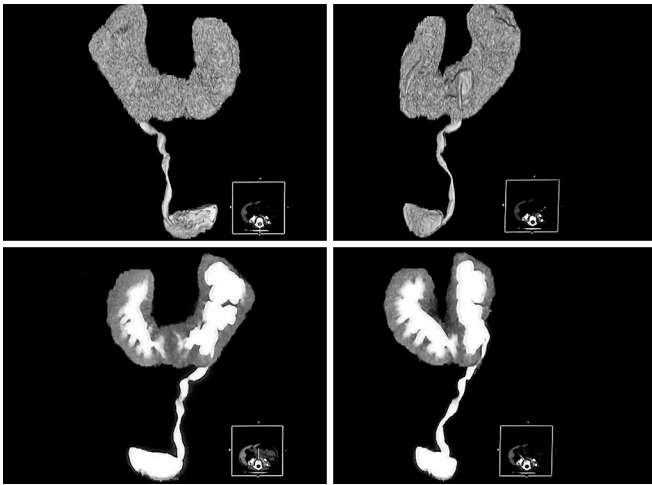
### Cloacal Exstrophy (Fig. 8)

It is a rare but complex anomaly comprising of a large exomphalos; two exposed hemibladders, one on each side of prolapsing terminal ileum in the center (often termed as elephant trunk appearance); two appendicular orifices and two ureteric orifices, one on each hemibladder. There is no anal opening in the perineum. Unlike classic bladder exstrophy, associated malformations are frequent. Neonatal work-up includes assessment for associated malformations and detailed discussion with parents about the outcomes. Surgical reconstruction is complex.

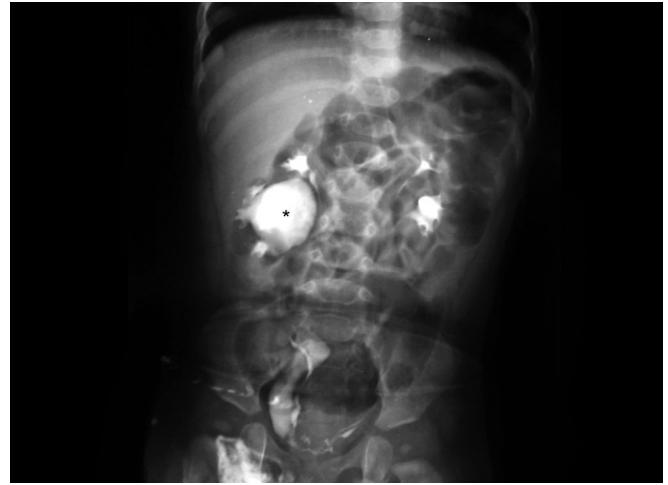
## HYPOSPADIAS

Because of the environmental androgen disruptors, increased use of chemical fertilizers and increased genetic pool, the incidence of hypospadias is steadily rising, current incidence being about 1 in





**Figure 2** MR urogram showing horseshoe kidney. Note VUR on the left. The child presented with UTI  
*Abbreviations:* MR, magnetic resonance; VUR, vesicoureteric reflux; UTI, urinary tract infection.



**Figure 3** Intravenous urogram (IVU) showing bilateral duplex system with all four moieties functioning. Right lower moiety has a dilated pelvis (asterisk) because of pelviureteric junction (PUJ) obstruction. The child underwent right lower moiety pyeloplasty



**Figure 4** Ureterocele seen as a filling defect (double arrow) in the bladder on MCUG. There is gross reflux in the lower moiety ureter



**Figure 5** Neonate with a flank mass. This was a Wilms tumor



**Figure 6** Epispadias. The phallus has been stretched to show the open urethral plate dorsally



**Figure 7** Classical Epispadias-Exstrophy complex. Exposed bladder plate is bulging. Phallus is short and turned dorsally

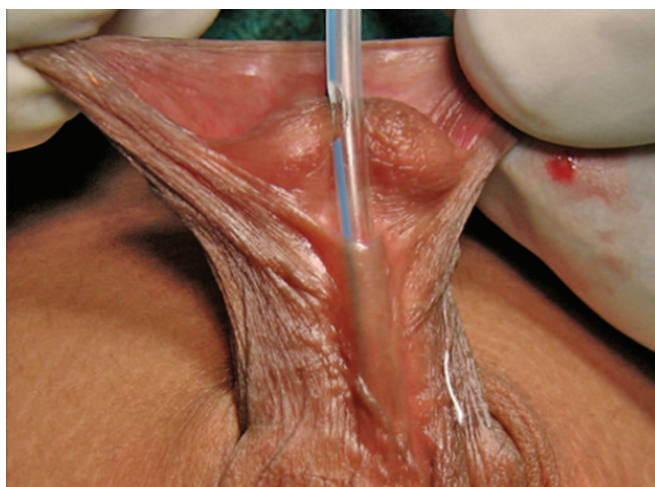


**Figure 8** Cloacal exstrophy. The central mucosa is from ileum. The two hemibladders are on the sides

150–200. It may have a genetic basis as suggested by transmission from father to son and among siblings. Babies born by in vitro fertilization techniques are at increased risk.

Hypospadias is defined as ventral hypoplasia of the penis. There is ventral deficiency of skin, dartos, spongy tissue and ventral urethral wall. The foreskin is dorsally crowded like a hood (hooded prepuce) and the glans is typically rotated outward, downward and laterally. The urethral opening is located on the ventral surface proximal to the site of normal opening. The meatus is often narrow giving rise to thin and forceful stream that falls between the legs of the patient. Often there is ventral curvature of the penis referred to as chordee. Hypospadias is classified depending upon the site of urethral meatus:

- **Anterior hypospadias (70% Cases):** The meatus is located at midshaft or distal shaft. Most common form is subcoronal hypospadias. They are usually isolated defects. The meatus may seem to open distally, but a length of urethra proximal to the meatus is often hypoplastic (**Fig. 9**). The severity of the defect is judged from the level at which the corpus spongiosum starts deviating on either side, therefore the location of the meatus may not truly reflect the severity.



**Figure 9** Hypospadias. The hooded foreskin has been stretched. The meatus is located distally. Note a visible feeding tube through the distal hypoplastic urethra

- **Posterior hypospadias (30% Cases):** It is a more severe variety with the meatus situated either on the proximal shaft or scrotum or the perineum. Penoscrotal transposition is often associated (**Fig. 10**). Severe hypospadias with undescended testes and/or asymmetric genitalia may be associated with disorders of sexual differentiation (**Fig. 11**).

## Surgery

The aim of hypospadias repair is to reconstruct a penis that is structurally and functionally normal. This can be achieved in most cases through a single stage repair performed at 12–18 months of age. A child born with hypospadias should not be circumcised for religious reasons at birth because the foreskin is used for urethral reconstruction during surgery. Meatal stenosis in hypospadias does not lead to back pressure changes and therefore meatotomy to improve the stream before definitive surgery is unnecessary. Surgery should be completed before the child starts going to school. Parental counseling and alleviating their fears about the child's sexual and married life is also an important aspect of management.



**Figure 10** Proximal hypospadias with penoscrotal transposition. The meatus is midscrotal



**Figure 11** Severe hypospadias with gonadal asymmetry. Such cases need evaluation for disorders of sexual differentiation



## PENILE AGENESIS (APHALLIA)

It is a rare malformation with an incidence of 1 in 10 million. Early insult to the developing genital tubercle is the cause. The scrotum and both testes are normal, but the phallus is not formed at all (**Fig. 12**). The urethra opens in the perineum or within the anal verge. The child is continent. It is a distressing condition for the family with parental concern regarding sex of rearing and child's body image. Generally, there is no urinary obstruction. The child should be reared as a male because of the hormonal milieu being testosterone dominated—their testes are normal. Several techniques are there to reconstruct the urethra and the phallus.

## MICROPHALLUS

Normal stretched penile length in a term neonate is 3–3.5 cm. If it is less than 2.5 cm, it is termed as microphallus. The corporal bodies are less developed. The urethra and bladder are normal. Testosterone assay should be done. If the level of testosterone is subnormal, topical or systemic testosterone should be given. Primary microphallus with normal hormones does not respond to testosterone.

## PRUNE BELLY SYNDROME

Congenital prune belly syndrome is characterized by a typical wrinkled abdominal wall (**Fig. 13**), deficient abdominal muscles, generalized dilatation of the upper and lower urinary tract and bilateral abdominal testes. The bladder is typically large and the posterior urethra is dilated. Problems arise because of functional urinary tract obstruction and stasis of urine leading to high propensity for urinary tract infections. Occasionally, anorectal malformation may be associated. The severity may vary with a wide spectrum. Management in the newborn period is generally conservative. Vesicostomy may be needed to facilitate urinary drainage. Urethral catheterization is often difficult in these babies because of an abnormal and hypoplastic posterior urethra and therefore anticipatory catheterization should not be done. Abdominoplasty is usually carried out at 1–2 years of age. Some surgeons advocate early major urinary and abdominal wall reconstruction.

## FEMALE GENITAL MALFORMATIONS

### Congenital Ovarian Cyst

It is not unusual to pick up a cyst in the abdomen of a female fetus on antenatal ultrasound. The most common reason for this is an



**Figure 13** Prune belly syndrome. Bilateral kidney masses are visible. Abdominal wall is wrinkled and lax

ovarian cyst. It should be confirmed by a postnatal scan. Size and symptoms determine the management. Most cysts which are less than 4 cm and asymptomatic are managed expectantly with serial ultrasound. They tend to resolve with time. If they are big or do not resolve with time, laparoscopy should be carried out at few months. The cyst may be aspirated or excised. The aim is to preserve normal ovarian tissue. Occasionally, the cyst is found to be tortuous, in this case it is best excised. Neonatal cystic torsion may be asymptomatic. Occasionally, an asymptomatic cyst of ovarian origin lies high in the subhepatic region mimicking a choledochal cyst. Laparoscopy provides good diagnostic and therapeutic tool in such cases.

### Mass at Vulva

A mass at vulva could be imperforate hymen causing distended vagina (**Fig. 14**). The vaginal secretions in response to maternal estrogens accumulate behind the hymen. Very large vagina may press on the urethra and bladder neck causing urethral obstruction. Treatment is fenestration of the hymen.

Urethral polyp (**Fig. 15**) and prolapsing ureterocele could also present as a vulval mass. A special variety of ureterocele (cecoureterocele) may have a urethral extension. They usually cause significant urinary obstruction and require surgery rather urgently.



**Figure 12** Aphallia. Testes and scrotum are normal. Urethra opens in the anal canal



**Figure 14** Imperforate hymen. Note the bulging hymen due to a distended vagina



**Figure 15** Urethral polyp. The polyp has been pulled out in preparation for excision. Note absence of anal opening

### Urogenital Sinus and Cloacal Malformations

Abnormalities of the vagina, uterus and urogenital sinus (UGS) are common with or without anorectal malformations in a female. They may consist of duplication anomalies—bifid vagina, septate vagina, uterus didelphus and bicornuate uterus. UGS is characterized by a common channel into which the urethra and the vagina open. The length of the common channel may vary. Isolated UGS malformations seldom cause symptoms and do not warrant neonatal treatment. Ultrasound evaluation of the urinary tract should be done to exclude obstructive uropathy, which may be seen in high UGS.

Cloacal malformation, in which the hind gut, the vagina and the urethra drain through a common single channel, is a severe anomaly that requires urgent evaluation of the urinary tract. The patient may have palpable vagina in the lower abdomen because of distal obstruction resulting in hydrocolpos. It can compress the bladder neck causing urinary obstruction. Besides making a colostomy, urgent decompression of the urinary tract and vagina may also be needed in the form of vesicostomy or vaginostomy. A more detailed description of cloaca is given with gastrointestinal malformations.

### Vaginal Atresia (Mayer-Rokitansky-Küster-Hauser Syndrome)

A defect in the formation, differentiation and fusion of the paramesonephric (Müllerian) ducts may result in a spectrum of anomalies of Müllerian agenesis. Typically the vagina, uterus and the fallopian tubes are absent. The lower vagina, which is of UGS origin, may remain as a dimple in the vulva. The ovaries are normal. Diagnosis is usually made either incidentally or near puberty because of primary amenorrhea. In females born with anorectal malformation, wherein there are two openings in the vulva—thought to be having rectovaginal fistula, should be suspected as having anovestibular fistula with vaginal atresia until investigations reveal normal Müllerian development. Many associated malformations have been described including vertebral and ear anomalies. Several techniques of vaginal reconstruction from skin and bowel are described.

### POSTERIOR URETHRAL VALVES

Posterior urethral valve is the most common obstructive uropathy of the lower urinary tract in a male neonate. There is an obstructing

membrane at the distal end of posterior urethra. This leads to upstream back pressure changes in the form of bladder neck hypertrophy, bladder trabeculations and hydroureteronephrosis. Besides urethral obstruction, the key factors contributing to the overall morbidity are: bladder dysfunction, functional ureteric obstruction and varying degrees of genetically determined renal dysplasia. Antenatal diagnosis on ultrasound is suggested by bilateral upper tract dilatation, distended bladder and dilated posterior urethra. The bladder neck is hypertrophied giving rise to a constriction between the bladder and the posterior urethra (keyhole sign). The bladder may not empty well leading to oligohydramnios. PUV is a wide spectrum disease varying from mild abnormality—late antenatal diagnosis, no oligohydramnios, mild hydronephrosis to severe disease—early fetal abnormality, oligohydramnios, echogenic kidneys, severe hydroureteronephrosis.

Clinical picture at birth can also vary. The child may be completely asymptomatic or may have poor urinary stream. Severe cases present with sepsis, azotemia, dyselectrolytemia and acidosis. A hypertrophied bladder is usually palpable even after micturition. Kidneys may also be palpable. If oligohydramnios was significant, the child may have respiratory distress (lung hypoplasia) and limb compression effects. The diagnosis should be confirmed by postnatal ultrasound and MCUG (**Fig. 16**).

### Treatment in Neonates

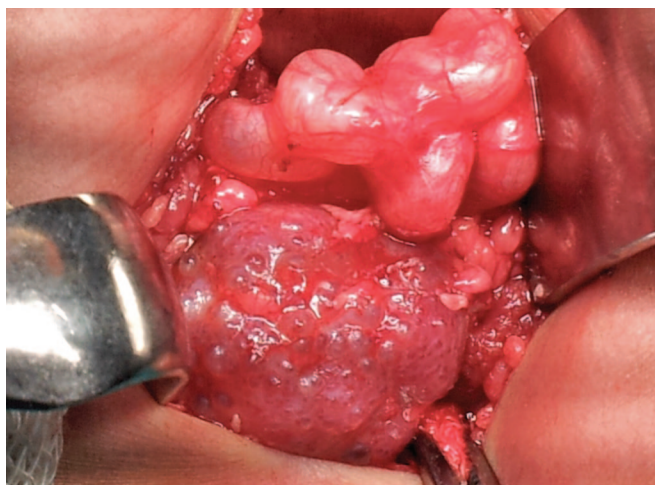
- *Baby well at birth, no oligohydramnios, and normal kidneys, baby feeding well and passing urine:* It indicates mild end of the spectrum. Prophylactic antibiotic is started. The child should be scheduled for surgery electively within a few days for an on table MCUG, primary endoscopic valve ablation and circumcision. Postoperatively urinary catheter is kept for 48 hours. Oxybutynin is started to relax a hypertrophied bladder. Check endoscopy should be performed after 3–4 months to confirm completion of valve ablation. Follow-up should be done jointly with a pediatric nephrologist and is aimed at evaluating bladder function, monitoring renal chemistry and management of chronic renal disease.
- *More severe disease [bilateral hydroureteronephrosis (HUN), kidneys dilated], child not passing urine well:* The child should



**Figure 16** MCUG in a case of PUV. Note hypertrophied bladder neck (white arrow) and dilated posterior urethra (black arrow). The bladder is trabeculated and there is severe reflux on the left. This is called VURD. The left kidney is dysplastic. This is a pop off mechanism to safeguard the other kidney  
*Abbreviations:* MCUG, micturating cystourethrogram; PUV, posterior urethral valve; VURD, valves with unilateral reflux dysplasia.



be catheterized with a silastic catheter. If the catheter drains well and the upper tracts decompress on ultrasound, primary valve ablation is carried out after few days. If appropriate equipment is not available, a vesicostomy may be considered followed by endoscopic valve ablation after few months. If the response to catheter is not good, high diversion (ureterostomy or pyelostomy) should be done. While doing ureterostomy often the kidneys are found dysplastic as evidenced by lobulations, and sometimes, cystic changes on the surface (**Fig. 17**). Valve ablation and ureterostomy closure is usually done at 1 year.



**Figure 17** Posterior urethral valve (PUV). There was no response to catheter drainage. Operative exposure for ureterostomy shows dilated and tortuous ureter and small dysplastic lobulated kidney. Note multiple cysts on the surface of the kidney

### Fluid and Electrolyte Management

Post obstructive diuresis can cause severe dehydration, hyponatremia and acidosis. A careful watch on the urinary output and electrolytes is mandatory. High sodium and fluid volumes are needed to offset the diuretic effect. Blood gas analysis should be repeated frequently to assess and treat acidosis. Many patients require long-term therapy with sodium bicarbonate.

## ANTENATAL HYDRONEPHROSIS

Unilateral hydronephrosis is the most common genitourinary abnormality detected on antenatal ultrasound. It leads to frequent in utero referral for parental counseling and prognostication. Although in nearly two-thirds cases it is caused by nonobstructive dilatation, which does not need any surgery, it is important to evaluate all cases to identify the one-third that are truly obstructive—needing surgical correction. Antenatal scan should aim to identify and measure the anteroposterior (AP) diameter of the pelvis, renal size, echogenicity, ureteric dilatation if any, bladder characteristics—filling and emptying, bladder wall thickness and dilatation of the posterior urethra. Ureteric dilation is nearly always pathological, it may be due to PUV, vesicoureteric reflux (VUR) or vesicoureteric junction obstruction (VUJO).

The differential diagnoses of antenatal hydronephrosis are:

- Unilateral hydronephrosis, no ureteric dilatation, bladder normal: *Nonobstructive dilatation, PUJO.*
- Unilateral hydroureteronephrosis, normal bladder: *VUR, VUJO*
- Unilateral or bilateral hydroureteronephrosis, thick bladder, full bladder not emptying well: *PUV*

- Bilateral hydronephrosis, no ureteric dilatation, bladder normal: *Bilateral PUJO, bilateral nonobstructive dilatation.*

## How to Differentiate Between Obstructive and Nonobstructive Unilateral Hydronephrosis

### Antenatal History and Progression of Dilatation

There is a direct correlation between AP diameter of the renal pelvis and probability of obstruction. If the AP diameter is above 50 mm, there is almost 100% chance of the baby needing surgery soon after birth. An AP diameter of 10 mm or less is associated with only 10% risk of obstruction. Antenatal onset and progression is also important. An abnormality picked up early at 18–20 weeks, which is progressive, is more likely to be obstructive than a nonprogressive dilatation picked up late in second or third trimester.

### Postnatal Ultrasound

The baby is usually well at birth. The progression of hydronephrosis should be checked by ultrasound performed at 1 week, 2 weeks and then every 3 months. A progressive dilatation indicates obstructive lesion. Nonobstructive dilatation tends to resolve with time. Progressive hydronephrosis with decreasing parenchymal thickness is almost always obstructive.

### Radionuclide Imaging

At 4 weeks, the kidneys are mature enough to handle radionuclide imaging agents. A radionuclide renogram performed with DTPA (diethylenetriaminepentaacetic acid)/MAG (mercaptoacetyl triglycerine) III/EC (ethyl cysteine) tells about excreting capacity, differential function and the pattern of pelvic clearance. The time activity curve indicates whether the drainage is normal or obstructive or equivocal. Equivocal cases can be resolved by adding diuretic. If the clearance follows a diuretic, it is nonobstructive—equivocal curve was because of reservoir effect of a dilated pelvis. Persistent obstruction despite diuretic indicates obstructive PUJO.

### Intravenous Urogram

Advent of radionuclide imaging has led to less frequent use of IVU. But it provides good anatomical details. It is especially useful in duplex systems with PUJO in one moiety (**Fig. 3**).

## Bilateral Upper Tract Dilatation without Ureteric Dilatation on Antenatal Scan

Bilateral PUJO can occur in 20% cases. Ureteric dilatation must be looked for very diligently to exclude lower urinary tract abnormality such as VUR and PUV. The baby should be put on prophylactic antibiotic. MCUG is done to exclude reflux and PUV. Early diuretic renogram with MAG III should be done and if PUJO confirmed, early surgery should be performed.

## HYDROCELE, HERNIA, UNDESCENDED TESTIS

These entities are described together because of a common embryological basis. The testis develops in the lumbar region but descends to the deep inguinal ring by 12 weeks. During the inguinal phase of its descent at 25–30 weeks, the testis carries a peritoneal diverticulum (processus vaginalis) with it, which obliterates later. Failure of obliteration of the processus vaginalis may cause hernia, hydrocele and encysted hydrocele of the cord. If the processus is narrow, allowing only peritoneal fluid to pass through, a hydrocele results. If it is wide enough to allow intestinal loops or omentum to pass through, a hernia results. The testis may remain undescended anywhere along the path of normal descent depending upon the timing of embryonic event leading to arrested descent. Occasionally, it may deviate from its normal path after exiting the superficial ring to lodge itself at ectopic location such as parascrotal and suprapubic.

## Hydrocele (Fig. 18)

A hydrocele is a collection of fluid between the layers of the tunica vaginalis, which communicates with the peritoneal cavity through a patent processus vaginalis. It is common in the first few months of life but resolves by the end of first year as the processus obliterates. Usually the swelling progresses during the day when the child is active. During sleep some fluid from the hydrocele seeps back into the peritoneal cavity making the swelling smaller. The swelling is painless, is situated around the testis, is brightly transilluminant, has no crying impulse and it cannot be emptied by pressure because of an ink-well effect. The underlying testis may be palpable when the hydrocele is lax. The upper limit of the hydrocele is clearly demonstrable—a finding used to distinguish it from a hernia. Most hydroceles disappear by the age of 1 year and surgery is only required if the hydrocele persists beyond 2 years.



**Figure 18** Right hydrocele. Note the scrotal swelling

## Inguinal Hernia

Indirect inguinal hernia is a common condition in children with an incidence of 0.8–1.4%. It is five times more common in males. Sixty percent occur on right side, 30% on left and 10% are bilateral. The incidence is higher in premature babies (30%). It presents as an intermittent inguinal or inguinoscrotal swelling, which enlarges with straining and reduces at rest. There is a characteristic crying impulse. The upper margin of the swelling cannot be reached. The swelling is reducible.

Treatment is herniotomy which should be performed electively soon after diagnosis. Waiting for too long (for the child to grow) is not advisable as the chances of obstruction and incarceration are high during infancy. Surgery should be performed under general anesthesia by a trained pediatric surgeon under magnified vision. Neonatal and infantile herniotomy is a very delicate operation with 1% risk of damage to vas and vessels leading to testicular atrophy. The operation can be performed through an open inguinal incision or laparoscopic approach. Premature babies who develop hernia in the neonatal unit should be operated when their medical condition is satisfactory and they are otherwise ready to be discharged.

Complications in form of irreducibility, incarceration and obstruction are common during infancy. Hence, there should not be any inordinate delay in surgery when a hernia is diagnosed. If the child presents with an irreducible hernia but is otherwise stable with no hemodynamic disturbances, a gentle attempt at manual reduction (taxis) under sedation may be given. If successful, herniotomy should be performed after 24–48 hours. If unsuccessful, emergency surgery should be done.

## Obstructed Hernia

The bowel within the sac is obstructed. There are features of intestinal obstruction with a tense, tender and irreducible swelling at the external inguinal ring and no crying impulse. Dilated bowel loops in the abdomen, and at times in the scrotum, are evident on X-ray.

## Strangulation

The vascularity of the herniated bowel is compromised. This can rapidly lead to gangrene of bowel and ischemia to the testis. Child presents with features of toxemia, shock and blood in stools. There is redness and induration over the swelling.

An obstructed or strangulated hernia needs urgent surgery after adequate resuscitation.

## Undescended Testis

Undescended testis (UDT) results when its descent gets halted somewhere along the path of normal descent. The incidence is about 4% at birth in term neonates and 20% in the premature. The incidence is also higher in low birthweight babies. It is more common on the right side. Up to 25% cases have bilateral UDT. A patent processus vaginalis is almost always associated with UDT and in some it may show as a clinically appreciable hernia. However, such hernias are usually wide necked and are unlikely to obstruct and strangulate.

An UDT staying outside the scrotum is exposed to temperature related damage to the germ cells. The scrotal temperature is generally from 1.5° to 2° lower than the abdomen. Seminiferous tubules suffer degenerative changes if exposed to higher temperature beyond 6 to 9 months of life. Leydig cells are not affected as much.

Clinically, UDT can be divided into *palpable* (80%) and *impalpable* (20%). Palpable testis may be felt along the inguinal canal, at the superficial ring or in the superficial inguinal pouch. Differential diagnosis of impalpable testis is:

- Abdominal testis (most common)
- Vanished testis that results from an intrauterine vascular accident
- Testicular agenesis (very rare)
- Inguinal testis in an obese child. The testis is difficult to palpate through fat.

The testis is examined in warm and relaxed surroundings in supine, frog-leg or squatting position. If the testis is not felt easily, it is gently *milked* down the inguinal canal to make it emerge from the inguinal canal, when it can be grasped. In most cases of palpable UDT, it can be easily felt above the scrotum. Retractable testis can be brought down to the scrotum without tension on the chord and it stays in the scrotum for some time on releasing it from the fingers' grip.

Investigations such as ultrasound and MRI to locate the testis are unnecessary. A palpable testis is best treated by orchidopexy through an inguinal incision. If the testis is clinically impalpable, the child should be posted for laparoscopy. Under anesthesia examination is repeated. If the testis becomes palpable under anesthesia, inguinal orchidopexy should be carried out. If it still remains impalpable, laparoscopy is performed to locate and bring the testis down. There is little role for hormonal treatment of undescended testes. At times, it can help increase the girth of vessels to facilitate surgery. Another possible use of hormones is to differentiate between true UDT and retractile testis.

Orchidopexy for congenital cryptorchidism is recommended at 6–12 months of age since degeneration of spermatocytes starts at 6 months of age and is nearly complete by 2 years. Other problems that can occur with UDT (hence the reason for surgery) are: increased risk of torsion, higher chances of malignancy especially



in intra-abdominal testis, decreased fertility potential related to thermal injury and increased risk of trauma to UDT.

### Retractile Testis

The retractile testis is a normal size testis which although normally descended, usually lies near the neck of scrotum because of an increased cremasteric activity. The testis is present in the scrotum on some occasions such as during a warm bath or sleep. It can be easily manipulated to the bottom of the scrotum and stays there for some time. In contrast, a truly UDT springs back immediately to its original position. With retractile testis, the ipsilateral scrotum is fully developed.

### MORE ON THIS TOPIC

- Dhua AK, Aggarwal SK, Sinha S, Ratan SK. Soft tissue covers in hypospadias surgery: Is tunica vaginalis better than dartos flap? *J Indian Assoc Pediatr Surg.* 2012;17:16-9.
- El-Sherbini MT, Hafez AT, Dawaba MS, et al. Comprehensive analysis of tubularized incised plate urethroplasty in primary and re-operative hypospadias. *BJU International.* 2004;93:1057-61.
- Hutson JM, Terada M, Baiyun Z, Williams MPL. Normal Testicular Descent and Aetiology of Cryptorchidism (Advances in Anatomy, Embryology and Cell Biology). Berlin: Springer Verlag; 1995.
- Stringer MD, Oldham KT, Mouriquand PDE, Howard ER. *Pediatric Surgery and Urology: Long-term Outcomes.* London: WB Saunders; 1998.
- Thomas DFM, Rickwood AMK, Duffy PG. *Essentials of Paediatric Urology.* UK: Martin Dunitz; 2002.
- Thomas DFM. *Urological Disease in the Fetus and Infant.* Oxford: Butterworth-Heinemann; 1997.

### IN A NUTSHELL

1. Antenatal ultrasound has had a huge impact on the early diagnosis and management of obstructive uropathy in children. Antenatal unilateral hydronephrosis should not be a reason for medical termination of pregnancy.
2. Most important differential diagnosis of bilateral antenatal hydronephrosis is PUV.
3. Differentiation between obstructive and nonobstructive dilatation of PUJ can be made by radionuclide renal dynamic scan. Early diagnosis and surgery for PUJ obstruction is important to prevent renal damage.
4. PUV, a common obstructive uropathy in males, present in a wide spectrum; normal asymptomatic neonate to very sick uremic and septic neonate.
5. Cystoscopic primary valve ablation is the best treatment for neonatal valves. Yet urinary diversion in the form of vesicostomy or ureterostomy may be lifesaving in certain situations.
6. An inguinal hernia in an infant should be surgically treated sooner. Delay may lead to obstruction and strangulation.
7. A hydrocele should be observed for 1–2 years for spontaneous regression.
8. Incidence of hypospadias is increasing because of environmental androgen disruptors and increasing genetic pool.
9. Surgery for hypospadias should be done between 6 months and 18 months of age.
10. Undescended testes are prone to trauma, torsion and temperature related damage to the germ cells. Impalpable abdominal testes may have higher incidence of testicular malignancy. Orchidopexy should be performed at 6 months to 1 year of age to prevent germ cell damage.

## Chapter 18.5

# CNS Malformations

Nidhi Sugandhi, Veereshwar Bhatnagar

Congenital central nervous system (CNS) malformations are one of the most common and debilitating congenital anomalies reported. They result in significant fetal wastage, neonatal deaths and long-term morbidity. Though decreasing in incidence due to meticulous prenatal care and antenatal detection, they still present a formidable challenge in terms of treatment and ensuring a good quality of life to these patients. The most common CNS malformations are neural tube defects (NTDs), spina bifida occulta and aperta (45%), followed by hydrocephalus (12%).

## EPIDEMIOLOGY

The incidence varies widely from less than 1 per 1000 livebirths in developed nations like Western Europe and USA to 5–12 per 1000 livebirths in under developed and developing nations, particularly in Africa, UAE and some pockets of Southeast Asia. These figures do not take into account the large number of spontaneous abortions, still births and increasing number of terminated pregnancies which would make the figures much higher.

The incidence of these malformations has been declining with time in concordance with socioeconomic development and improvement in maternal nutrition and prenatal care. In the 1970s–1980s the incidence was routinely reported to be 5–10 per 1000 livebirths. Presently the incidence has fallen to as low as 0.5 per 1000 livebirths in certain developed countries. This corresponds to the mass programs of screening, nutritional fortification and preconceptional counseling. However, increase in the rate of prenatal diagnosis and increased elective termination of pregnancies may also have some role to play in these statistics.

## EMBRYOLOGY

Understanding the various stages of development provides an insight into the malformations developing at each stage. The development of central nervous system begins at third week of gestation by strictly coordinated cellular interactions.

## Induction and Neural Tube Formation (Neurulation)

At the three layer stage of the embryo, the mesoderm (inducer) initiates the overlying ectoderm to proliferate and form a thickened plate of tissue called as the *Neural Plate* on the dorsum of the embryo. Further proliferation of this plate leads to formation of *Neural Folds* by the upturning of the lateral edges around a linear depression in the center, the *Neural Groove*. The neural folds finally fuse in the midline giving rise to the *Neural Crest*. The neural crest is a site of development of highly specialized neurons which migrate all over the developing embryo and form the peripheral nervous system and its derivatives. The fusion of neural folds begins in the cervical region and proceeds cranially and caudally except at two extreme ends called as the *Cranial and Caudal Neuropores* that continue to communicate with the overlying amniotic cavity for some more time before finally closing by the 25th–28th day of gestation (**Figs 1A to G**). Failure of fusion of these neural folds is responsible for the NTDs.

## Regionalization

Signaling molecules secreted by structures adjacent to the neural tube activate certain genes (sonic hedgehog, homeobox genes)

responsible for formation of a cranio-caudal and dorso-ventral axis of the CNS. The forebrain, midbrain and hind brain develop at the cranial end and the spinal cord at the caudal end of the axis. Similarly different populations of cells (neural crest, sensory, interneurons, glial and motor neurons) occupy specific regions of the dorso-ventral axis. Abnormalities in ventral induction cause malformations of the brain and facial structures such as holoprosencephaly.

## Proliferation and Migration

The neuronal stem cells in the central neural tube proliferate, differentiate and migrate to their particular locations to form the various layers of the cortex, medulla and spinal cord. Incongruities at this stage lead to the disorders of proliferation and organization such as agenesis, lissencephaly, etc.

## Connection and Organization

This refers to the final stage of establishment of neural pathways through synapse formation and axon growth. This is a poorly understood process and is more likely to cause functional defects rather than gross malformations.

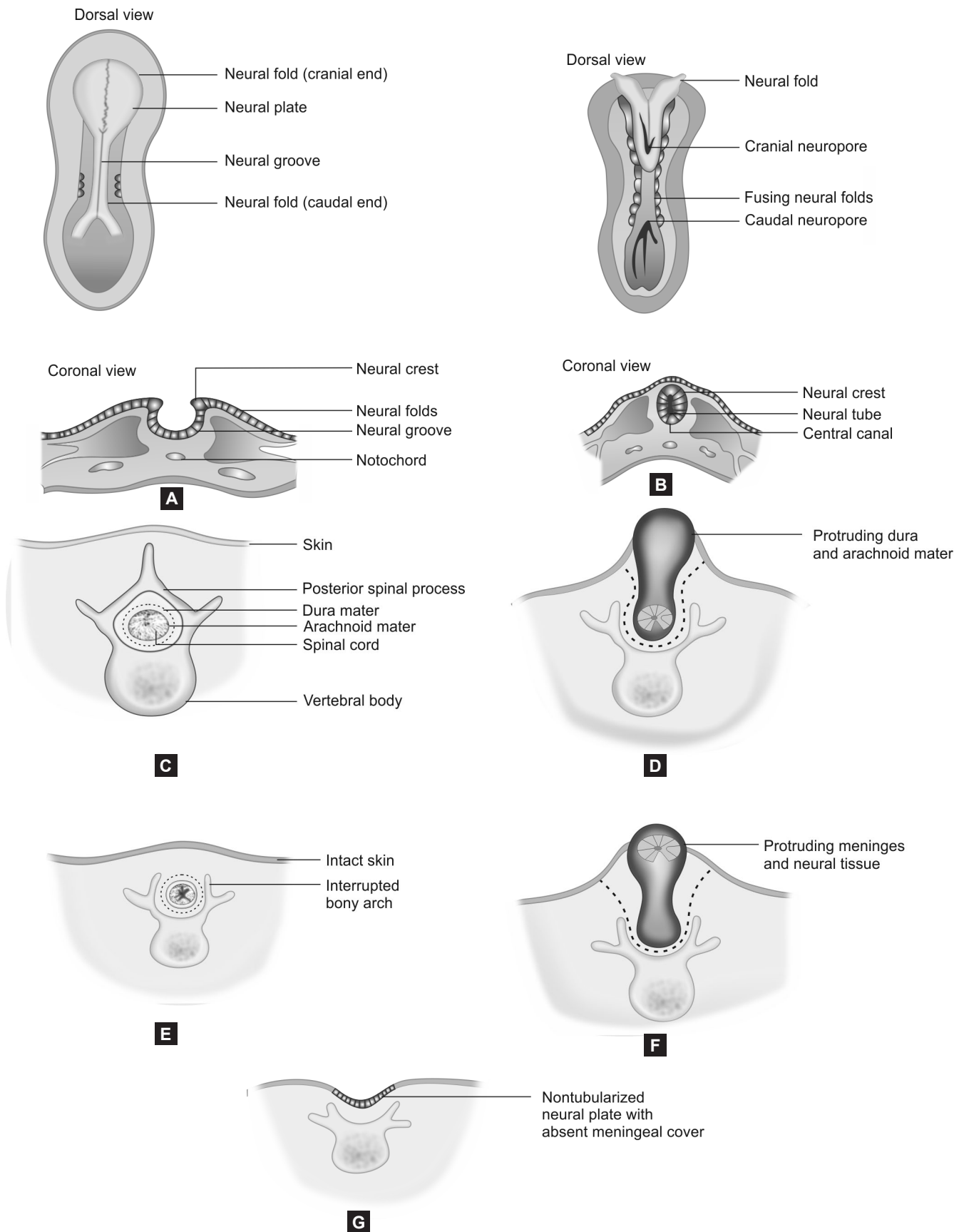
## ETIOPATHOGENESIS

Central nervous system malformations are multifactorial and result from complex interactions between environmental, genetic and nutritional factors (**Box 1**).

### BOX 1 Etiology of CNS malformations

- Nutritional
  - Folic acid deficiency
  - Vitamin B<sub>12</sub> deficiency
  - Zinc deficiency
  - Hypervitaminosis A
- Metabolic
  - Maternal diabetes mellitus
  - Homocystinemia
  - Abnormalities of cholesterol metabolism
- Drugs
  - Trimethoprim
  - Triamterene
  - Carbamazepine
  - Phenytoin
  - Phenobarbitone
- Genetic
  - Mutations in signaling pathways: *HOX* gene, *SHH* gene
  - Mutations in 1 carbon metabolism
  - Trisomies 13, 18, 21
  - Consanguinity
- Others
  - Radiation exposure
  - Hyperthermia.

Folic acid and vitamin B<sub>12</sub> (methylcobalamine) have well delineated roles in the cellular interactions and signaling pathways, especially in 1-carbon metabolism which contributes significantly in DNA synthesis. Deficiency of folic acid during the crucial organogenesis phase in the first trimester results in anomalies of closure of neural tube and is responsible for the majority of NTDs. Despite adequate supplementation, 30% NTDs may still occur. These are believed to be due to genetic factors. Nonsyndromic familial NTDs occur due to mutations in genes involved in 1-carbon metabolism such as *MTHFR* gene (methyl tetra hydro folate reductase). Mutations in genes responsible for signaling during organogenesis such as homeobox (*HOX*) and sonic hedgehog (*SHH*) genes also cause CNS malformation in addition to a spectrum of other congenital malformations.



**Figures 1A to G** Line diagrams showing the normal and abnormal development of the central nervous system and in particular the spinal cord. (A) Neurulation at day 18 of embryonic life; (B) Fusing neural folds to form neural tube at day 22; (C) Transverse section through normal spinal cord; (D) Transverse section showing meningocele; (E) Spina bifida occulta; (F) Meningomyelocele; (G) Transverse section of Rachischisis

Most of these mutations are autosomal recessive. The risk of recurrence of a NTD in a sibling is 3–4% after one affected child and increases to 10% after two affected children. Syndromic malformations occur due to specific defects, e.g. defective cholesterol biosynthesis leads to holoprosencephaly in Smith-Lemli-Opitz syndrome.

Maternal intake of drugs interfering with folic acid metabolism such as trimethoprim, triamterene, carbamazepine, phenytoin, phenobarbitone increases the risk of NTDs, as does alcohol abuse, which selectively destroys the midline neural cells. Hypervitaminosis A, radiation exposure, maternal diabetes mellitus and hyperthermia are other teratogens implicated in NTDs. Fetal infection by toxoplasmosis, cytomegalovirus, and rubella can also lead to these malformations. Consanguinity has a definite role to play in syndromic CNS malformations with one series reporting 12 out of 13 syndromic CNS malformations to be a product of consanguineous marriages.

## INVESTIGATIONS (BOX 2)

### Antenatal Diagnosis

#### *Maternal Serum Alpha Fetoprotein (MSAFP)*

Open NTDs lead to a leak of fetal substances into the amniotic fluid and thence into maternal blood. Alpha fetoprotein (AFP) is one such glycoprotein produced in the fetal liver which escapes through the open neural tube into the amniotic fluid and maternal serum. An increased level of AFP in maternal serum at 16–18 weeks of gestation is a sensitive indicator of CNS malformations. A value greater than 2.5 times has a sensitivity of over 90% for anencephaly and 80% for other NTDs. However, MSAFP may be raised in other fetal disorders also such as abdominal wall defects and thus is nonspecific and requires further confirmation. Several countries recommend MSAFP as a screening test for fetal NTDs in all pregnant women.

#### BOX 2 Investigations for CNS malformations

- Antenatal
  - MSAFP
  - Amniotic fluid acetylcholinesterase
  - Ultrasonography
  - Chorionic villus sampling
- Postnatal
  - CECT/MRI of the head/spinal cord
  - USG cranium
  - Muscle charting
  - Urological investigations- USG KUB, MCU, DMSA, DTPA, GFR and UDS
  - X-ray/CT of lower limb anomalies
  - Neurodevelopmental assessment.

#### *Ultrasonography*

High resolution antenatal ultrasound scan can pick up gross CNS malformations such as anencephaly from as early as 12 weeks of gestation and NTDs by 16–20 weeks. However, small NTDs especially in L5-S2 region may be missed on an USG. Thus, this test should be interpreted in conjunction with other markers like MSAFP and amniotic fluid acetylcholinesterase.

#### *Amniotic Fluid Acetylcholinesterase*

Similar to AFP, open NTDs lead to leak of acetyl cholinesterase into the amniotic fluid and can be detected by amniocentesis after 14 weeks of gestation. It is more sensitive and specific as compared to MSAFP (98–99% sensitivity and > 90% specificity) and is usually not markedly raised in other fetal anomalies as abdominal wall defects. However, this is an invasive procedure and fraught with risks.

#### *Chorionic Villi Sampling*

This can be used to diagnose specific known mutations in fetal cells such as MTHFR gene polymorphism in case of familial history of malformations. However this is invasive and carries a risk of fetal loss, hence is used in very selective cases.

### Postnatal Diagnosis

The common CNS malformations such as NTDs and anencephaly are grossly visible in a neonate and require no specific investigations for diagnosis. Investigations are however required to seek associated anomalies (such as cardiac and genitourinary) and for long-term management of functional losses such as for neurogenic bladder and paraplegia. CECT and MRI are good investigations to delineate most of the malformations of the CNS. USG of the head gives useful information in neonates and infants until the anterior fontanel closes. Coupled with a Doppler to assess the cerebral blood flow and resistive index, this can be a very convenient investigation to monitor hydrocephalus. It is also important to routinely screen for associated cardiac and renal anomalies with echo and urinary tract imaging. Radiological and functional assessment of associated lower limb anomalies like CTEV is required. Muscle charting for assessment of power in different muscle groups of the limbs should be done before the surgical repair of the NTDs. Investigations for assessment of vision and hearing is also indicated.

## CLASSIFICATION

CNS malformations have been classified in a variety of ways. The easiest to remember is the one based on the developmental stages at which the malformations occur and their mechanism of pathogenesis (**Box 3**).

## DISORDERS OF STRUCTURE

### **Neural Tube Defects**

Neural tube defects are the most common congenital CNS malformations. They result due to defective neurulation and improper closure of the neural tube. Spina Bifida is a general term which denotes splitting of vertebral arches in the midline, which may or may not be associated with underlying neural tissue defects. There are two types of NTDs, open and closed based on the presence or absence of exposed neural tissue (**Box 4**). In open NTDs the neural tube does not close and the overlying vertebrae, muscles and skin are absent, thus exposing the neural tissue to the environment. In closed NTDs, the overlying skin is intact even though there may be an abnormality in the neural tube or the overlying bones or membranes.



**BOX 3 Classification of CNS malformations**

- **Nonsyndromic**
  - Disorders of structure
    - Neural tube defects
      - Spina bifida
      - Encephelocele
      - Exencephaly and anencephaly
    - Hydrocephalus
    - Arachnoid cysts
    - Arnold Chiari malformations
    - Dandy Walker malformation
    - Craniosynostosis
  - Disorders of segmentation and regionalization
    - Holoprosencephaly
  - Disorders of proliferation
    - Microcephaly
    - Agenesis of corpus callosum
    - Agenesis of cranial nerves
  - Disorders of neuronal migration
    - Lissencephaly
    - Schizencephaly
    - Porencephaly
  - Vascular malformations
- **Syndromic**
  - Von-Hippel-Lindau syndrome
  - Sturge Weber syndrome
  - Osler-Weber-Rendau syndrome
  - Ataxia-telangiectasia
  - Smith-Lemli-Opitz syndrome
  - Cobb syndrome.

**Anencephaly**

When the cranial end of the neural tube fails to close, the developing cerebral hemispheres herniate into the amniotic cavity, a condition called *exencephaly*. Continuous exposure of the developing tissue to amniotic fluid leads to degeneration of the tissue and disappearance of the forebrain. The child is born with absent cerebral hemispheres as well as absent cranial vault with the rudimentary tissue protruding freely from the base of the skull. This is not compatible with life and most fetuses affected with this undergo spontaneous abortions or intrauterine deaths. If detected before 20 weeks with an antenatal USG, the parents may be counseled for elective termination of the pregnancy.

If there is a small defect in the cranial closure of the neural tube, it results in herniation of meninges covered brain tissue from the defect, known as *encephalocele*. The most common site is the occipital region. The herniated tissue is dysplastic and if it contains the hindbrain including the vital respiratory and cardiovascular centers, the survival of the neonate can be difficult. The other common site is the frontonasal region and sometimes these encephaloceles can be mistaken for nasal polyps.

**Spina Bifida**

Meningocele is a sac like protrusion of the meninges containing CSF through a defect in the vertebral arches, muscle and skin. It does not contain any neural tissues and the underlying spinal cord does not enter the sac. When the neural placode or the nerves enter this sac, a *meningomyelocele* is formed. The neural placode at this defect usually consists of an open neural tube and everted central canal covered by the meninges. The exiting motor nerves lie in the wall of this sac. The central canal and the neural tube may reconstitute normally distal to this lesion, but more commonly may have defects like diastematomyelia or syringomyelia. The dural sac is in close apposition with the skin since the muscles and posterior spinous processes are absent (**Figs 2A to C**).

**BOX 4 Types of neural tube defects (NTDs)**

- Open NTDs
    - Anencephaly
    - Meningocele
    - Myelomeningocele
    - Rachischisis
  - Closed NTDs
    - Spina bifida occulta
    - Tethered cord
    - Split cord malformations: Diastematomyelia, Diplomyelia
    - Dermal sinus
    - Intradural lipoma
    - Caudal regression/sacral agenesis.
- } Spina Bifida Aperta

In most severe cases the meningeal sac covering the placode may be absent, leaving the placode, exiting nerves and the central canal fully exposed, called as *rachischisis*. The exposed neural structures suffer from severe damage and thus the fetuses with this condition usually have severe neurological deficiencies.

Frequently, spina bifida aperta is associated with Arnold Chiari malformation and hydrocephalus. This is because the spinal cord is tethered to the vertebral column, and progressive lengthening of the column pulls the cerebrum into the foramen magnum, also hindering the flow of CSF. Even though hydrocephalus may not be evident initially, up to 80–85% of the children will develop this after repair of the meningomyelocele.

Anomalies of the sacrum, anorectal malformations, urogenital system and lower limbs such as CTEV may be present and are caused by involvement of the sacral nerve roots. *Currarino triad* refers to coexistence of NTD (presacral mass), anorectal malformation and sacral anomalies.

Individual NTDs, their clinical features, evaluation, and supportive management are discussed in the chapter on NTDs in Section 42.

**Surgical Intervention**

Early closure of the defect after appropriate investigations and stabilization needs to be planned, unless there are associated conditions increasing the risk of general anesthesia. It is very important to counsel the parents before surgery so that they have realistic expectations about the immediate and long-term results and quality of life. The basic surgical objectives are summarized in **Box 5**. Wound infection and prolonged CSF leak are two common immediate postoperative complications. Long-term complications include development of hydrocephalus, neurogenic bladder and bowel and paraplegia or limb anomalies.

**Closed NTDs**

Presence of closed NTDs may be suggested by cutaneous stigmata like dermal nevus, tuft of hair, hemangiomas, subcutaneous lipoma or a patch of atrophic skin. All of these lesions must be carefully evaluated with MRI to diagnose occult spinal dysraphism (**Figs 3A and B**).

**Neurogenic Bladder and Bowel in Spina Bifida**

Neurogenic bladder and consequent renal dysfunction is the most important determinant of mortality after a successful surgical closure of a NTD. Depending on the level of the lesion, the bladder can either be flaccid (inert) or spastic. A flaccid bladder is seen when the S2-4 nerve roots are affected by lower motor neuron type of pathology. It shows poor detrusor contractions and poor emptying, leading to large amount of stagnant urine and overflow incontinence. A spastic bladder is characterized by uninhibited



**Figures 2A to C** Spina bifida aperta. (A) Meningocele; (B) Meningo-myelocele: 1. Lumbosacral, 2. Thoracic, 3. Cervical; (C) Rachischisis

detrusor contractions and detrusor-sphincter dyssynergia, causing urinary dribbling and ineffectual emptying. Both can lead to infections, increased back pressure, vesicoureteric reflex and renal damage.

Thorough assessment of the urinary system is required including micturating cystourethrogram, nuclear scans of the kidney [diethylene triamine pentacetic acid (DTPA), dimercapto succinic acid (DMSA) and glomerular filtration rate (GFR)] and urodynamic studies. Depending on the pattern of bladder dysfunction, treatment is initiated. Clean intermittent catheterization (CIC) and timed voiding are simple but effective measures to empty an inert

bladder. Drug therapy with anticholinergics is useful to combat the uninhibited detrusor contractions and detrusor-sphincter dyssynergia. Despite all the measures, incontinence may be a huge social and psychological problem. Surgical interventions such as ureteric reimplantation and bladder augmentation are required in the interest of preserving renal function. Still neurogenic dysfunction remains one of the common causes of end stage renal disease all over the world.

Children with NTD may be plagued with constipation or fecal incontinence, further compromising their social integration. An integrated bowel management program including dietary





**Figures 3A and B** Tell-tale signs in spina bifida occulta: (A) Tuft of hair; (B) Dermal sinus

#### BOX 5 Objectives of surgery of neural tube defects

1. Detethering of the neural placode from the meninges and vertebral column, and its tubularization to restore the integrity of the neural tube (spinal cord).
2. Separation of the meningeal sac from the posterior spinal structures and adjacent subcutaneous tissue and closure of the dura in a watertight fashion.
3. Covering of the defect with a fascial or muscle flap.
4. Tension free skin closure with help of rotational or advancement flaps if required.
5. If significant hydrocephalus is present, ventriculoperitoneal shunt may also be performed.

modifications, laxatives, enemas and possibly even antegrade washes from a surgically created stoma can improve the quality of life to some extent.

### Spina Bifida Occulta

This refers to simple vertebral arch defect due to failure of fusion of posterior spinal elements, usually in the lumbosacral region. There are no defects in the meninges, cord or nerve roots. Pure spina bifida occulta is asymptomatic and only detected incidentally. However, it is necessary to rule out neural defects with a MRI as these may require intervention. It should be noted that a diagnosis of spina bifida occulta should be made very carefully before the age of 1 year as the neural arches are not completely fused by then. If underlying neural defects are absent, no intervention is required.

### Tethered Cord

The developing cord initially extends till the sacrum and gradually ascends to its final level of L2 vertebra, due to the differential growth of the cord and the vertebral bodies. In case of tethering, the cord is forcibly fixed at upper sacral vertebrae and its upward migration prevented, leading to severe traction and neurological damage. The traction induced damage progressively worsens with the growth of the vertebral column and with spinal movement. The tethering may be due to a fibrous band, bony or cartilaginous spur or the stalk of a lipoma. It is commonly associated with a thickened fibrous filum.

Isolated tethering is typically diagnosed in toddlers as ambulation worsens the spinal traction and precipitates neurological symptoms like lower limb paresis and bladder/bowel symptoms.

Once diagnosed, it is recommended to perform detethering sooner rather than later as neurological deterioration may be rapid in a growing child.

### Diastematomyelia

Splitting of the cord into two halves, each with a separate dural covering is known as diastematomyelia. In contrast a split cord within a single dural tube is called *Diplomyelia*. The splitting is due to a septum which is ordinarily a bony or cartilaginous spur attached anteriorly to the vertebral body. It may have variable length with the hemi-cords merging into a single entity distal to the spur. One half of the cord may show hypoplasia or dysplasia. The dividing spur needs to be removed surgically if it causes tethering of any part of the hemi-cords.

### Congenital Hydrocephalus

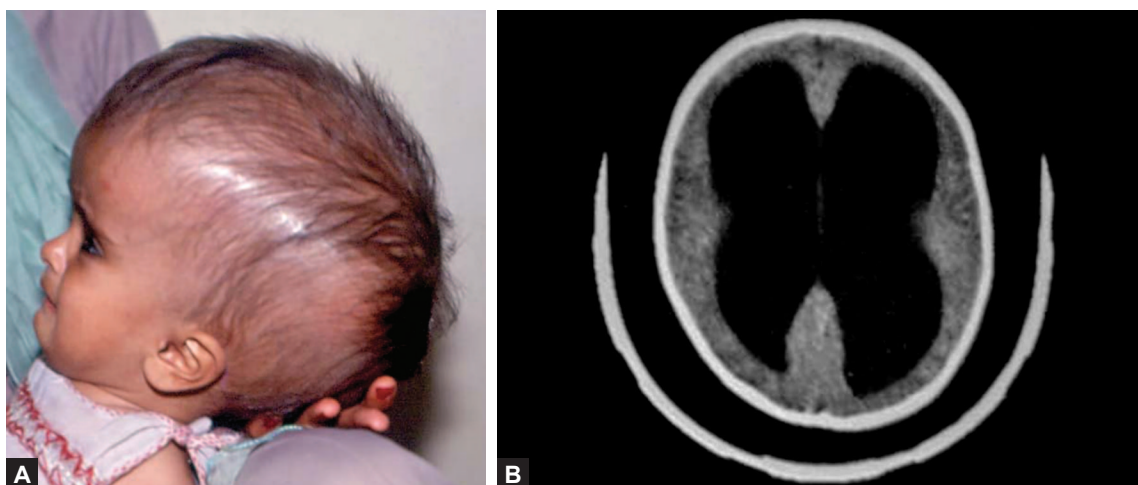
Congenital causes of hydrocephalus are enumerated in **Box 6**. Increased CSF pressure in hydrocephalus compromises the cerebral blood flow leading to retarded growth and atrophy of the brain in severe cases.

#### BOX 6 Congenital causes of hydrocephalus

- *Excess production*
  - Choroid plexus papilloma
- *Obstruction to flow*
  - Atresia/stenosis of Aqueduct of Sylvius/Foramina of Munroe/Magendie or Luschka
  - Arnold-Chiari malformation (with or without NTDs)
  - Dandy-Walker malformation
  - Intracranial cysts: Porencephalic/subarachnoid/colloid cysts
  - Vascular malformations.

### Diagnosis

Macrocephaly occurs before the signs of increased intracranial tension set in. This is accompanied by bulging anterior fontanel, splaying of cranial sutures, thin scalp with distended scalp veins and frontal bossing (**Figs 4A and B**). Increased intracranial tension (ICT) initially manifests as increased irritability, headache, nausea, vomiting, lethargy, impaired upward gaze (setting sun sign), diplopia (sixth nerve palsy) and papilledema. An USG of the head with high resistive index can diagnose hydrocephalus in children with open fontanel.



**Figures 4A and B:** Hydrocephalus: (A) Large head with shiny skin and frontal bossing; (B) CT scan showing dilated lateral ventricles

### *Treatment of Congenital Hydrocephalus*

Treatment of congenital hydrocephalus is mainly surgical and involves correction of the underlying anomaly (for example removal of the secreting papilloma or the obstructive lesion) if possible, and measures to drain the excess CSF. Restoration of the CSF drainage is done by shunting it from an area proximal to the obstruction to a site capable of its reabsorption. The most commonly performed procedures shunt the CSF into the peritoneal cavity (ventriculoperitoneal shunt), pleural cavity (ventriculopleural shunt), atrium (ventriculoatrial shunt) or any hollow viscus such as gallbladder or urinary bladder. Endoscopic third ventriculostomy (ETV) is another option in which a window is created endoscopically between the third ventricle and the basal cisterns, bypassing the aqueduct and the fourth ventricles. This works well in aqueductal stenosis and posterior fossa obstructive lesions.

Nonprogressive hydrocephalus secondary to NTDs may be managed medically after the treatment of the NTD. The CSF production is inhibited by means of carbonic anhydrase inhibitors like acetazolamide and ICT is controlled by osmotic agents like glycerine. This requires close monitoring with readiness to intervene surgically at the earliest indication of increased ICT causing compromised cerebral blood flow and clinical deterioration.

### **Arnold Chiari Malformations**

Chiari malformations refer to a group of similar abnormalities characterized primarily by a hypoplastic posterior fossa and altered structural relationship between the cerebellum, brainstem, spinal cord and the base of the skull. They occur 4 times more frequently in females. The term Arnold Chiari malformation is preferably reserved for Chiari Type II malformation.

#### *Chiari I Malformation*

This is the commonest and mildest of the Chiari malformations and the only one which may be acquired. It is characterized by the herniation of only the cerebral tonsils through the foramen magnum. It may be associated with cervico-thoracic syringomyelia. Hypermobility occipito-atlantal joint in Marfan syndrome or Ehler Danlos syndrome may lead to this malformation.

#### *Chiari II Malformation*

This is seen almost exclusively with NTDs. Both the cerebral tonsils and the brainstem herniate through the foramen magnum. This

is thought to occur due to spinal cord tethering and consequent traction on the posterior fossa structures leading to herniation. It causes obstruction of the flow of CSF from the brain to the spinal cord and therefore leads to hydrocephalus.

#### *Chiari III Malformation*

It causes the most severe neurological deficit and involves herniation of the entire cerebellum and brainstem into the spinal cord. An occipital encephalocele may be an associated pathology.

#### *Chiari IV Malformation*

This is extremely rare and usually incompatible with life. It involves incompletely developed or undeveloped cerebellum with exposed parts of skull and spinal cord.

*Signs and symptoms* are related to cerebellar and brainstem dysfunction and associated hydrocephalus. These include headache, tinnitus, nausea, vertigo, nystagmus, bulbar palsy, impaired muscle coordination, dysautonomic symptoms, syncope and motor weakness. MRI is the best investigation, though CT is most commonly used for diagnosis.

*Treatment* of Chiari malformations is guided by clinical symptoms rather than the radiological findings. It involves decompression of the posterior fossa by laminectomy of the cervical vertebrae and occipital bone flaps. A shunt procedure is usually added for the associated hydrocephalus.

### **Dandy Walker Malformation (DWM)**

This malformation consists of a spectrum of anomalies, resulting from a hypoplastic or absent cerebellar vermis which is replaced by a thin membrane. There is associated obstruction to the fourth ventricle outflow, resulting in hydrocephalus and ballooning of the thin membrane as a posterior fossa cyst. It is usually associated with other anomalies of proliferation and migration including corpus callosum agenesis and lissencephaly. It has also been reported with trisomies 13 and 18 and with maternal warfarin intake. The children may demonstrate a range of symptoms from being totally asymptomatic to being severely debilitated due to hydrocephalus and cerebellar hypoplasia. The affected children show poor motor development, lack of muscle coordination, jerky movements, occipital bulging and lower cranial nerve palsies in addition to signs of raised ICT. MRI is the recommended investigation for diagnosis. Treatment is mainly directed towards relief of hydrocephalus.



## Craniosynostosis

Craniosynostosis refers to premature closure of one or more sutures of the skull. It may be syndromic or isolated. The common syndromes associated with craniosynostosis are enumerated in **Box 7**. The bone is unable to grow in a direction perpendicular to the fused suture and therefore disproportionate growth occurs in a parallel direction leading to characteristic appearance of the head (**Box 8**) (**Figs 5A and B**).

The severity and phenotype of the craniosynostosis depends on the number and the specific suture showing premature fusion. A single prematurely closing suture does not lead to significant functional impairment and surgery may be done only for cosmetic correction. Fusion of multiple sutures results in restricted growth of the brain leading to retarded development and increased ICT. In this case surgery is aimed at excision of the fused suture to allow for the growing brain to expand appropriately. If corrective surgery is carried out before complete growth of the brain (preferably before 2 years), the overall mental development suffers minimally and prognosis is good.

### BOX 7 Common syndromes associated with craniosynostosis

- Apert syndrome
- Crouzon syndrome
- Pfeiffer syndrome
- Jackson-Weiss syndrome
- Muenke syndrome
- Loeys-Dietz syndrome
- Saethre-Chotzen syndrome
- Shprintzen-Goldberg syndrome.

### BOX 8 Prematurely fusing sutures and resultant phenotypes

- Scaphocephaly or Dolicocephaly: Sagittal suture
- Brachycephaly: Bilateral coronal sutures
- Trigonocephaly: Metopic suture
- Plagiocephaly: Unilateral coronal or lambdoid sutures
- Oxycephaly or Turricephaly: Coronal and lambdoid suture
- Kleeblattschädel (cloverleaf skull)/Pansynostosis : Fusion of all the sutures.

## DISORDERS OF REGIONALIZATION

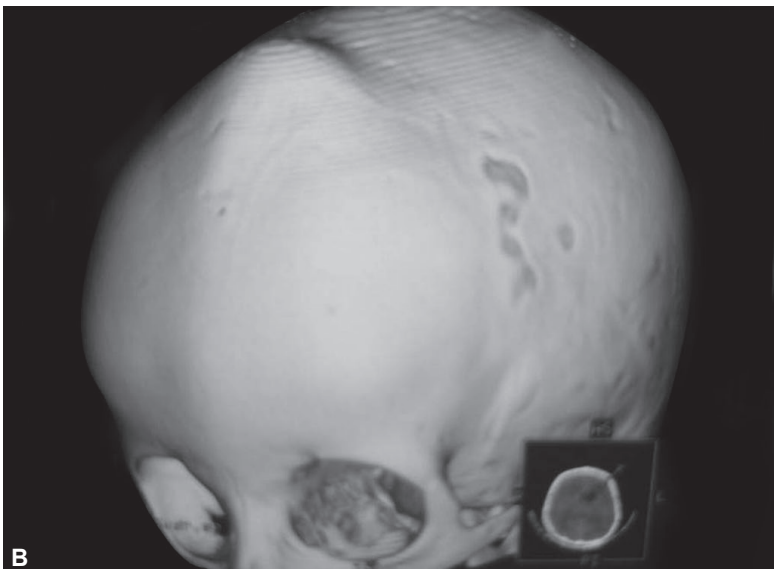
### Holoprosencephaly

Abnormalities of ventral induction in the anterior part of the neural tube lead to malformations of the midline brain and facial structures. This is most commonly due to mutations in sonic hedgehog gene which plays a major role in intercellular signaling and structural induction. It presents as a spectrum of varying severity ranging from isolated olfactory aplasia (arhinencephaly), mild hypotelorism or single central incisor to the most severe malformation where there is failure of the forebrain or prosencephalon to separate into two cerebral hemispheres. In the most severe types the midline intracranial structures are fused leading to a single ventricle, fused basal ganglia and absent falx cerebri. This is associated with fusion of the facial structures in midline, resulting in single eye (cyclopia), single nasal chamber and premaxillary agenesis. The mortality associated with the severe variant is high; however, milder variants may not even be recognized except for cosmetic reasons.

## DISORDERS OF NEURONAL MIGRATION

Migration of neuroblasts begins from the center of the neural tube or the ventricular region. The glioblasts and their axons provide the scaffolding which directs the developing neurons to the right position in the cerebral cortex leading to organization of a six layer cortex. Disorders of migration can be diffuse or focal. The failure of migration may occur due to lack of initiation or arrest of migration anywhere along the path, giving rise to heterotopic tissue rests. No cure can be offered for gross structural anomalies, however symptomatic heterotopic cell rests may be managed symptomatically or even offered surgery.

Lissencephaly (agyria-pachgyria), schizencephaly (presence of clefts), and porencephaly (presence of cysts) are the three main malformations in this group. The first two will be described in detail in the Chapter on brain malformations in Section 42. Porencephaly refers to the presence of white matter lined cysts in the brain, communicating with the ventricles or the subarachnoid space. It occurs due to arrest of migration of neurons intended for the area of the cyst. However they should be differentiated from pseudo-porencephalic cysts developing perinatally due to hemorrhage or infarction. True porencephalic cysts have smooth



**Figures 5A and B** Craniosynostosis: (A) Fusion of multiple sutures; (B) Reconstructed 3D image of a CECT scan showing the fusion of the sutures

walls, pericystic polymicrogyria and distorted pattern of gyri. The symptoms depend on the location of the cyst and include mental retardation, spastic hemi or quadriplegia, optic atrophy, seizures and microcephaly.

## DISORDERS OF PROLIFERATION

### Microcephaly

Microcephaly is defined as head circumference less than 3 standard deviations below the mean for that age. It is not a single malformation but a product of arrested proliferation of neurons due to various causes (**Box 9**). It may be accompanied by any of the disorders of migration described above. It may not be purely congenital, and can also occur due to poor brain development during first two years of life.

Microcephaly can be *microcephaly Vera (MV)* which is purely due to nonproliferation of the germinal neuroblasts or *microcephaly with simplified gyral pattern (MSG)* in which hypoplasia is coupled with disordered migration. MV is characterized by thin cortex and scarcity of neurons in layer II and III of the cortex. The children have varying degree of mental retardation but seizures are rare. In contrast MSG is associated with lissencephaly and has a much worse prognosis. Severe mental retardation is accompanied by intractable seizures developing in the neonatal period along with diffuse spasticity.

Serial head circumference measurement along with CT or MRI features of thin cortex and dilated ventricles can confirm microcephaly. It is also important to investigate for any underlying metabolic or genetic cause, if any, to prevent recurrence in the family. Treatment is mainly supportive and includes counseling and special education to help the child integrate into the society in the best possible way.

#### BOX 9 Causes of microcephaly

- Primary (genetic):
  - Trisomies 18, 21
  - Autosomal recessive (Familial)
  - Autosomal dominant mutations
  - Syndromic
    - Cri-du-chat syndrome
    - Cornelia de Lange syndrome
    - Smith-Lemli-Opitz syndrome
- Secondary
  - Maternal alcohol or cocaine abuse
  - Metabolic disorders –phenylketonuria, maternal diabetes
  - TORCH infection
  - Radiation exposure of developing fetus
  - Malnutrition during first two years of life.

## VASCULAR MALFORMATIONS

Vascular malformations of the CNS include arteriovenous malformations (most common), capillary telangiectasias, hemangiomas and aneurysms of the intracerebral vasculature. They represent 5–10% of all intracranial space occupying lesions and are responsible for 30–80% of all intracranial hemorrhages. These cause symptoms due to local mass effect, hemorrhage, perilesional edema and increased ICT. Seizures and headaches are the most common manifestations, but localizing symptoms such as ataxia, visual or speech disturbances are also seen. Spinal vascular malformations can cause cord compression and symptoms of paraplegia. However, a large number of them may not cause any symptoms and may be detected only incidentally. Malformations

of vein of Galen deserve special mention because they manifest soon after birth and cause severe symptoms, especially due to obstructive hydrocephalus.

MR angiography is the diagnostic modality of choice for vascular malformations. Treatment options include focused radiotherapy, endovascular embolization and open surgical excision.

## PROGNOSIS

Despite best efforts, the long-term picture for cure of congenital CNS malformations is not rosy. Most of the malformations like disorders of migration and proliferation cannot be cured. Mental retardation and physical handicaps are often severe. Ensuring an independent self-sustaining existence for many of the patients may be an uphill task. Functional training including speech and auditory therapy, physical rehabilitation and occupational training are some of the means of meaningful integration of these children in the society. Even in the surgically *curable* disorders like NTD, the quality of life is highly compromised due to fecal and urinary incontinence, renal dysfunction, lower limb paraplegia, hydrocephalus with repeated shunt complications, etc. The parents and caretakers of these children suffer from enormous physical, emotional, financial and social trauma.

It is for this reason many parents now opt for termination of pregnancy in case of antenatal diagnosis. The increasing antenatal detection and subsequent termination may be partly responsible for the decreasing incidence of these malformations in live born neonates. What increases the ethical predicament of such a decision both for the doctor and the parents is the fact that no sign or physical finding can accurately predict the extent of the expected physical and mental disability in the child except in a few drastic situations like anencephaly.

The situation is even more difficult after the child is born with an NTD. There is no confusion about need of surgery in a child with minimal or no preexisting neurological deficits. However, in a child with established severe neurological deficits like paraplegia the decision to operate or not is very tough. On one hand it appears unethical to withhold surgery, especially since the survival rate with good surgical care is greater than 90%. On the other hand is the very real possibility of saddling the parents with a child who may have a repaired NTD but cannot walk, has no control on his bowel or bladder, is mentally retarded, requires multiple orthopedic and shunt surgeries and extensive rehabilitation programs, and is probably going to spend all his life in and out of treatment and rehabilitative facilities and still may not be a happy, functional, independent individual. The parents should be honestly counseled about the condition and expected outcome and allowed to have the major role in the decision making. In most centers, children with severe neurological deficits are operated, only if they survive till one month or beyond, for the ease of future nursing care.

## Recent Research

It was observed that the neurological damage worsened with exposure of the neural tissue to amniotic fluid. Management of Meningomyelocele Study (MOMS) was a multicentric prospective trial that compared the neurological outcome after fetal and postnatal repair of NTDs. It was found that in utero repair of NTDs between 19 weeks and 26 weeks of pregnancy improved the motor function and decreased the incidence of hydrocephalus and requirement of shunts at 1 year. However fetal surgery carries the risk of fetal wastage and prematurity and presently can be offered only at selective centers.

### IN A NUTSHELL

1. CNS malformations are one of the commonest individual malformations afflicting neonates, though their incidence is decreasing. Neural tube defects are the most common CNS malformations.
2. Though the etiology is multifactorial, folic acid deficiency is responsible for almost 70% of the NTDs. Genetic, environmental and metabolic factors also contribute.
3. Teratogenic insults during the first 3 months of embryogenesis leads to CNS malformations. The malformations are classified according to the stage of faulty embryogenesis responsible.
4. NTDs have a spectrum of manifestations ranging from defects that can only be detected on MRI to completely exposed spinal cord and central canal with complete neurological deficit below the lesion. Therefore even small midline abnormalities should be investigated thoroughly. The anatomic location and severity of damage to the exposed neural tissue determines the extent of associated neurological deficit.
5. In addition to local treatment of the lesion, complete assessment and treatment of associated disabilities like hydrocephalus, paraplegia and neurogenic bladder, bowel dysfunction is required. Multispecialty coordination with long-term follow-up is essential for good quality of life.
6. Fetal repair of NTDs has shown a decrease in the requirement of shunts and better neurological function according to the MOMS trial results. However intrauterine intervention carries the risk of fetal wastage and prematurity.
7. Folic acid supplementation has been the most effective public health measure to decrease the morbidity from NTDs. Supplementation should begin 3 months before conception and continue through the first trimester to be effective.

### PREVENTION

The best bet to reduce the morbidity from congenital CNS malformation is by preventing them. Periconceptional folic acid intake has been conclusively proven to decrease the incidence of CNS malformations. To be effective folic acid supplementation must begin at least 3 months before conception. The recommended dose is 0.4 mg per day to prevent first occurrence and 4 mg to prevent recurrence in subsequent pregnancies. Many countries have resorted to routine fortification of flour to ensure adequate folic acid supplementation.

### MORE ON THIS TOPIC

- Cherian A, Seena S, Bullock RK, Antony AC. Incidence of neural tube defects in the least developed area of India: A population based study. *Lancet*. 2005;366:9230-931.
- Kulkarni ML, Jose S. Folic acid prevents neural tube defects in high prevalence area. *Indian Pediatr*. 1997;34:561-2.
- Leland A, Pollock IF, Adelson PD. *Principles and Practice of Pediatric Neurosurgery*, 2<sup>nd</sup> ed. Thieme Publishers; 2008.
- MRC Vitamin Study Research Group. Prevention of neural tube defects : Results of Medical Research Council Vitamin Study. *Lancet*. 1991;338:131-7.
- Smith JL. Management of Neural Tube Defects, Hydrocephalus, Refractory Epilepsy and Central nervous System infections. In: Grosfeld JL, O'Neill Jr J, Coran AG, Fonkalsrud EW. *Pediatric Surgery*, 6<sup>th</sup> ed. USA: Mosby-Elsevier Publishers; 2006.
- Stark GD. *Spina Bifida: Problems and Management*. Blackwell Scientific Publications; 1977.
- Verity C, Firth H, French-Constant C. Congenital abnormalities of the central nervous system. *J Neurol Neurosurg Psychiatry*. 2003;74:suppl\_1.i3.

# PART V The Childhood Years

## Section 19 GROWTH: NORMAL AND ABNORMAL

Section Editor Anju Seth

### Chapter 19.1

### Normal Growth

Ruchi Mishra, Vandana Jain

*Growth* is the process of increase in size or mass of a living being as a result of increase in size or number of cells and/or increase in the intracellular matrix. The term *development* is used to connote the process of attainment of functional maturity. Growth occurs in an orderly and organized manner from the time of conception till the closure of epiphyses. It is an integral component of childhood and a marker of health. Deviation from the expected pattern of growth, in terms of gain in length, weight and head circumference may be the first indicator of an underlying illness. In this chapter an outline of the physiology and pattern of normal growth from conception to adolescence is presented.

#### FETAL GROWTH

This is the period of maximum growth. At conception, the zygote measures 130  $\mu\text{m}$  in length and 10  $\mu\text{g}$  in weight. It multiplies its length and weight several times to reach the size of 50 cm and 3 kg at term. Normal fetal growth involves an increase in cell number during the earlier part of gestation, followed by an increase in cell size, which becomes dominant after 32 weeks gestation.

#### Phases of Growth

Fetal growth can be broadly divided into four phases according to the rate of growth:

1. *Up to 16 weeks—Slow rate, less than 10 g per week:* The period from conception to 9 weeks of gestation is termed as embryonic period. Implantation begins on the 6th postconceptional day. At this time, the embryo is a spherical mass of cells with a central cavity and is termed as the blastocyst. By the 2nd week, as the implantation completes, the uteroplacental circulation starts developing. At this time, the embryo is bilaminar. By the 3rd week, mesoderm appears along with primitive neural tube and blood vessels. Between 4th week and 9th week, there is growth at the cranial and caudal ends leading to the development of arms and legs. Skeletal muscles and vertebral precursor also appear. Structures of the face and neck differentiate and lens placode appears. There is rapid growth of the brain along with formation of rudimentary organ systems, the heart and gastrointestinal system begin developing at 5th week, while the formation of lungs begins at 8th week. By the end of the embryonic period (9 weeks), the average embryo weighs about 9 g and measures about 5 cm. By the
2. *16–28 weeks—Accelerated rate, approximately 85 g per week:* During this period, there is further growth and maturation of the organ systems. In the lungs, alveoli develop and production of surfactant begins at about 22–24 weeks. Myelination of the nervous system begins around midgestation and continues till around 2 years of age.
3. *28–37 weeks—Maximal rate, nearly 200 g per week:* There is accrual of protein, fat, iron, calcium and phosphorus during this period along with further maturation of organ systems. The weight triples and the length doubles during this period.
4. *37–42 weeks—Decelerated rate, approximately 70 g per week:* The fetus is considered full term beyond 37 completed weeks. There is minimal growth beyond 42 weeks.

#### Physiology of Fetal Growth

Normal growth *in utero* depends on the genetic potential of the fetus modulated by environmental hormonal and other biological factors, including maternal health and nutrition. The primary regulators of fetal growth are nutrition, insulin and insulin-like growth factors (IGFs). A strong correlation exists between maternal height and weight, and birthweight. This is also referred to as maternal constraint, and is important to limit fetal overgrowth to prevent subsequent dystocia, and preserve mother's capacity for future successful pregnancies. Other maternal factors that affect fetal growth include her nutrient intake during pregnancy, anemia, smoking, alcohol consumption, infections and chronic diseases, and pre-eclampsia.

The placenta is a highly efficient multifunctional organ that integrates signals from both mother and fetus to match fetal demand with the maternal substrate supply of nutrients and gases, while ensuring that fetal waste products are transferred back to the mother. The total placental surface area for exchange is 11  $\text{m}^2$  at term. In fetal growth restriction, the placental villus surface area and placental volume are decreased. Several aspects of placental function are critical for human fetal growth and development, including adequate trophoblast invasion, increase in uteroplacental blood flow, transport of glucose and amino acids from mother to fetus, and the production and transfer of growth regulating hormones.

Placental adaptation in early pregnancy can overcome maternal undernutrition so that fetal nutrition is maintained during the phase of rapid growth in late gestation. A classical example of this is the Dutch Famine of 1944–1945. Women who suffered starvation in their third trimester of pregnancy had lower weight of the placentae as well as of the newborns, with placental weight: birthweight ratio comparable to nonstarved women. In contrast, exposure to famine only during first trimester resulted in enhanced



placental weight, with no adverse effect on newborn weight, suggesting that the plasticity of placenta allows it to compensate for some of the environmental stressors in early gestation.

### Hormonal Influence on Intrauterine Growth

The hormones produced by placenta include estrogens and progesterone, human chorionic gonadotropin (hCG), human growth hormone (GH) variant, and human placental lactogen (hPL), besides organ specific hormones, such as, corticotropin releasing hormone (CRH) as well as hepatic and epidermal growth factors.

Among the various endocrine factors controlling growth in intrauterine life, insulin, IGF-1 and IGF-2 are the most important. The fetal pancreas produces *insulin* in response to nutrient supply and this has a direct growth promoting effect. Insulin induces protein synthesis and hepatic glycogen deposition, increases nutrient uptake and utilization and stimulates the lipogenic activity leading to rapid accumulation of adipose tissue mostly during third trimester. Insulin deficiency results in a reduction in fetal growth, while increased fetal insulin production (as occurs in fetal hyperglycemia in diabetic mothers) results in macrosomia.

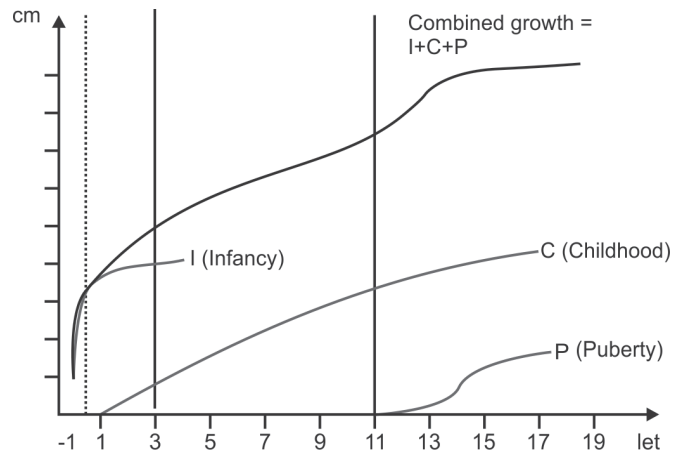
Early evidence for the role of *IGF-1* and *IGF-2* in fetal growth was mostly associative. Serum IGF-1 levels were lower and GH levels higher in small for gestational age (SGA) newborns as compared to those with normal weight. Mouse models of IGF-1 and IGF-2 deficiency are born small and have the phenotype of intrauterine growth restricted (IUGR) humans, such as, slow postnatal growth and increased insulin resistance. Insulin, placental lactogen, growth factors, nutrient flux and glucose availability control IGF-1 secretion *in utero*. Experimentally, fetal pancreatectomy reduces IGF-1 levels with resultant compromise of fetal growth, and glucose or insulin infusion stimulates growth.

*Glucocorticoids* are essential for the development and maturation of fetal organs before birth. There is a rise in cortisol concentration during late pregnancy that parallels the increased maturity of fetal organs. In human pregnancy, endogenous maternal cortisol concentrations are 5–10 times higher than fetal cortisol concentrations, and this difference is maintained by the presence of 11 $\beta$  hydroxysteroid dehydrogenase 2 (11 $\beta$ -HSD2) in the placenta, which acts as a barrier enzyme to control the passage of cortisol from mother to fetus. Alterations in the activity of the placental 11 $\beta$ -HSD2 barrier, which result in an increase in maternal glucocorticoids crossing to the fetus, may have a deleterious effect on fetal growth and postnatal development.

*Other factors* like epidermal growth factor, fibroblast growth factor and leptin, a hormone produced by adipose tissue, also play a role in fetal growth and nutritional homeostasis. Any damage to the placenta or placental failure due to any cause results in fetal growth restriction, which may be symmetrical, i.e., weight, length and head circumference are all evenly decreased, if it occurs early in pregnancy, or asymmetrical, i.e., predominant effect on weight, if it occurs later in pregnancy.

### THE INFANCY-CHILDHOOD-PUBERTY MODEL OF GROWTH

Human growth curve has been described by various mathematical models. The hormonal regulation of human growth is very well described by the infancy-childhood-puberty (ICP) model proposed by Karlberg et al (Figure 1). It places the assessment of growth in a dynamic context. It presents growth as an additive function of various biological processes. The rapid growth of the first 2–3 years is represented by an exponential curve, which is largely nutrition-dependent. Both over- and undernutrition in this phase have long-term effects. The childhood phase is represented by a second degree polynomial regression. Until 3 years of age,



**Figure 1** The infancy-childhood-puberty (ICP) growth model for height for boys (Karlberg, 1989)

Reproduced with permission from John Wiley and Sons. Copyright© 2008, John Wiley and Sons. Karlberg J. Acta Paediatrica Scand. 1989;350:70-94.

growth is the additive combination of infancy and childhood components. The childhood component is chiefly GH-dependent. The final component of the model deals with puberty, when growth is described by a logistic function dependent on a combination of GH and sex steroids. This is superimposed on the decelerating childhood model which shows that the magnitude of growth spurt of adolescents is inversely related to the age at peak height velocity.

### INFANCY AND EARLY CHILDHOOD

The terminology used for the various phases of childhood growth is presented in **Box 1**.

#### BOX 1 Nomenclature for different age groups

- **Neonate:** From birth till 28 days of life
- **Infant:** Birth to 12 months of life
- **Toddler:** Children between 1 year and 3 years of life
- **Preschooler:** Children between 3 years and 5 years of age
- **School-aged:** Boys 6–12 years, girls 6–10 years
- **Adolescent:** Children between 10 years and 19 years of life.

### The First Year

The first year of life is marked by rapid physical growth, maturation and acquisition of competence. The newborn shows 7–10% decrease in birthweight in the 1st week of life due to loss of excess extravascular fluid and limited intake. Nutrition improves as colostrum is replaced by breastmilk with higher fat content and as the mother and child regularize the feeding process and schedule. Birthweight is again achieved or exceeded by the end of 2nd week of life and the subsequent rate of weight gain is approximately 30 g/day for the first 2 months. This is the period of fastest postnatal growth. Between 3 months and 4 months, weight gain is at the rate of 20 g/day, so that the infants double their body weight by 4–5 months of age. Between 6 months and 12 months, physical growth slows further. By the first birthday, weight is approximately three times the birthweight, head circumference has increased by 10–12 cm, and length by 50% (Table 1).

### The Second Year

The growth rate declines in the 2nd year along with a decline in appetite and increase in physical activity. Children reach half their adult height by the end of 2nd year. Toddlers have a long torso and short limbs with a protruding abdomen. The head circumference also increases as myelination proceeds. Ninety percent of the head

circumference is achieved by the end of 2nd year with an additional 5 cm achieved over the next few years (**Table 1**).

### Preschool Years

During the preschool years (age 3–5 years), the child grows by 6–8 cm/year and gain 2–3 kg weight/year. Weight is four times the birthweight by 2½ years. Many preschool children have physiological pes cavus and genu valgum that correct spontaneously with age. Growth in the first 2–3 years of life is determined predominantly by nutrition, bone metabolism and a normal thyroid function. Nutritional requirements are high during this period as there is rapid somatic growth. Good nutrition involves adequate calorie and protein intake, sufficient micronutrients like iron and zinc and good social stimulation, i.e., happy and encouraging home environment.

About two-thirds of the infants with IUGR show catch-up growth in the first 2 years of life as the growth-restraining intrauterine influences are removed and postnatal nutrition is adequate. On the other hand, inadequate nutritional intake, due to organic or inorganic causes results in growth deceleration, referred to as *failure to thrive*. Growth deceleration is an adaptive response to suboptimal nutrition. Diminished growth brings the nutrient demand into balance with the nutritional intake without adversely affecting the biochemical and functional homeostatic measures.

Sufficient intake of calcium and vitamin D is required for adequate bone turnover. Thyroid hormones are of paramount importance in postnatal growth by having a direct effect on epiphyseal cartilage as well as a permissive effect on growth hormone secretion.

### Growth in Mid-childhood

From 5 years of age until the onset of puberty, linear growth velocity is the slowest (4.5–6 cm/year) and weight gain is approximately 2 kg/year. Growth occurs irregularly in 3–6 timed spurts per year. A growth velocity less than 4.5 cm/year should alert the physician to evaluate for cause of growth retardation. Head circumference increases by 2–3 cm in the entire period.

Growth in mid-childhood is chiefly hormone dependent. GH acting directly, and through IGF-1, is the main growth promoting factor for cell division and growth. GH is produced in a pulsatile manner under the reciprocal influences of growth-hormone-releasing hormone (GHRH) and somatostatin. This balance is maintained by a number of neurotransmitters, neuropeptides, as well as metabolic, neurologic and hormonal influences. Ghrelin, a 28 amino acids or exogenic polypeptide secreted from the oxyntic cells of gastric fundus, also promotes GH release. GH directly stimulates the division of resting chondrocytes in the reserve zone of the cartilage plate, as well as stimulates their secretion of IGF-1. The locally produced IGF-1 exerts paracrine effect on the chondrocytes, resulting in an increase in the number of cells in the proliferation zone, and their differentiation and progression into the hypertrophic zone. IGFs constitute a family of peptides that is partly GH dependent, and mediates many of the anabolic and mitogenic actions of GH. IGF-1 is a 70 amino acid peptide with an approximately 50% homology to insulin. IGF-1 level in newborns is generally 30–50% of adults. There is a gradual rise in serum concentration with age with attainment of adult levels at the onset of puberty. Hepatic IGF-1 circulates almost entirely bound to IGF binding proteins (IGFBPs) with less than 1% being free. IGFBPs control the action of IGF by controlling its storage and release in extracellular matrix. The principal binding protein is IGFBP-3, which binds 75–90% of circulating IGF-1 in a large ternary complex consisting of IGFBP3, IGF-1 molecule and acid labile subunit (ALS).

### Adolescent Growth

Adolescence is the period in human growth and development, from ages 10 years to 19 years, during which there is a gradual attainment of physical, reproductive, social and mental maturity. With the onset of puberty, there is an increase in growth velocity. The peak growth velocity during this period is nearly double the velocity in the prepubertal phase. There is asymmetric pattern in growth with the hands and feet growing first, followed by arms and legs, and finally the trunk and chest.

*Girls* have a peak in growth velocity during early puberty and before menarche, i.e., Tanner stage II–III with a mean velocity of 9 cm/year (range 7–11 cm/year). The appearance of breast buds (age 8–12 years) marks the onset of puberty. Menarche occurs after 2–3 years of onset of puberty (age 9–16 years, median 12 years). There is change in body habitus with female pattern of fat deposition, i.e., around hips and thighs. The adolescent growth spurt lasts for 2.5–3 years, during which the average height gain is 24–26 cm in girls. The average gain in height postmenarche is 6–8 cm, being more in girls who attain menarche at a younger age and lesser in those who attain menarche at an older age.

In *boys*, peak growth typically begins 2–3 years later than girls (at age 12–15 years) and at a later sexual maturity rating (SMR) stage. Boys have peak growth velocity around Tanner stage III–IV during which they have a mean growth velocity of 7–13 cm/year (average 10.3 cm/year). Testicular enlargement marks the beginning of puberty in boys, peak growth occurs when the testicular volume reaches 9–10 mL. The average total growth during the pubertal spurt is 27–30 cm. Boys have longer growth spurt period than girls. Rapid enlargement in the larynx and pharynx leads to voice cracking followed by changes in the voice. There may be considerable variation in these figures depending upon the age at onset of puberty. A kind of compensatory mechanism is seen to occur where individuals with earlier puberty grow less before puberty and more during puberty while those with late pubertal development start their puberty taller but grow less during puberty.

### Physiology of Adolescent Growth Spurt

At puberty the pulsatility and the basal levels of GH secretion increase 2–3 fold, enhanced primarily by estrogen. Along with the increase in estrogen, androgens and GH there is increase in the synthesis of hepatic and chondrocyte IGF-1 resulting in rapid chondrocyte proliferation, thus leading to growth surge.

Estrogen in both boys and girls (through peripheral aromatization of testosterone) brings about epiphyseal maturation, with eventual bony fusion and growth cessation. At low levels, estrogen enhances the growth of chondrocytes in the proliferative zone; while at higher levels, it decreases chondrocyte proliferation, and accelerates maturation, senescence, apoptosis and osteoblastic invasion of the cartilaginous growth plate. Estrogen also enhances the local production of IGF-1 and its receptors directly.

### CHANGE IN BODY PROPORTION

Assessment of body proportion is an important part of the assessment of linear growth in children. Different parts of the skeleton grow at different rates. In the initial phases of growth, upper part of the body (torso and head) are larger, but as the child becomes older, there is greater growth of the extremities, thus changing the upper segment (US) to lower segment (LS) ratio.

Lower segment is the distance between the upper border of pubic symphysis and the floor in a patient who is standing against a vertical board/wall in proper position for height measurement. This reading may be erroneous because it is difficult to palpate the upper border of symphysis pubis, especially in obese children, and is seldom recommended. Sitting height can be taken as a

**Table 1** Rate of growth in terms of weight, length and head circumference from birth to 6 years

Age	Increase in head circumference (cm/month)	Increase in length (cm/month)	Increase in weight
0–3 months	2.0	3.5	30 g/day
3–6 months	1.0	2.0	20 g/day
6–9 months	0.5	1.5	0.5 kg/month
9–12 months	0.5	1.2	0.5 kg/month
1–3 years	0.25	1.0	2 kg/year
4–6 years	1 cm/year	5 cm/year	2 kg/year

surrogate marker of US. This is measured by making the child sit on a horizontal stool with straight edges (square or rectangular stool) of known height against the vertical board. LS can be derived by subtracting the sitting height from the total height.

Upper to lower segment ratio is 1.7:1 at birth and goes on decreasing as the limb length increases to reach 1:1 at 10 years of age and 0.9:1 after the completion of adolescent growth. In precocious puberty, as the bones fuse early the body proportion is childlike (higher US:LS ratio), whereas in hypogonadism, extremities are much longer than the trunk. US:LS ratio is affected in skeletal dysplasia, being higher in short-limbed dysplasias such as achondroplasia, and lower in conditions with short trunk such as spondylo-epiphyseal dysplasia.

Arm span is estimated by making the child stand with outstretched hands against a flat wall with the arms held horizontally to create 90° angle to torso. The fingertip to fingertip distance is measured. Arm span is shorter than the height in boys before the age of 10–11 years and in girls before the age of 11–14 years after which it exceeds the height. In adults, the arm span is greater

than the height by about 5.3 cm in males and 1.2 cm in females. Measurement of arm span is useful in the clinical diagnosis of disproportionate short and tall stature. For example, arm span is increased (compared to height) in Marfan syndrome and decreased in achondroplasia. Arm span is also useful for estimation of height in children with severe spinal deformity or severe cerebral palsy who cannot stand.

### IN A NUTSHELL

1. Growth in children is an important marker of the overall health.
2. Fetal period is the period of maximum growth, modulated by intrinsic fetal factors as well as maternal factors.
3. Growth in infancy and early childhood is driven chiefly by adequate nutritional intake and in mid-childhood by hormonal balance.
4. Adolescence is the next rapid phase of growth during which there is a gradual attainment of physical, reproductive, social and mental maturity. This phase is driven by growth hormone and sex steroids.

### MORE ON THIS TOPIC

- Delemarre-van de Waal HA, van Coeverden SC, Rotteveel J. Hormonal determinants of pubertal growth. *J Pediatr Endocrinol Metab.* 2001;14(6):1521-6.
- Gasser T, Kneip A, Binding A, et al. The dynamics of linear growth in distance, velocity and acceleration. *Ann Hum Biol.* 1991;18:187-205.
- Karlberg J. A biologically-oriented mathematical model (ICP) for human growth. *Acta Paediatr Scand Suppl.* 1989;350:70-94.
- Sferruzzi-Perri AN, Vaughan OR, Forhead AJ, Fowden AL. Hormonal and nutritional drivers of intrauterine growth. *Curr Opin Clin Nutr Metab Care.* 2013;16:298-309.

## Chapter 19.2

# Factors Affecting Growth

*Devi Dayal, Anil Kumar Bhalla*

Growth in children and adolescents is a dynamic process that may be affected by several factors and still remains remarkably predictable. An understanding of these factors allows pediatricians to timely identify and treat nutritional, chronic systemic and endocrine disorders that have growth deviation as one of the components. Major factors that affect growth in children are described in this chapter.

## HEREDITY AND GENETICS

The genetics of human growth is very complex and all inherited traits have not been identified yet. The growth of a child represents the results of interaction of genetic and environmental forces. Genetic potential as determined from the parents' anthropometry has a direct influence on a child's growth potential and the predicted adult height. The genetic influence on height is usually well established by 2–3 years of age. Assuming the normal process of heredity and almost similar environmental effects on growth in both generations, most children would achieve heights within  $\pm 2$  standard deviation (SD) of their mid-parental height. Height, head size, chest shape, fatty tissue, etc., have better genetic association than other somatic characteristics. The genetic factors also determine the pubertal patterns in children. For example, daughters attain menarche at similar age as their mothers and usually have similar length of menstrual cycle. Mutations of numerous genes encoding proteins that affect multiple pathways of regulation of cell proliferation have been shown to influence growth in children. Various chromosomal abnormalities result in distinct syndromes associated with short stature, e.g., Turner syndrome, Down syndrome and 18q deletion syndrome.

## ETHNICITY

Traditionally, it was believed that different ethnic groups show different patterns of growth. For example, Asian and Chinese population groups are shorter and lighter when compared with Caucasians and African-Caribbean groups who are taller and heavier. However, the recent Multicenter Growth Reference Study (MGRS) by World Health Organization (WHO) showed that variability in infant growth was greater within population groups of similar ethnicity than between the different country groups. It implies that the effect of ethnicity is negligible if other environmental and socioeconomic conditions are similar.

## SEASON AND CLIMATE

About 30% of children show seasonal variations in growth velocity. Height growth is fastest in spring while weight growth is fastest in autumn. The underlying mechanisms for these variations are largely unknown but probably involve variations in hormone secretion. Climate also has a minor effect on overall rate of growth. The racial variations in stature are also believed to be related to the differences in climates.

## SOCIOECONOMIC FACTORS

Children from different socioeconomic strata differ in average body size at all ages. These differences in growth result from factors

like nutrition, regularity of meals, sleep, exercise, frequency of acquiring infections, etc. Economic conditions also influence the secular trends in heights. Children living in average economic conditions have shown approximately 1–2 cm increase in height per decade. Family size also exerts an indirect influence on the rate of growth probably through factors like nutrition, individual care and attention. Psychosocial dwarfing resulting from child abuse/neglect or emotional deprivation is one of the important social causes of growth failure in children. Disturbances of growth hormone (GH) secretion, function of thyroid hormones and insulin-like growth factor-1 (IGF-1) have been noted in children with psychosocial dwarfism.

## ALTITUDE

Various biochemical, physiological and micro-anatomical responses due to fall in partial pressure of oxygen at high altitudes may affect growth of children. Children born at high altitude have lower birthweight probably due to relative intrauterine hypoxia. In general, children at very high altitudes are thinner. However, recent data from Saudi Arabia indicates that hypoxia of the degree found at altitudes of approximately 3,000 m above sea level is not sufficient to adversely affect the growth of children and altitude of this height may be more favorable to growth. Children living at low altitudes were reported to be comparatively thinner probably due to the prevailing tropical environmental conditions at low altitudes in that study.

## MATERNAL FACTORS

Intrauterine growth depends on maternal health and nutrition, the placenta that supplies food and oxygen to the fetus and the fetal genetic information. Conditions like maternal malnutrition, placental abnormalities, high blood pressure/toxemia, diabetes mellitus, infections, uterine malformations, smoking, alcohol or other drugs abuse may affect intrauterine growth. The role of fetal pituitary and thyroid hormones in fetal growth is evolving. Infants with athyreosis and anencephaly have normal size at birth. Fetal pituitary derived GH is now believed to play a small but significant contribution to fetal and immediate postnatal growth.

Weight and fat gain during pregnancy and lactation are also powerful determinants of infant size at birth and during first 6 months. Energy deficits as well as zinc and vitamin B<sub>12</sub> deficiencies in mothers living in less developed countries show up in the lesser weight and length increases in both fetal and early infancy growth. Similarly, excessive gestational weight gain is associated with increased risk of childhood overweight/obesity.

## NUTRITION

Nutrition is a major determinant of growth, especially during early childhood and adolescence. Worldwide, undernutrition is the single most important cause of growth retardation. Nutritional status also modulates the pubertal growth spurt and timing of adolescent sexual development. While undernutrition is usually associated with later age of menarche, moderate obesity may result in early sexual maturation. Voluntary undernutrition usually seen in adolescent girls, gymnasts and dancers impairs growth before epiphyseal fusion and delays puberty.

A well-balanced, age-appropriate diet that includes carbohydrates, protein, fats, vitamins, and minerals is necessary for optimal growth. The effects of nutrition and especially the effects of specific nutrients are often difficult to isolate as growth is affected by a multitude of factors. Deficiency of essential amino acids results in stunted growth. Zinc is a constituent of certain enzymes and is involved in protein synthesis; a deficiency of zinc causes stunting and interferes with sexual development. Iodine is essential for



synthesis of thyroid hormones. Iron deficiency anemia is known to affect linear growth. Vitamin A is needed for adequate osteoblastic activity and vitamin C for adequate formation of intercellular substance of bone. Similarly, calcium, phosphorus and other inorganic constituents such as magnesium and manganese are required for bone growth. Vitamin D deficiency causes rickets and retardation of linear growth.

The roles of specific nutrients like carbohydrates, protein, zinc, iron, copper, iodine and vitamin A, in the general linear growth faltering that occurs in developing countries are debated due to lack of adequate data. Interventions with each specific nutrient have been shown to have a positive effect on length gain in few studies, only weight gain in others or no effect in some studies. Also community-based interventions with supplementary feeding for promoting physical growth of children have produced conflicting results. Infant feeding practices have an influence on growth during first year of life with the breastfed infants generally remaining 0.5–0.6 kg lighter than formula fed infants.

The impaired growth in malnutrition especially in marasmus is associated with low GH and IGF-1 concentrations. However, GH levels are often elevated particularly in nonmarasmic malnutrition indicating a state of GH insensitivity. The elevation of GH is an adaptive mechanism to spare protein by lipolytic and anti-insulin actions of GH. The low IGF-1 probably shifts precious calories from growth to survival needs of the child. The accelerated linear growth after treatment of nutritional vitamin D deficiency is probably mediated through activation of the GH-IGF1 axis.

## HORMONES

A normal hormonal milieu is essential for growth during childhood and puberty. In fact, dysfunction of any hormonal system may affect growth. Major hormonal factors that affect growth are GH, IGF, testosterone, estrogen, thyroid hormones, cortisol and insulin.

### Growth Hormone

This is the most important hormone controlling growth from birth up to adolescence. GH promotes protein synthesis, inhibits the formation of fat and carbohydrate and is required for the proliferation of cartilage cells at the epiphyseal plate. Its synthesis and release from anterior pituitary are promoted by GH-releasing hormone (GHRH) and ghrelin, and inhibited by somatostatin. Thyroid and gonadal hormones particularly estradiol and testosterone and deep sleep increase pulsatile GH secretion and release whereas adiposity has a negative effect on GH production. Glucocorticoids, previously thought to have a negative influence on GH production, are now believed to play a positive role in maturation of functional somatotrophs.

Growth hormone stimulates growth through synthesis and release of IGF-1 in liver as well as through its direct effects on target tissues. In addition, it also stimulates production of acid-labile subunit and IGF-binding protein 3 (IGFBP3) in liver; proteins that are involved in the control of IGF-1 delivery to target tissues. GH related longitudinal growth is facilitated by stimulation of chondrocyte activity at the growth plate. This GH mediated chondroplasia and osteogenesis involve expression of new genes like IGF-1, IGF-1R and estrogen receptor and results in bone elongation that contributes about 60% to the total bone growth. GH also contributes to growth of other organs such as kidneys, adrenal glands and heart.

Factors that affect GH production or action at the tissue level affect growth. General factors like stress, exercise, malnutrition, and anorexia alter GH secretion and release. Changes in concentrations of various hormones that affect the GH-IGF1 axis as mentioned earlier may also result in growth retardation.

Growth hormone deficiency may result from disruption of GH axis in the higher brain, hypothalamus or pituitary by congenital or acquired conditions. Developmental anomalies of hypothalamus-pituitary area, mutations in *GHRHR* and *GH* genes, developmental defects of sella turcica and congenital absence or hypoplasia of pituitary gland are some of the congenital conditions that may result in GH deficiency either isolated or combined with other hormone deficiencies. Acquired or secondary GH deficiency may result from trauma, inflammation, tumors or irradiation involving brain and/or hypothalamus or pituitary.

Resistance to GH action either congenital as seen in Laron dwarfism or acquired as seen in malnutrition, hepatic or renal disease, and poorly controlled diabetes may result in growth faltering. GH resistance may also develop during GH therapy due to formation of GH inhibiting antibodies in patients harboring *GHI* mutations.

### Thyroxine

Thyroid hormones are essential for normal skeletal development; the growth plate being exquisitely sensitive to triiodothyronine (T3). The molecular mechanisms of thyroid hormone action within the developing bone are incompletely understood. Thyroid hormones act via two receptors, TR $\alpha$  and TR $\beta$  which are expressed by chondrocytes of the reserve, proliferative and pre-hypertrophic zones as well as by osteoblasts of the primary spongiosum but not by differentiated chondrocytes. It appears that T3 is essential for stimulating resting zone cells to differentiate to proliferating chondrocytes, for chondrocyte hypertrophy and differentiation, and for vascular invasion or angiogenesis of the growth plate.

In hypothyroid states, the growth plate is separated from the primary spongiosum by a mineralized interface that seals it off from vascular invasion and prevents further bone lengthening ultimately leading to growth retardation. Also, there is disruption of the normal functional continuity between maturing chondrocytes and mineralizing osteoblasts with markedly reduced osteoblast invasion and fewer, thinner bone trabeculae. Additionally, T3 influences expression of several components of GH-IGF-1 signaling in bone and also helps maintaining circulating concentrations of glucocorticoids (essential for maturation of somatotrophs) by regulating hepatic 11 $\beta$ -hydroxysteroid dehydrogenase.

### Sex Steroids

These are secreted by adrenals and gonads and interact with GH and IGF-1 during puberty to determine the pubertal growth spurt. Both GH and sex steroid hormones must be present for normal pubertal growth to occur. The role of sex steroids in promoting growth is limited in absence of GH and IGF-1 although they are known to have direct effect on growth. In patients with GH deficiency, GH replacement produces minimal pubertal spurt unless accompanied by sex steroid replacement. In conditions of sex steroid deficiency, the pubertal growth spurt is limited although prepubertal growth is unaffected. Both testosterone and estrogen modulate GH secretion by increasing the amplitude of GH pulses. Gonadal steroids also enhance bone mineral accrual and affect adult height by promoting epiphyseal fusion through direct effects on the growth plate. The sex steroid related growth is mainly mediated through estrogens rather than androgens. Children with complete androgen insensitivity have normal adolescent growth and achieve pubertal levels of GH and IGF-1 if sufficient concentrations of estrogen are present. Boys with inactivating mutations of estrogen receptor or aromatase gene show delayed skeletal maturation despite high levels of testosterone and continue to grow well into adulthood.

Gonadotropins secreted by anterior pituitary enhance skeletal maturation through growth of ovaries and testis which then secrete increased amounts of estrogen and testosterone. In cases of precocious puberty, the increase in sex steroids increase the immediate growth rate and the total pubertal height gain but the faster skeletal maturation decreases the period of prepubertal growth leading to loss of final height.

### Glucocorticoids

Adequate glucocorticoid production by adrenal glands is necessary for normal function of the somatotrophic axis as these help in maturation of somatotrops. In addition, glucocorticoids appear to regulate skeletal bone accumulation. However, glucocorticoid excess, especially if chronic, suppresses the secretion of GH and inhibits growth. Children with Cushing syndrome have short stature, excess adiposity and lower bone mineral density. Also chronic glucocorticoid administration in several common inflammatory conditions in children is known to be associated with linear growth failure.

### Insulin

Insulin plays an important role in the regulation of growth; its peripheral action may promote weight gain by facilitating storage of metabolic fuels and increased appetite while central action on appetite regulation appears anorectic. Insulin also interacts with other growth factors to influence fetal growth. Fetal macrosomia is common in diabetic pregnancies and correlates with fetal hyperinsulinemia. Weight gain is also noted in patients on insulin treatment. In children, however, the effect of insulin on body weight has remained a controversial topic. Growth studies in children with type 1 diabetes while exploring the relationship between insulin induced changes in weight and body composition have shown inconsistent results. Also, no effect of 2 years of insulin supplementation on body weight or physical development was seen in normal children in the diabetes prevention trial-type 1.

### Leptin and Ghrelin

Leptin produced in the adipose tissue sends satiety signals to brain thereby suppressing appetite and ghrelin, produced in the stomach provides hunger signals to the brain. Both these hormones may influence growth particularly during infancy. Plasma leptin concentrations have a positive relation to bodyweight while ghrelin is negatively associated with bodyweight in infants. The long-term effects of alterations in concentrations of leptin and ghrelin on bodyweight and composition are however unknown at present. *Leptin deficiency*, usually congenital, causes severe obesity in children. Relative leptin deficiency associated with shorter duration of sleep causes overweight or obesity in adults. Decreased ghrelin synthesis in children suffering from iron deficiency anemia affects their growth by reduction in appetite. The elevation of ghrelin concentrations in children with protein energy malnutrition occurs as an adaptation mechanism and may have a role in catch-up growth.

### Parathyroid Hormone and Vitamin D

They mediate bone growth probably through regulation of osteoblast proliferation and differentiation. Growth failure is a common manifestation of problems of parathyroid hormone (PTH) deficiency or action at the tissue level. Adequate levels of vitamin D are required for efficient calcium absorption to maintain blood levels of calcium and phosphorus essential for normal bone mineralization. Children with vitamin D deficiency develop rickets and short stature. Also vitamin D resistant states due to mutations of vitamin D receptor genes result in similar growth failure.

## MINOR GROWTH FACTORS

Numerous peptides and their receptors identified recently are proposed to play a role in somatic growth. The most notable are fibroblast growth factors and their receptors considered essential for normal bone growth. Mutations in *FGFR3* and *FGFR2* gene cause achondroplasia and craniosynostosis respectively. Epidermal growth factors may be involved in fetal growth. Certain peptides like hepatocyte growth factor, endothelin, nerve growth factor, etc., may have a role in promoting growth of specific tissues.

## PHYSICAL ACTIVITY

Physical activity and general fitness affects linear growth. Moderate physical activity is associated with cardiovascular benefits, favorable changes in body composition and bone mass accrual but excessive physical activity has a negative effect on growth and pubertal development. Wrestlers, gymnasts and dancers show decreased linear growth during the periods of intense training and catch-up growth afterwards. Physical exercise is associated with an increase in circulating levels of GH and IGF-1 as well as alterations in levels of several other hormones associated with appetite control.

## SYSTEMIC DISEASES

Growth failure is one of the usual manifestations of chronic systemic diseases. Infectious illnesses like recurrent diarrhea, human immunodeficiency virus (HIV) and tuberculosis account for majority of the cases of growth failure due to systemic diseases in many countries. Disturbances of GH-IGF-1 axis are presumed to be partly responsible for growth failure in HIV. Congenital heart disease can cause growth failure in affected infants and children due to excessive energy expenditures and chronic hypoxemia. Chronic renal disease especially renal tubular acidosis (RTA) and chronic renal failure (CRF) also cause growth faltering. Multiple mechanisms like reduced caloric intake, protein wasting, loss of electrolytes necessary for growth, reduced synthesis of activated vitamin D, insulin resistance, anemia and decreased cardiac functions combine to result in growth retardation in renal disease. Additionally, chronic systemic acidosis impairs growth partly through disturbances of GH-IGF-1 axis and patients with CRF may show GH resistance and decreases in IGF bioactivity due to impaired clearance of IGF-BPs. Gastrointestinal diseases like celiac disease, inflammatory bowel disease and cystic fibrosis affect growth by impairing intake or absorption of nutrients. Hematological disorders like thalassemia, sickle cell disease and leukemia cause growth failure probably through chronic anemia-related impaired oxygen delivery to tissues, increased cardiac workload, increased energy demands of hematopoiesis and impaired nutrition. Multiple hormone deficiencies (thyroid, IGF-1, gonadal steroids etc.) in thalassemia resulting from transfusion related iron overload also contribute to growth failure. Patients with diabetes mellitus especially those with a poor control also manifest growth failure probably due to caloric wasting, chronic acidosis, increased glucocorticoid production and associated hypothyroidism. Chronic hypoinsulinemia inhibits IGF-1 action by elevating IGF-BP1 concentrations as well as reducing IGF-1 levels by altering *GHR* expression. Severe growth retardation is however unusual in diabetes and modern management of diabetes is demonstrated to be associated with normal physical growth. Many inborn errors of metabolism like glycogen storage disorders, mucopolysaccharidoses and mucopolipidoses are associated with growth failure. Chronic pulmonary diseases especially cystic fibrosis (CF) and bronchial asthma affect growth through combined effects of pulmonary and pancreatic dysfunction in CF.

and effect of chronic steroid administration in asthma. In India, chronic worm infestations also cause growth failure by nutritional debilitation in many children.

### IN A NUTSHELL

1. Knowledge of factors that influence physical growth helps pediatricians to timely diagnose and treat conditions associated with growth deviation.
2. Normal growth represents constant interaction of genetic, hormonal, nutritional and several other environmental factors.
3. Nutrition is the single most important factor affecting body growth during early childhood and adolescence.
4. Normal functioning endocrine system, in particular the pituitary-thyroid unit, is essential for normal physical growth.

### MORE ON THIS TOPIC

- Allen LH. Nutritional influences on linear growth: a general review. *Eur J Clin Nutr.* 1994;48(1):S75-89.
- Backeljauw PF, Dattani MT, Cohen P, Rosenfeld RG. Disorders of Growth hormone/insulin like growth factor secretion and action. In: Sperling MA (Ed). *Pediatric Endocrinology*, 4<sup>th</sup> ed. Philadelphia, PA: Elsevier Saunders; 2014. pp. 292-404.
- Bharati S, Mukherji D, Pal M, et al. Influence of ethnicity, geography and climate on the variation of stature among Indian populations. *Coll Antropol.* 2010;34:1207-13.
- Katzmarzyk PT, Leonard WR. Climatic influences on human body size and proportions: ecological adaptations and secular trends. *Am J Phys Anthropol.* 1998;106:483-503.
- Khalid ME, Al-Hashem FH. The relationship of body weight to altitude in preschool children of southwestern Saudi Arabia. *J Family Community Med.* 2007;14:71-6.
- Malina RM, Bouchard C, Bar-Or O. *Growth, Maturation, and Physical Activity*. 2<sup>nd</sup> ed. Champaign, IL: Human Kinetics Books; 2004.
- Neumann CG, Harrison GG. Onset and evolution of stunting in infants and children. Examples from the Human Nutrition Collaborative Research Support Program. Kenya and Egypt studies. *Eur J Clin Nutr.* 1994;48(1):S90-102.
- Sguassero Y, de Onis M, Bonotti AM, Carroli G. Community-based supplementary feeding for promoting the growth of children under five years of age in low and middle income countries. *Cochrane Database Syst Rev.* 2012;6:CD005039.
- Soliman AT, Al Dabbagh MM, Habboub AH, et al. Linear growth in children with iron deficiency anemia before and after treatment. *J Trop Pediatr.* 2009;55:324-7.
- Sridhar SB, Darbinian J, Ehrlich SF, et al. Maternal gestational weight gain and offspring risk for childhood overweight or obesity. *Am J Obstet Gynecol.* 2014;211(3):259.e1-8.

## Chapter 19.3

# Assessment of Physical Growth

Anju Seth, Rajni Sharma

Growth is an integral aspect of childhood and being able to accurately measure, record and interpret a child's growth parameters is an essential clinical skill for pediatricians. The most important parameters for assessing physical growth include weight, length/height and head circumference. Other parameters such as mid-arm circumference, waist circumference and skinfold thickness are measured when indicated. There are certain prerequisites to ensure accurate measurement. First, the instruments used for measurement should be well maintained and functioning appropriately. It is important to calibrate the instruments at regular intervals especially weighing scales against standard weights. The person taking the measurements should be well-trained and should follow a standardized technique of taking measurements.

## TECHNIQUES OF GROWTH MEASUREMENT

### Weight

Weight is measured by a spring balance, beam balance or a digital scale. The spring balance tends to give inaccurate readings due to change in the elasticity of the spring over time and is therefore not the preferred device. Irrespective of type of weighing scale used, always check for and correct zero error. Infants should ideally be weighed nude on an infant weighing scale. Ensure that the infant is centered on the measuring tray. Older children should be weighed wearing minimum clothing after removing footwear. If the child cannot be weighed individually, she/he can be placed in the parent's arms and the parent's weight can later be deducted from the combined weight to get the child's weight. Many electronic weighing machines have the provision of taking *tare weight*. In commercial language, *tare weight* refers to the weight of the container/packaging. In practice, when the caregiver stands on the scale, the *tare weight* button is pressed which resets the weight to zero. Subsequently, the child can be placed in the caregiver's arms while the latter is still standing on the scale and the child's weight can be directly read. The weighing scale used for infants should be able to measure weight to the nearest 10 g, while the scale for older children should measure to the nearest 100 g.

### Length/Height

Recumbent length is measured for children less than 2 years of age by an *infantometer*. This consists of a fixed headboard with a moveable foot-board. Two persons are required to take an accurate measurement. The first person holds the infant's head against the headboard with the eyes looking straight up (the Frankfurt plane, an imaginary line from the center of the external auditory meatus to the lower border of the eye socket, should be vertical) while the second person keeps the knees straight by pressing them down gently and moves the footboard up till the soles are resting flat on it and the toes are pointing upwards (**Figs 1A to C**). If a child is less than 2 years old and does not lie down for measurement, one can measure standing height and add 0.7 cm to convert it to length.

After the age of 2 years, standing height should be measured by the *stadiometer*. This consists of a vertical ruler and horizontal sliding headpiece which rests on the top of the head. The child should stand without shoes and socks with the heels, buttocks and shoulder blades touching the wall and the Frankfurt plane parallel to the ground. The measurer applies slight pressure on the mastoid processes to make the child stand erect (**Figs 2A and B**). A simple

stature-meter that can be fixed to the wall manually and pulled down to measure height is a satisfactory alternative in clinical practice (**Figs 3A and B**). If a child aged 2 years or older cannot stand, one can measure recumbent length and subtract 0.7 cm to convert it to height.

### Head Circumference

Head circumference is routinely measured in infants and children up to 3 years of age. All newborn babies should have their head circumference measured but not before 36 hours of age (due to the presence of caput). The tape should pass around the occipital prominence at the back and over the supraorbital ridges just above the eyebrows so that the maximal circumference is measured. One should use a flexible nonstretchable tape and measure to the nearest 0.1 cm (**Fig. 4**).

### Other Measurements

#### Mid-upper Arm Circumference

The measurement of mid-upper arm circumference (MUAC) is useful to assess the nutritional status of children between 6 months and 5 years of age. It can be used as an age-independent criterion to identify malnutrition and is especially useful in the community setting when weight and stature cannot be measured or the child's exact age is not known. MUAC is measured in the left arm after locating the mid-point (between the tip of the left shoulder, i.e., acromion process and tip of the elbow, i.e., olecranon process). The arm should be hanging loosely at the side while measuring MUAC. One should take care that the tape is neither too tight nor too loose when encircling the arm (**Fig. 5**).

#### Waist Circumference

Central or truncal obesity is considered a risk factor for developing cardiovascular disease and diabetes (metabolic syndrome). Waist circumference is an easy and validated measure of central obesity. It is measured midway between iliac crest and lowermost margin of the ribs. While absolute cut-off levels of waist circumference are available for screening for obesity related complications in adults, age and gender related waist circumference percentiles should be used in children. Ideally, ethnic specific charts should be used.

#### Skinfold Thickness

Skinfold thickness helps to assess the degree of fat deposits or adiposity at particular body sites including triceps, chest, abdomen, suprailiac region and thigh. A pinch of skin is taken between the thumb and forefinger above the muscle plane and calipers are applied for reading. The values can be compared to reference data or can be used in standardized equations to calculate total fat mass or percentage of body fat. Agarwal KN et al. (2001) have published Indian reference data for skinfold thickness in children. Skinfold thickness has limited application in routine clinical practice, being used mostly as a research tool.

### Common Errors in Recording and Interpreting

#### Anthropometric Parameters

Familiarity with the technique of measurement and the instrument is essential for accurate measurements; lack of training and experience can lead to errors. Errors can arise if one attempts to take length in infants without using the infantometer or if a single person attempts to use the infantometer (at least two persons are required). For height, it is important to ensure that the head end of the instrument is not floppy. If using a stature-meter, it is critical to affix it to a smooth wall or another suitable surface at the exact height specified by the manufacturer. All headgear, hair accessories, thick socks and shoes should be removed while measuring height. Care must be taken that proper position is maintained and the child





**Figures 1A to C** Technique of recording length of a child using an infantometer

does not stand on his/her heels. Weight may vary with the time of day, feeding and excessive clothing as in winters. While measuring head circumference, errors may arise if a stretchable tape is used or if the tape slips off the head while measuring.

Errors can also arise while interpreting the measured parameters, the most common error being erroneous determination of child's age, use of inappropriate growth reference table/chart (described later) and in selecting the correct line on the growth reference table for comparison. It is advisable to familiarize



**Figures 2A and B** (A) Technique of recording height using a stadiometer; (B) Measuring tape with sliding head-board

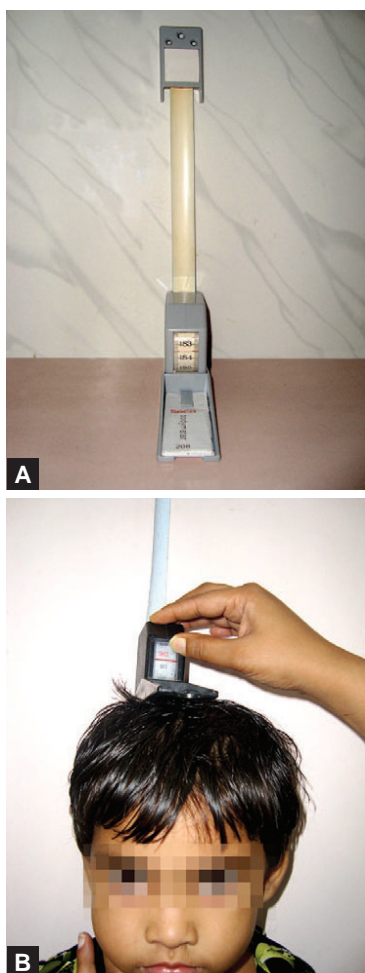
oneself with one particular set of reference tables/graphs and use the same consistently in clinical practice. This would provide a uniform reference over time and minimize errors as well.

### Recommendations for Intervals and Parameters for Growth Monitoring

Weight, length and head circumference should be measured at birth and subsequently at immunization contacts at 6 weeks, 10 weeks and 14 weeks, 9 months, 15 months and 18 months. Between the ages of 18 months and 5 years, weight and height should be monitored 6 monthly. Beyond 5 years, as the rate of growth becomes slower, annual assessment of height, weight and body mass index (BMI) will suffice. Growth can also conveniently be assessed as and when the child is brought to the physician for any other reason.

### GROWTH REFERENCE STANDARDS

Though growth is a complex process regulated by multiple factors such as genes, health, nutrition and socioeconomic factors, it follows a fairly predictable pattern. This has led to the concept of *growth reference standards* to depict expected patterns of growth. Growth standards are usually generated from cross-sectional data by single-time observations on a large population of children of various ages. They can also be derived from longitudinal data collected over a period of time from a large cohort. The data



**Figures 3A and B** (A) A stature-meter; (B) Height being recorded using a stature-meter by pulling down the headpiece of the meter fixed on the wall



**Figure 4** Technique of recording the head circumference

so generated is statistically computed and presented as tables. Growth charts are graphic representations of the data presented in growth tables and typically depict 3rd, 10th, 25th, 50th, 75th and 97th percentile lines. An individual child's growth parameters can be compared to these reference standards using the reference table

in office practice or, ideally by plotting on a growth chart where a longitudinal record of an individual child's growth can be kept. Various types of growth tables/charts are available separately for both genders, including weight-for-age, height-for-age, weight-for-height, head circumference-for-age and BMI-for-age.

### Growth Charts

The first Indian growth charts available for clinical use were derived from the Indian Council of Medical Research (ICMR) Technical Report Series no. 18 (1972), which were developed more than four decades ago and were based on studies on children from mixed socioeconomic strata. Despite being criticized for the method of sample selection and data collection, they remained in use for many years for growth monitoring in India.

Common growth reference data being used in clinical practice are compared in **Table 1** and discussed here.

### World Health Organization (WHO) Charts

World Health Organization (WHO) growth standard tables and charts are available from birth to 19 years of age. The standards for preschool children (age 0–60 months) were developed from data collected in the WHO International Multicenter Growth Reference Study (MGRS) carried out from 1997 to 2003 in six centers worldwide—California (USA), Muscat (Oman), Oslo (Norway), Pelotas (Brazil), Accra (Ghana) and Delhi (India). The subjects of this study included healthy breastfed infants living in optimal socioeconomic conditions and thus the growth charts describe how children should grow in all settings rather than describing how they grow in a specific setting and time. This study combined longitudinal follow-up as well as cross-sectional data of children and provides the best physiological growth standards from birth to 5 years of age in breastfed infants. These standards are used to assess growth of children in all parts of the world irrespective of ethnicity. When using the WHO growth standard, fewer children aged 0–60 months are diagnosed with poor weight gain, compared with the US Centers for Disease Control and Prevention (CDC) growth reference.



**Figure 5** Technique of recording mid-upper arm circumference (MUAC)

The WHO reference curves for ages 5–19 years, were developed from the original 1977 National Center for Health Statistics (NCHS) data (given later) based on anthropometric data of American children. To develop reference curves for this age group, WHO used the original nonobese sample from NCHS data supplemented with



**Table 1** Growth charts available for clinical use

Country	USA	Multicountry/USA	India		
Growth Chart	CDC 2000	WHO	Agarwal KN et al.	Khadilkar VV et al.	Marwaha RK et al.
Year	1964–1994	1997–2003	1988–1991	2007–2008	2006–2009
Data	Weight data from original NCHS 1977	Primary data for 0–5 years, reconstructed NCHS data for > 5 years	Primary data	Primary data	Primary data
Population	USA, nationwide data, mixed feeding	Six countries pooled data, healthy breastfed children	Affluent Indian population, mixed infant feeding, multicentric	Affluent Indian population, multicentric	Affluent Indian population, multicentric
Age	Birth to 20 years	Birth to 19 years	Birth to 18 years	2–5 years, 5–18 years	5–18 years
Characteristics	Cross-sectional data	Cross-sectional and longitudinal data	Cross-sectional data	Cross-sectional data	Cross-sectional data
Type	Reference	Standards	Reference	Reference	Reference
Data	Weight-for-age	Weight-for-age	Weight-for-age	Weight-for-age	Weight-for-age
	Height-for-age	Height-for-age	Height-for-age	Height-for-age	Height-for-age
	Weight-for-height	Weight-for-height	—	—	—
	Head circumference-for-age (up to 36 months)	Head circumference-for-age	Head circumference-for-age (up to 6 years)	—	—
	BMI-for-age (> 2 years)	BMI-for-age	BMI-for-age (> 2 years)	BMI-for-age	BMI-for-age

data from the WHO MGRS study to facilitate smooth transition at 5 years. This was achieved by applying state-of-the-art statistical methods. The full set of WHO reference tables and charts are freely available on the WHO website ([www.who.int/childgrowth/en](http://www.who.int/childgrowth/en)).

### Centers for Disease Control and Prevention (CDC) Charts

The CDC 2000 growth charts are revised versions of NCHS 1977 growth charts, which were based on cross-sectional data collected in the USA from nation-wide studies. The CDC charts comprised of revision of previous existing 14 charts using improved statistical tools, and introduction of two new BMI charts. The CDC 2000 charts are based on data from five nationally representative surveys conducted at various times and places between 1963 and 1994 with supplementary data for birthweight and for infants under 2–3 months of age from other sources since no national data was available.

The sample population was ethnically heterogeneous and infants were predominantly on formula/mixed feeding as breastfeeding was not the norm at the time data was collected. Hence, CDC 2000 may not truly reflect the ideal growth of breastfed babies. The full set of charts is freely available at [www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts).

### Indian Reference Charts

In 1992, Agarwal DK et al. published growth reference data from a major multicenter study from India which were subsequently used to develop growth charts. In this study, height and weight were recorded cross-sectionally from 1988 to 1991 in affluent Indian children aged 0–18 years and percentile charts were generated for the same. The data for birth to 6 years was collected from six cities over 1985–1987 using a mixed longitudinal study design (1994). Data for the age group 5–18 years was collected from nine Indian states over 1988–1991 using a cross-sectional study design (1992 and 2001).

Apart from the growth reference data by Agarwal KN et al., several recent multicentric studies including those by Khadilkar VV et al. (2009 and 2010) and Marwaha RK et al. (2011) have generated more recent reference data on height, weight and BMI in Indian children. A comparison of growth reference data from these studies is shown in **Figures 6A and B**.

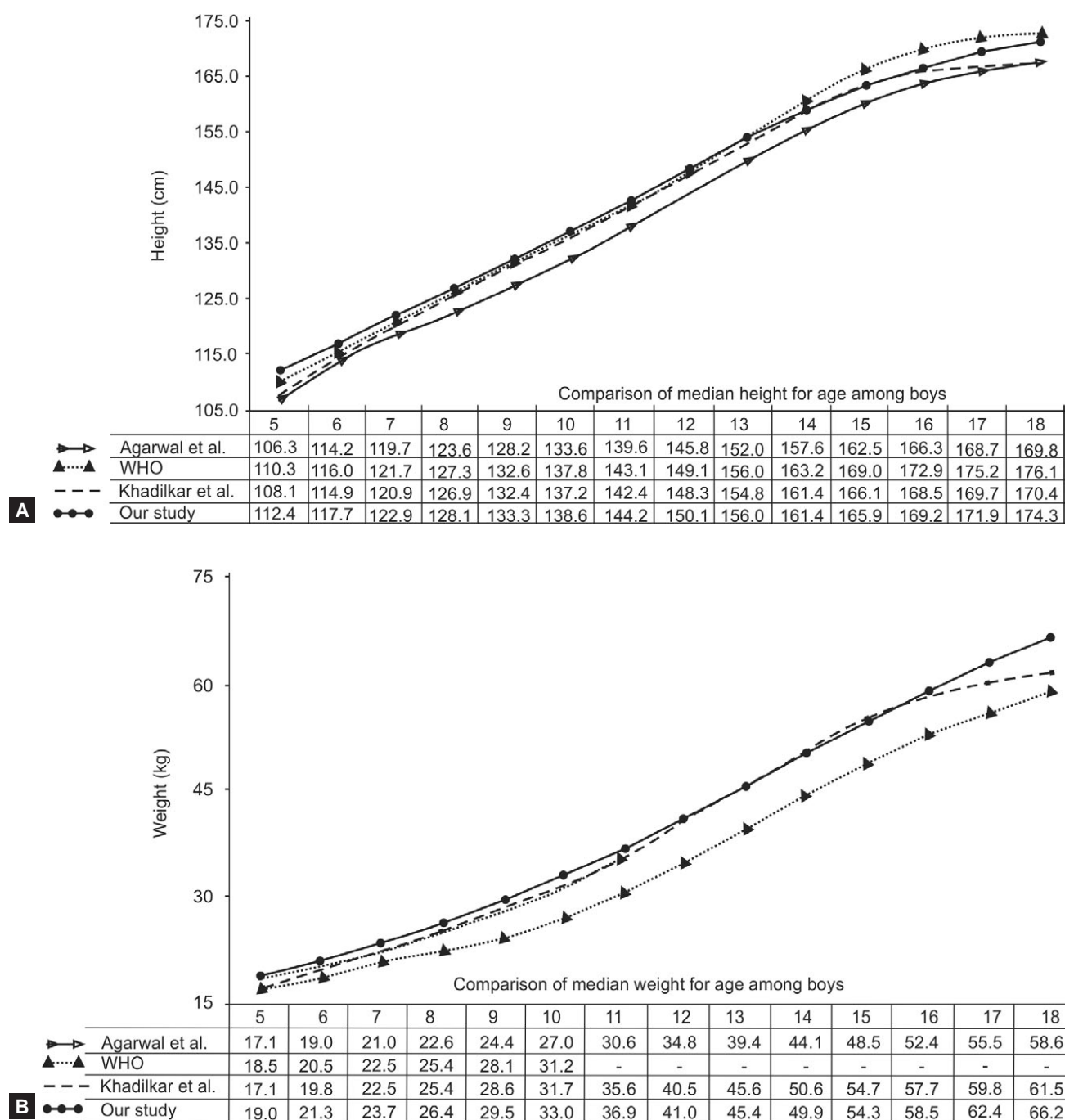
Since their introduction, WHO 2006 standards have been widely accepted world-over for monitoring growth of under-five children. The Government of India has endorsed these standards for under-five growth monitoring. The United Kingdom and the United States of America have adopted the WHO 2006 standards till the age of 4 and 2 years, respectively for growth monitoring followed by charts based on local references. It is important to realize that while interpretation of growth in a child may vary depending on the reference standards used for comparison, and will therefore have implications at community/national level, choice of a specific growth reference chart may not be critical for growth monitoring of a particular child in clinical practice. It is more important to be accurate in assessment and plotting and to be consistent with the type of reference used for that individual.

WHO growth reference data tables and charts are presented in **Tables 2 to 10 and Figures 7 to 12**. After the age of 5 years, nationally representative references for height and weight should be used. Growth reference data by Agarwal DK et al., and growth charts based on them are included in **Tables 11 to 16 and Figures 13 and 14**.

## INTERPRETATION OF ANTHROPOMETRIC PARAMETERS

### Concept of Z-Score, Percentiles, and Percentage of Median

Growth parameters of an individual needs to be compared with the reference data to interpret them. This can be done in various ways. *Percentiles* are obtained by dividing an ordered set of data into 100 equal sized groups. An observed measurement at the 50th percentile indicates the median value and that half of the population has values above and other half has values below the median. If an individual's height is at 3rd percentile value, it means that 3% of all individuals in the population have height less or equal to that value and 97% of the population has height above that value. The 3rd and 97th percentile, which roughly correspond to  $\pm 2$  standard deviation (SD) and include 95% of all observations, are conventionally considered as limits of normalcy for height and weight.



**Figures 6A and B** Median height and weight of Indian boys as per data from study by Marwaha RK et al. in comparison to World Health Organization (WHO) data and other Indian studies

Source: Marwaha RK, Tandon N, Ganie MA, et al. Nationwide reference data for height, weight and body mass index of Indian school children. Natl Med J India. 2011;24:269-77; Reproduced with permission.

*Standard deviation score (SDS) or Z-score* refers to the number of standard deviations an individual measurement is away from the median. A positive (+) SDS denotes a value above the median and negative (-) SDS denotes a value below the median. Measurements that lie between +2 and -2 SDS of the median value are considered to be normal whereas, measurements that have an SDS more than +2 or less than -2 are considered to lie outside the range considered normal for a given population. In a normally distributed population, approximately 95% of individuals have values between -2 and +2 SDS. A Z-score of -2 corresponds to the 2.5th percentile and Z-score of +2 to the 97.5th percentile. Individuals with their

parameters lying outside this range thus constitute 5% of all subjects of that gender and age and should therefore be carefully evaluated for any disorder of growth. For normally distributed (parametric) data, like height, the following formula can be used for calculating SDS or Z-score of a given observation:

$$\text{SDS (Z-score)} = \frac{(\text{observed value} - \text{median value of the reference population})}{\text{Standard deviation value of reference population}}$$

For nonparametric data like weight, more complicated formulae are required to calculate the SD score of a given observation



**Table 2** Weight (kg) by age of boys, percentile and Z-scores, 0–5 years [World Health Organization (WHO) standards]

Age		Percentiles							Z (SD) score					
Years	Month	3rd	15th	25th	50th	75th	85th	97th	−3Z	−2Z	−1Z	+1Z	+2Z	+3Z
	0	2.5	2.9	3.0	3.3	3.7	3.9	4.3	2.1	2.5	2.9	3.9	4.4	5.0
	1	3.4	3.9	4.1	4.5	4.9	5.1	5.7	2.9	3.4	3.9	5.1	5.8	6.6
	2	4.4	4.9	5.1	5.6	6.0	6.3	7.0	3.8	4.3	4.9	6.3	7.1	8.0
	3	5.1	5.6	5.9	6.4	6.9	7.2	7.9	4.4	5.0	5.7	7.2	8.0	9.0
	4	5.6	6.2	6.5	7.0	7.6	7.9	8.6	4.9	5.6	6.2	7.8	8.7	9.7
	5	6.1	6.7	7.0	7.5	8.1	8.4	9.2	5.3	6.0	6.7	8.4	9.3	10.4
	6	6.4	7.1	7.4	7.9	8.5	8.9	9.7	5.7	6.4	7.1	8.8	9.8	10.9
	7	6.7	7.4	7.7	8.3	8.9	9.3	10.2	5.9	6.7	7.4	9.2	10.3	11.4
	8	7.0	7.7	8.0	8.6	9.3	9.6	10.5	6.2	6.9	7.7	9.6	10.7	11.9
	9	7.2	7.9	8.3	8.9	9.6	10.0	10.9	6.4	7.1	8.0	9.9	11.0	12.3
	10	7.5	8.2	8.5	9.2	9.9	10.3	11.2	6.6	7.4	8.2	10.2	11.4	12.7
	11	7.7	8.4	8.7	9.4	10.1	10.5	11.5	6.8	7.6	8.4	10.5	11.7	13.0
1	0	7.8	8.6	9.0	9.6	10.4	10.8	11.8	6.9	7.7	8.6	10.8	12.0	13.3
1	1	8.0	8.8	9.2	9.9	10.6	11.1	12.1	7.1	7.9	8.8	11.0	12.3	13.7
1	2	8.2	9.0	9.4	10.1	10.9	11.3	12.4	7.2	8.1	9.0	11.3	12.6	14.0
1	3	8.4	9.2	9.6	10.3	11.1	11.6	12.7	7.4	8.3	9.2	11.5	12.8	14.3
1	4	8.5	9.4	9.8	10.5	11.3	11.8	12.9	7.5	8.4	9.4	11.7	13.1	14.6
1	5	8.7	9.6	10.0	10.7	11.6	12.0	13.2	7.7	8.6	9.6	12.0	13.4	14.9
1	6	8.9	9.7	10.1	10.9	11.8	12.3	13.5	7.8	8.8	9.8	12.2	13.7	15.3
1	7	9.0	9.9	10.3	11.1	12.0	12.5	13.7	8.0	8.9	10.0	12.5	13.9	15.6
1	8	9.2	10.1	10.5	11.3	12.2	12.7	14.0	8.1	9.1	10.1	12.7	14.2	15.9
1	9	9.3	10.3	10.7	11.5	12.5	13.0	14.3	8.2	9.2	10.3	12.9	14.5	16.2
1	10	9.5	10.5	10.9	11.8	12.7	13.2	14.5	8.4	9.4	10.5	13.2	14.7	16.5
1	11	9.7	10.6	11.1	12.0	12.9	13.4	14.8	8.5	9.5	10.7	13.4	15.0	16.8
2	0	9.8	10.8	11.3	12.2	13.1	13.7	15.1	8.6	9.7	10.8	13.6	15.3	17.1
2	1	10.0	11.0	11.4	12.4	13.3	13.9	15.3	8.8	9.8	11.0	13.9	15.5	17.5
2	2	10.1	11.1	11.6	12.5	13.6	14.1	15.6	8.9	10.0	11.2	14.1	15.8	17.8
2	3	10.2	11.3	11.8	12.7	13.8	14.4	15.9	9.0	10.1	11.3	14.3	16.1	18.1
2	4	10.4	11.5	12.0	12.9	14.0	14.6	16.1	9.1	10.2	11.5	14.5	16.3	18.4
2	5	10.5	11.6	12.1	13.1	14.2	14.8	16.4	9.2	10.4	11.7	14.8	16.6	18.7
2	6	10.7	11.8	12.3	13.3	14.4	15.0	16.6	9.4	10.5	11.8	15.0	16.9	19.0
2	7	10.8	11.9	12.4	13.5	14.6	15.2	16.9	9.5	10.7	12.0	15.2	17.1	19.3
2	8	10.9	12.1	12.6	13.7	14.8	15.5	17.1	9.6	10.8	12.1	15.4	17.4	19.6
2	9	11.1	12.2	12.8	13.8	15.0	15.7	17.3	9.7	10.9	12.3	15.6	17.6	19.9
2	10	11.2	12.4	12.9	14.0	15.2	15.9	17.6	9.8	11.0	12.4	15.8	17.8	20.2
2	11	11.3	12.5	13.1	14.2	15.4	16.1	17.8	9.9	11.2	12.6	16.0	18.1	20.4
3	0	11.4	12.7	13.2	14.3	15.6	16.3	18.0	10.0	11.3	12.7	16.2	18.3	20.7
3	1	11.6	12.8	13.4	14.5	15.8	16.5	18.3	10.1	11.4	12.9	16.4	18.6	21.0
3	2	11.7	12.9	13.5	14.7	15.9	16.7	18.5	10.2	11.5	13.0	16.6	18.8	21.3
3	3	11.8	13.1	13.7	14.8	16.1	16.9	18.7	10.3	11.6	13.1	16.8	19.0	21.6
3	4	11.9	13.2	13.8	15.0	16.3	17.1	19.0	10.4	11.8	13.3	17.0	19.3	21.9
3	5	12.1	13.4	14.0	15.2	16.5	17.3	19.2	10.5	11.9	13.4	17.2	19.5	22.1
3	6	12.2	13.5	14.1	15.3	16.7	17.5	19.4	10.6	12.0	13.6	17.4	19.7	22.4
3	7	12.3	13.6	14.3	15.5	16.9	17.7	19.7	10.7	12.1	13.7	17.6	20.0	22.7
3	8	12.4	13.8	14.4	15.7	17.1	17.9	19.9	10.8	12.2	13.8	17.8	20.2	23.0
3	9	12.5	13.9	14.6	15.8	17.3	18.1	20.1	10.9	12.4	14.0	18.0	20.5	23.3
3	10	12.7	14.1	14.7	16.0	17.4	18.3	20.4	11.0	12.5	14.1	18.2	20.7	23.6
3	11	12.8	14.2	14.9	16.2	17.6	18.5	20.6	11.1	12.6	14.3	18.4	20.9	23.9
4	0	12.9	14.3	15.0	16.3	17.8	18.7	20.9	11.2	12.7	14.4	18.6	21.2	24.2
4	1	13.0	14.5	15.2	16.5	18.0	18.9	21.1	11.3	12.8	14.5	18.8	21.4	24.5
4	2	13.1	14.6	15.3	16.7	18.2	19.1	21.3	11.4	12.9	14.7	19.0	21.7	24.8
4	3	13.3	14.7	15.4	16.8	18.4	19.3	21.6	11.5	13.1	14.8	19.2	21.9	25.1
4	4	13.4	14.9	15.6	17.0	18.6	19.5	21.8	11.6	13.2	15.0	19.4	22.2	25.4
4	5	13.5	15.0	15.7	17.2	18.8	19.7	22.1	11.7	13.3	15.1	19.6	22.4	25.7
4	6	13.6	15.2	15.9	17.3	19.0	19.9	22.3	11.8	13.4	15.2	19.8	22.7	26.0
4	7	13.7	15.3	16.0	17.5	19.2	20.1	22.5	11.9	13.5	15.4	20.0	22.9	26.3
4	8	13.8	15.4	16.2	17.7	19.3	20.3	22.8	12.0	13.6	15.5	20.2	23.2	26.6
4	9	13.9	15.6	16.3	17.8	19.5	20.5	23.0	12.1	13.7	15.6	20.4	23.4	26.9
4	10	14.1	15.7	16.5	18.0	19.7	20.7	23.3	12.2	13.8	15.8	20.6	23.7	27.2
4	11	14.2	15.8	16.6	18.2	19.9	20.9	23.5	12.3	14.0	15.9	20.8	23.9	27.6
5	0	14.3	16.0	16.7	18.3	20.1	21.1	23.8	12.4	14.1	16.0	21.0	24.2	27.9

**Table 3** Weight (kg) by age of girls, percentiles and Z (SD) score for 0–5 years (WHO standards)

Age		Percentiles							Z (SD) score					
Years	Month	3rd	15th	25th	50th	75th	85th	97th	–3Z	–2Z	–1Z	+1Z	+2Z	+3Z
	0	2.4	2.8	2.9	3.2	3.6	3.7	4.2	2.0	2.4	2.8	3.7	4.2	4.8
	1	3.2	3.6	3.8	4.2	4.6	4.8	5.4	2.7	3.2	3.6	4.8	5.5	6.2
	2	4.0	4.5	4.7	5.1	5.6	5.9	6.5	3.4	3.9	4.5	5.8	6.6	7.5
	3	4.6	5.1	5.4	5.8	6.4	6.7	7.4	4.0	4.5	5.2	6.6	7.5	8.5
	4	5.1	5.6	5.9	6.4	7.0	7.3	8.1	4.4	5.0	5.7	7.3	8.2	9.3
	5	5.5	6.1	6.4	6.9	7.5	7.8	8.7	4.8	5.4	6.1	7.8	8.8	10.0
	6	5.8	6.4	6.7	7.3	7.9	8.3	9.2	5.1	5.7	6.5	8.2	9.3	10.6
	7	6.1	6.7	7.0	7.6	8.3	8.7	9.6	5.3	6.0	6.8	8.6	9.8	11.1
	8	6.3	7.0	7.3	7.9	8.6	9.0	10.0	5.6	6.3	7.0	9.0	10.2	11.6
	9	6.6	7.3	7.6	8.2	8.9	9.3	10.4	5.8	6.5	7.3	9.3	10.5	12.0
	10	6.8	7.5	7.8	8.5	9.2	9.6	10.7	5.9	6.7	7.5	9.6	10.9	12.4
	11	7.0	7.7	8.0	8.7	9.5	9.9	11.0	6.1	6.9	7.7	9.9	11.2	12.8
1	0	7.1	7.9	8.2	8.9	9.7	10.2	11.3	6.3	7.0	7.9	10.1	11.5	13.1
1	1	7.3	8.1	8.4	9.2	10.0	10.4	11.6	6.4	7.2	8.1	10.4	11.8	13.5
1	2	7.5	8.3	8.6	9.4	10.2	10.7	11.9	6.6	7.4	8.3	10.6	12.1	13.8
1	3	7.7	8.5	8.8	9.6	10.4	10.9	12.2	6.7	7.6	8.5	10.9	12.4	14.1
1	4	7.8	8.7	9.0	9.8	10.7	11.2	12.5	6.9	7.7	8.7	11.1	12.6	14.5
1	5	8.0	8.8	9.2	10.0	10.9	11.4	12.7	7.0	7.9	8.9	11.4	12.9	14.8
1	6	8.2	9.0	9.4	10.2	11.1	11.6	13.0	7.2	8.1	9.1	11.6	13.2	15.1
1	7	8.3	9.2	9.6	10.4	11.4	11.9	13.3	7.3	8.2	9.2	11.8	13.5	15.4
1	8	8.5	9.4	9.8	10.6	11.6	12.1	13.5	7.5	8.4	9.4	12.1	13.7	15.7
1	9	8.7	9.6	10.0	10.9	11.8	12.4	13.8	7.6	8.6	9.6	12.3	14.0	16.0
1	10	8.8	9.8	10.2	11.1	12.0	12.6	14.1	7.8	8.7	9.8	12.5	14.3	16.4
1	11	9.0	9.9	10.4	11.3	12.3	12.8	14.3	7.9	8.9	10.0	12.8	14.6	16.7
2	0	9.2	10.1	10.6	11.5	12.5	13.1	14.6	8.1	9.0	10.2	13.0	14.8	17.0
2	1	9.3	10.3	10.8	11.7	12.7	13.3	14.9	8.2	9.2	10.3	13.3	15.1	17.3
2	2	9.5	10.5	10.9	11.9	12.9	13.6	15.2	8.4	9.4	10.5	13.5	15.4	17.7
2	3	9.6	10.7	11.1	12.1	13.2	13.8	15.4	8.5	9.5	10.7	13.7	15.7	18.0
2	4	9.8	10.8	11.3	12.3	13.4	14.0	15.7	8.6	9.7	10.9	14.0	16.0	18.3
2	5	10.0	11.0	11.5	12.5	13.6	14.3	16.0	8.8	9.8	11.1	14.2	16.2	18.7
2	6	10.1	11.2	11.7	12.7	13.8	14.5	16.2	8.9	10.0	11.2	14.4	16.5	19.0
2	7	10.3	11.3	11.9	12.9	14.1	14.7	16.5	9.0	10.1	11.4	14.7	16.8	19.3
2	8	10.4	11.5	12.0	13.1	14.3	15.0	16.8	9.1	10.3	11.6	14.9	17.1	19.6
2	9	10.5	11.7	12.2	13.3	14.5	15.2	17.0	9.3	10.4	11.7	15.1	17.3	20.0
2	10	10.7	11.8	12.4	13.5	14.7	15.4	17.3	9.4	10.5	11.9	15.4	17.6	20.3
2	11	10.8	12.0	12.5	13.7	14.9	15.7	17.6	9.5	10.7	12.0	15.6	17.9	20.6
3	0	11.0	12.1	12.7	13.9	15.1	15.9	17.8	9.6	10.8	12.2	15.8	18.1	20.9
3	1	11.1	12.3	12.9	14.0	15.3	16.1	18.1	9.7	10.9	12.4	16.0	18.4	21.3
3	2	11.2	12.5	13.0	14.2	15.6	16.3	18.4	9.8	11.1	12.5	16.3	18.7	21.6
3	3	11.4	12.6	13.2	14.4	15.8	16.6	18.6	9.9	11.2	12.7	16.5	19.0	22.0
3	4	11.5	12.8	13.4	14.6	16.0	16.8	18.9	10.1	11.3	12.8	16.7	19.2	22.3
3	5	11.6	12.9	13.5	14.8	16.2	17.0	19.2	10.2	11.5	13.0	16.9	19.5	22.7
3	6	11.8	13.1	13.7	15.0	16.4	17.3	19.5	10.3	11.6	13.1	17.2	19.8	23.0
3	7	11.9	13.2	13.9	15.2	16.6	17.5	19.7	10.4	11.7	13.3	17.4	20.1	23.4
3	8	12.0	13.4	14.0	15.3	16.8	17.7	20.0	10.5	11.8	13.4	17.6	20.4	23.7
3	9	12.1	13.5	14.2	15.5	17.0	17.9	20.3	10.6	12.0	13.6	17.8	20.7	24.1
3	10	12.3	13.7	14.3	15.7	17.3	18.2	20.6	10.7	12.1	13.7	18.1	20.9	24.5
3	11	12.4	13.8	14.5	15.9	17.5	18.4	20.8	10.8	12.2	13.9	18.3	21.2	24.8
4	0	12.5	14.0	14.7	16.1	17.7	18.6	21.1	10.9	12.3	14.0	18.5	21.5	25.2
4	1	12.6	14.1	14.8	16.3	17.9	18.9	21.4	11.0	12.4	14.2	18.8	21.8	25.5
4	2	12.8	14.3	15.0	16.4	18.1	19.1	21.7	11.1	12.6	14.3	19.0	22.1	25.9
4	3	12.9	14.4	15.1	16.6	18.3	19.3	22.0	11.2	12.7	14.5	19.2	22.4	26.3
4	4	13.0	14.5	15.3	16.8	18.5	19.5	22.2	11.3	12.8	14.6	19.4	22.6	26.6
4	5	13.1	14.7	15.4	17.0	18.7	19.8	22.5	11.4	12.9	14.8	19.7	22.9	27.0
4	6	13.2	14.8	15.6	17.2	18.9	20.0	22.8	11.5	13.0	14.9	19.9	23.2	27.4
4	7	13.4	15.0	15.8	17.3	19.1	20.2	23.1	11.6	13.2	15.1	20.1	23.5	27.7
4	8	13.5	15.1	15.9	17.5	19.3	20.4	23.3	11.7	13.3	15.2	20.3	23.8	28.1
4	9	13.6	15.3	16.1	17.7	19.6	20.7	23.6	11.8	13.4	15.3	20.6	24.1	28.5
4	10	13.7	15.4	16.2	17.9	19.8	20.9	23.9	11.9	13.5	15.5	20.8	24.4	28.8
4	11	13.8	15.5	16.4	18.0	20.0	21.1	24.2	12.0	13.6	15.6	21.0	24.6	29.2
5	0	14.0	15.7	16.5	18.2	20.2	21.3	24.4	12.1	13.7	15.8	21.2	24.9	29.5

**Table 4** Length (cm) by age of boys and girls aged 0–2 years (WHO standards)

Boys		Percentiles							Z (SD) score					
Age	(month)	3rd	15th	25th	50th	75th	85th	97th	−3Z	−2Z	−1Z	+1Z	+2Z	+3Z
	0	46.3	47.9	48.6	49.9	51.2	51.8	53.4	44.2	46.1	48.0	51.8	53.7	55.6
	1	51.1	52.7	53.4	54.7	56.0	56.7	58.4	48.9	50.8	52.8	56.7	58.6	60.6
	2	54.7	56.4	57.1	58.4	59.8	60.5	62.2	52.4	54.4	56.4	60.4	62.4	64.4
	3	57.6	59.3	60.1	61.4	62.8	63.5	65.3	55.3	57.3	59.4	63.5	65.5	67.6
	4	60.0	61.7	62.5	63.9	65.3	66.0	67.8	57.6	59.7	61.8	66.0	68.0	70.1
	5	61.9	63.7	64.5	65.9	67.3	68.1	69.9	59.6	61.7	63.8	68.0	70.1	72.2
	6	63.6	65.4	66.2	67.6	69.1	69.8	71.6	61.2	63.3	65.5	69.8	71.9	74.0
	7	65.1	66.9	67.7	69.2	70.6	71.4	73.2	62.7	64.8	67.0	71.3	73.5	75.7
	8	66.5	68.3	69.1	70.6	72.1	72.9	74.7	64.0	66.2	68.4	72.8	75.0	77.2
	9	67.7	69.6	70.5	72.0	73.5	74.3	76.2	65.2	67.5	69.7	74.2	76.5	78.7
	10	69.0	70.9	71.7	73.3	74.8	75.6	77.6	66.4	68.7	71.0	75.6	77.9	80.1
	11	70.2	72.1	73.0	74.5	76.1	77.0	78.9	67.6	69.9	72.2	76.9	79.2	81.5
	12	71.3	73.3	74.1	75.7	77.4	78.2	80.2	68.6	71.0	73.4	78.1	80.5	82.9
	13	72.4	74.4	75.3	76.9	78.6	79.4	81.5	69.6	72.1	74.5	79.3	81.8	84.2
	14	73.4	75.5	76.4	78.0	79.7	80.6	82.7	70.6	73.1	75.6	80.5	83.0	85.5
	15	74.4	76.5	77.4	79.1	80.9	81.8	83.9	71.6	74.1	76.6	81.7	84.2	86.7
	16	75.4	77.5	78.5	80.2	82.0	82.9	85.1	72.5	75.0	77.6	82.8	85.4	88.0
	17	76.3	78.5	79.5	81.2	83.0	84.0	86.2	73.3	76.0	78.6	83.9	86.5	89.2
	18	77.2	79.5	80.4	82.3	84.1	85.1	87.3	74.2	76.9	79.6	85.0	87.7	90.4
	19	78.1	80.4	81.4	83.2	85.1	86.1	88.4	75.0	77.7	80.5	86.0	88.8	91.5
	20	78.9	81.3	82.3	84.2	86.1	87.1	89.5	75.8	78.6	81.4	87.0	89.8	92.6
	21	79.7	82.2	83.2	85.1	87.1	88.1	90.5	76.5	79.4	82.3	88.0	90.9	93.8
	22	80.5	83.0	84.1	86.0	88.0	89.1	91.6	77.2	80.2	83.1	89.0	91.9	94.9
	23	81.3	83.8	84.9	86.9	89.0	90.0	92.6	78.0	81.0	83.9	89.9	92.9	95.9
	24	82.1	84.6	85.8	87.8	89.9	91.0	93.6	78.7	81.7	84.8	90.9	93.9	97.0
Girls		Percentiles							Z (SD) score					
Age	(month)	3rd	15th	25th	50th	75th	85th	97th	−3Z	−2Z	−1Z	+1Z	+2Z	+3Z
	0	45.6	47.2	47.9	49.1	50.4	51.1	52.7	43.6	45.4	47.3	51.0	52.9	54.7
	1	50.0	51.7	52.4	53.7	55.0	55.7	57.4	47.8	49.8	51.7	55.6	57.6	59.5
	2	53.2	55.0	55.7	57.1	58.4	59.2	60.9	51.0	53.0	55.0	59.1	61.1	63.2
	3	55.8	57.6	58.4	59.8	61.2	62.0	63.8	53.5	55.6	57.7	61.9	64.0	66.1
	4	58.0	59.8	60.6	62.1	63.5	64.3	66.2	55.6	57.8	59.9	64.3	66.4	68.6
	5	59.9	61.7	62.5	64.0	65.5	66.3	68.2	57.4	59.6	61.8	66.2	68.5	70.7
	6	61.5	63.4	64.2	65.7	67.3	68.1	70.0	58.9	61.2	63.5	68.0	70.3	72.5
	7	62.9	64.9	65.7	67.3	68.8	69.7	71.6	60.3	62.7	65.0	69.6	71.9	74.2
	8	64.3	66.3	67.2	68.7	70.3	71.2	73.2	61.7	64.0	66.4	71.1	73.5	75.8
	9	65.6	67.6	68.5	70.1	71.8	72.6	74.7	62.9	65.3	67.7	72.6	75.0	77.4
	10	66.8	68.9	69.8	71.5	73.1	74.0	76.1	64.1	66.5	69.0	73.9	76.4	78.9
	11	68.0	70.2	71.1	72.8	74.5	75.4	77.5	65.2	67.7	70.3	75.3	77.8	80.3
	12	69.2	71.3	72.3	74.0	75.8	76.7	78.9	66.3	68.9	71.4	76.6	79.2	81.7
	13	70.3	72.5	73.4	75.2	77.0	77.9	80.2	67.3	70.0	72.6	77.8	80.5	83.1
	14	71.3	73.6	74.6	76.4	78.2	79.2	81.4	68.3	71.0	73.7	79.1	81.7	84.4
	15	72.4	74.7	75.7	77.5	79.4	80.3	82.7	69.3	72.0	74.8	80.2	83.0	85.7
	16	73.3	75.7	76.7	78.6	80.5	81.5	83.9	70.2	73.0	75.8	81.4	84.2	87.0
	17	74.3	76.7	77.7	79.7	81.6	82.6	85.0	71.1	74.0	76.8	82.5	85.4	88.2
	18	75.2	77.7	78.7	80.7	82.7	83.7	86.2	72.0	74.9	77.8	83.6	86.5	89.4
	19	76.2	78.7	79.7	81.7	83.7	84.8	87.3	72.8	75.8	78.8	84.7	87.6	90.6
	20	77.0	79.6	80.7	82.7	84.7	85.8	88.4	73.7	76.7	79.7	85.7	88.7	91.7
	21	77.9	80.5	81.6	83.7	85.7	86.8	89.4	74.5	77.5	80.6	86.7	89.8	92.9
	22	78.7	81.4	82.5	84.6	86.7	87.8	90.5	75.2	78.4	81.5	87.7	90.8	94.0
	23	79.6	82.2	83.4	85.5	87.7	88.8	91.5	76.0	79.2	82.3	88.7	91.9	95.0
	24	80.3	83.1	84.2	86.4	88.6	89.8	92.5	76.7	80.0	83.2	89.6	92.9	96.1

**Table 5** Height by age (cm) of boys and girls aged 2–5 years (WHO standards)

Boys		Percentiles							Z (SD) score					
Years	months	3rd	15th	25th	50th	75th	85th	97th	–3Z	–2Z	–1Z	+1Z	+2Z	+3Z
2	0	81.4	83.9	85.1	87.1	89.2	90.3	92.9	78.0	81.0	84.1	90.2	93.2	96.3
2	1	82.1	84.7	85.9	88.0	90.1	91.2	93.8	78.6	81.7	84.9	91.1	94.2	97.3
2	2	82.8	85.5	86.7	88.8	90.9	92.1	94.8	79.3	82.5	85.6	92.0	95.2	98.3
2	3	83.5	86.3	87.4	89.6	91.8	93.0	95.7	79.9	83.1	86.4	92.9	96.1	99.3
2	4	84.2	87.0	88.2	90.4	92.6	93.8	96.6	80.5	83.8	87.1	93.7	97.0	100.3
2	5	84.9	87.7	88.9	91.2	93.4	94.7	97.5	81.1	84.5	87.8	94.5	97.9	101.2
2	6	85.5	88.4	89.6	91.9	94.2	95.5	98.3	81.7	85.1	88.5	95.3	98.7	102.1
2	7	86.2	89.1	90.3	92.7	95.0	96.2	99.2	82.3	85.7	89.2	96.1	99.6	103.0
2	8	86.8	89.7	91.0	93.4	95.7	97.0	100.0	82.8	86.4	89.9	96.9	100.4	103.9
2	9	87.4	90.4	91.7	94.1	96.5	97.8	100.8	83.4	86.9	90.5	97.6	101.2	104.8
2	10	88.0	91.0	92.3	94.8	97.2	98.5	101.5	83.9	87.5	91.1	98.4	102.0	105.6
2	11	88.5	91.6	93.0	95.4	97.9	99.2	102.3	84.4	88.1	91.8	99.1	102.7	106.4
3	0	89.1	92.2	93.6	96.1	98.6	99.9	103.1	85.0	88.7	92.4	99.8	103.5	107.2
3	1	89.7	92.8	94.2	96.7	99.3	100.6	103.8	85.5	89.2	93.0	100.5	104.2	108.0
3	2	90.2	93.4	94.8	97.4	99.9	101.3	104.5	86.0	89.8	93.6	101.2	105.0	108.8
3	3	90.8	94.0	95.4	98.0	100.6	102.0	105.2	86.5	90.3	94.2	101.8	105.7	109.5
3	4	91.3	94.6	96.0	98.6	101.3	102.7	105.9	87.0	90.9	94.7	102.5	106.4	110.3
3	5	91.9	95.2	96.6	99.2	101.9	103.3	106.6	87.5	91.4	95.3	103.2	107.1	111.0
3	6	92.4	95.7	97.2	99.9	102.5	104.0	107.3	88.0	91.9	95.9	103.8	107.8	111.7
3	7	92.9	96.3	97.7	100.4	103.1	104.6	108.0	88.4	92.4	96.4	104.5	108.5	112.5
3	8	93.4	96.8	98.3	101.0	103.8	105.2	108.6	88.9	93.0	97.0	105.1	109.1	113.2
3	9	93.9	97.4	98.9	101.6	104.4	105.8	109.3	89.4	93.5	97.5	105.7	109.8	113.9
3	10	94.4	97.9	99.4	102.2	105.0	106.5	109.9	89.8	94.0	98.1	106.3	110.4	114.6
3	11	94.9	98.5	100.0	102.8	105.6	107.1	110.6	90.3	94.4	98.6	106.9	111.1	115.2
4	0	95.4	99.0	100.5	103.3	106.2	107.7	111.2	90.7	94.9	99.1	107.5	111.7	115.9
4	1	95.9	99.5	101.0	103.9	106.7	108.3	111.8	91.2	95.4	99.7	108.1	112.4	116.6
4	2	96.4	100.0	101.6	104.4	107.3	108.9	112.5	91.6	95.9	100.2	108.7	113.0	117.3
4	3	96.9	100.5	102.1	105.0	107.9	109.5	113.1	92.1	96.4	100.7	109.3	113.6	117.9
4	4	97.4	101.1	102.6	105.6	108.5	110.1	113.7	92.5	96.9	101.2	109.9	114.2	118.6
4	5	97.9	101.6	103.2	106.1	109.1	110.7	114.3	93.0	97.4	101.7	110.5	114.9	119.2
4	6	98.4	102.1	103.7	106.7	109.6	111.2	115.0	93.4	97.8	102.3	111.1	115.5	119.9
4	7	98.8	102.6	104.2	107.2	110.2	111.8	115.6	93.9	98.3	102.8	111.7	116.1	120.6
4	8	99.3	103.1	104.7	107.8	110.8	112.4	116.2	94.3	98.8	103.3	112.3	116.7	121.2
4	9	99.8	103.6	105.3	108.3	111.4	113.0	116.8	94.7	99.3	103.8	112.8	117.4	121.9
4	10	100.3	104.1	105.8	108.9	111.9	113.6	117.4	95.2	99.7	104.3	113.4	118.0	122.6
4	11	100.8	104.7	106.3	109.4	112.5	114.2	118.1	95.6	100.2	104.8	114.0	118.6	123.2
5	0	101.2	105.2	106.8	110.0	113.1	114.8	118.7	96.1	100.7	105.3	114.6	119.2	123.9
Girls		Percentiles							Z (SD) score					
Years	months	3rd	15th	25th	50th	75th	85th	97th	–3Z	–2Z	–1Z	+1Z	+2Z	+3Z
2	0	79.6	82.4	83.5	85.7	87.9	89.1	91.8	76.0	79.3	82.5	88.9	92.2	95.4
2	1	80.4	83.2	84.4	86.6	88.8	90.0	92.8	76.8	80.0	83.3	89.9	93.1	96.4
2	2	81.2	84.0	85.2	87.4	89.7	90.9	93.7	77.5	80.8	84.1	90.8	94.1	97.4
2	3	81.9	84.8	86.0	88.3	90.6	91.8	94.6	78.1	81.5	84.9	91.7	95.0	98.4
2	4	82.6	85.5	86.8	89.1	91.4	92.7	95.6	78.8	82.2	85.7	92.5	96.0	99.4
2	5	83.4	86.3	87.6	89.9	92.2	93.5	96.4	79.5	82.9	86.4	93.4	96.9	100.3
2	6	84.0	87.0	88.3	90.7	93.1	94.3	97.3	80.1	83.6	87.1	94.2	97.7	101.3
2	7	84.7	87.7	89.0	91.4	93.9	95.2	98.2	80.7	84.3	87.9	95.0	98.6	102.2
2	8	85.4	88.4	89.7	92.2	94.6	95.9	99.0	81.3	84.9	88.6	95.8	99.4	103.1
2	9	86.0	89.1	90.4	92.9	95.4	96.7	99.8	81.9	85.6	89.3	96.6	100.3	103.9
2	10	86.7	89.8	91.1	93.6	96.2	97.5	100.6	82.5	86.2	89.9	97.4	101.1	104.8
2	11	87.3	90.5	91.8	94.4	96.9	98.3	101.4	83.1	86.8	90.6	98.1	101.9	105.6
3	0	87.9	91.1	92.5	95.1	97.6	99.0	102.2	83.6	87.4	91.2	98.9	102.7	106.5
3	1	88.5	91.7	93.1	95.7	98.3	99.7	103.0	84.2	88.0	91.9	99.6	103.4	107.3
3	2	89.1	92.4	93.8	96.4	99.0	100.5	103.7	84.7	88.6	92.5	100.3	104.2	108.1
3	3	89.7	93.0	94.4	97.1	99.7	101.2	104.5	85.3	89.2	93.1	101.0	105.0	108.9
3	4	90.3	93.6	95.1	97.7	100.4	101.9	105.2	85.8	89.8	93.8	101.7	105.7	109.7
3	5	90.8	94.2	95.7	98.4	101.1	102.6	106.0	86.3	90.4	94.4	102.4	106.4	110.5
3	6	91.4	94.8	96.3	99.0	101.8	103.3	106.7	86.8	90.9	95.0	103.1	107.2	111.2
3	7	92.0	95.4	96.9	99.7	102.4	103.9	107.4	87.4	91.5	95.6	103.8	107.9	112.0
3	8	92.5	96.0	97.5	100.3	103.1	104.6	108.1	87.9	92.0	96.2	104.5	108.6	112.7
3	9	93.0	96.6	98.1	100.9	103.7	105.3	108.8	88.4	92.5	96.7	105.1	109.3	113.5
3	10	93.6	97.2	98.7	101.5	104.4	105.9	109.5	88.9	93.1	97.3	105.8	110.0	114.2
3	11	94.1	97.7	99.3	102.1	105.0	106.6	110.2	89.3	93.6	97.9	106.4	110.7	114.9
4	0	94.6	98.3	99.8	102.7	105.6	107.2	110.8	89.8	94.1	98.4	107.0	111.3	115.7
4	1	95.1	98.8	100.4	103.3	106.3	107.8	111.5	90.3	94.6	99.0	107.7	112.0	116.4
4	2	95.7	99.4	100.9	103.9	106.9	108.4	112.1	90.7	95.1	99.5	108.3	112.7	117.1
4	3	96.2	99.9	101.5	104.5	107.5	109.1	112.8	91.2	95.6	100.1	108.9	113.3	117.7
4	4	96.7	100.4	102.0	105.0	108.1	109.7	113.4	91.7	96.1	100.6	109.5	114.0	118.4
4	5	97.2	101.0	102.6	105.6	108.6	110.3	114.1	92.1	96.6	101.1	110.1	114.6	119.1
4	6	97.6	101.5	103.1	106.2	109.2	110.9	114.7	92.6	97.1	101.6	110.7	115.2	119.8
4	7	98.1	102.0	103.6	106.7	109.8	111.5	115.3	93.0	97.6	102.2	111.3	115.9	120.4
4	8	98.6	102.5	104.2	107.3	110.4	112.1	116.0	93.4	98.1	102.7	111.9	116.5	121.1
4	9	99.1	103.0	104.7	107.8	111.0	112.6	116.6	93.9	98.5	103.2	112.5	117.1	121.8
4	10	99.6	103.5	105.2	108.4	111.5	113.2	117.2	94.3	99.0	103.7	113.0	117.7	122.4
4	11	100.0	104.0	105.7	108.9	112.1	113.8	117.8	94.7	99.5	104.2	113.6	118.3	123.1
5	0	100.5	104.5	106.2	109.4	112.6	114.4	118.4	95.2	99.9	104.7	114.2	118.9	123.7



**Table 6** Head Circumference (cm) by age Z (SD) scores in boys and girls aged 0–5 years

Age		Boys							Girls						
Year	month	−3SD	−2SD	−1SD	Median	+1SD	+2SD	+3SD	−3SD	−2SD	−1SD	Median	+1SD	+2SD	+3SD
1	0	30.7	31.9	33.2	34.5	35.7	37.0	38.3	30.3	31.5	32.7	33.9	35.1	36.2	37.4
	1	33.8	34.9	36.1	37.3	38.4	39.6	40.8	33.0	34.2	35.4	36.5	37.7	38.9	40.1
	2	35.6	36.8	38.0	39.1	40.3	41.5	42.6	34.6	35.8	37.0	38.3	39.5	40.7	41.9
	3	37.0	38.1	39.3	40.5	41.7	42.9	44.1	35.8	37.1	38.3	39.5	40.8	42.0	43.3
	4	38.0	39.2	40.4	41.6	42.8	44.0	45.2	36.8	38.1	39.3	40.6	41.8	43.1	44.4
	5	38.9	40.1	41.4	42.6	43.8	45.0	46.2	37.6	38.9	40.2	41.5	42.7	44.0	45.3
	6	39.7	40.9	42.1	43.3	44.6	45.8	47.0	38.3	39.6	40.9	42.2	43.5	44.8	46.1
	7	40.3	41.5	42.7	44.0	45.2	46.4	47.7	38.9	40.2	41.5	42.8	44.1	45.5	46.8
	8	40.8	42.0	43.3	44.5	45.8	47.0	48.3	39.4	40.7	42.0	43.4	44.7	46.0	47.4
	9	41.2	42.5	43.7	45.0	46.3	47.5	48.8	39.8	41.2	42.5	43.8	45.2	46.5	47.8
	10	41.6	42.9	44.1	45.4	46.7	47.9	49.2	40.2	41.5	42.9	44.2	45.6	46.9	48.3
	11	41.9	43.2	44.5	45.8	47.0	48.3	49.6	40.5	41.9	43.2	44.6	45.9	47.3	48.6
	0	42.2	43.5	44.8	46.1	47.4	48.6	49.9	40.8	42.2	43.5	44.9	46.3	47.6	49.0
	1	42.5	43.8	45.0	46.3	47.6	48.9	50.2	41.1	42.4	43.8	45.2	46.5	47.9	49.3
	2	42.7	44.0	45.3	46.6	47.9	49.2	50.5	41.3	42.7	44.1	45.4	46.8	48.2	49.5
	3	42.9	44.2	45.5	46.8	48.1	49.4	50.7	41.5	42.9	44.3	45.7	47.0	48.4	49.8
	4	43.1	44.4	45.7	47.0	48.3	49.6	51.0	41.7	43.1	44.5	45.9	47.2	48.6	50.0
	5	43.2	44.6	45.9	47.2	48.5	49.8	51.2	41.9	43.3	44.7	46.1	47.4	48.8	50.2
	6	43.4	44.7	46.0	47.4	48.7	50.0	51.4	42.1	43.5	44.9	46.2	47.6	49.0	50.4
	7	43.5	44.9	46.2	47.5	48.9	50.2	51.5	42.3	43.6	45.0	46.4	47.8	49.2	50.6
	8	43.7	45.0	46.4	47.7	49.0	50.4	51.7	42.4	43.8	45.2	46.6	48.0	49.4	50.7
	9	43.8	45.2	46.5	47.8	49.2	50.5	51.9	42.6	44.0	45.3	46.7	48.1	49.5	50.9
	10	43.9	45.3	46.6	48.0	49.3	50.7	52.0	42.7	44.1	45.5	46.9	48.3	49.7	51.1
	11	44.1	45.4	46.8	48.1	49.5	50.8	52.2	42.9	44.3	45.6	47.0	48.4	49.8	51.2
2	0	44.2	45.5	46.9	48.3	49.6	51.0	52.3	43.0	44.4	45.8	47.2	48.6	50.0	51.4
	1	44.3	45.6	47.0	48.4	49.7	51.1	52.5	43.1	44.5	45.9	47.3	48.7	50.1	51.5
	2	44.4	45.8	47.1	48.5	49.9	51.2	52.6	43.3	44.7	46.1	47.5	48.9	50.3	51.7
	3	44.5	45.9	47.2	48.6	50.0	51.4	52.7	43.4	44.8	46.2	47.6	49.0	50.4	51.8
	4	44.6	46.0	47.3	48.7	50.1	51.5	52.9	43.5	44.9	46.3	47.7	49.1	50.5	51.9
	5	44.7	46.1	47.4	48.8	50.2	51.6	53.0	43.6	45.0	46.4	47.8	49.2	50.6	52.0
	6	44.8	46.1	47.5	48.9	50.3	51.7	53.1	43.7	45.1	46.5	47.9	49.3	50.7	52.2
	7	44.8	46.2	47.6	49.0	50.4	51.8	53.2	43.8	45.2	46.6	48.0	49.4	50.9	52.3
	8	44.9	46.3	47.7	49.1	50.5	51.9	53.3	43.9	45.3	46.7	48.1	49.6	51.0	52.4
	9	45.0	46.4	47.8	49.2	50.6	52.0	53.4	44.0	45.4	46.8	48.2	49.7	51.1	52.5
	10	45.1	46.5	47.9	49.3	50.7	52.1	53.5	44.1	45.5	46.9	48.3	49.7	51.2	52.6
	11	45.1	46.6	48.0	49.4	50.8	52.2	53.6	44.2	45.6	47.0	48.4	49.8	51.2	52.7
3	0	45.2	46.6	48.0	49.5	50.9	52.3	53.7	44.3	45.7	47.1	48.5	49.9	51.3	52.7
	1	45.3	46.7	48.1	49.5	51.0	52.4	53.8	44.4	45.8	47.2	48.6	50.0	51.4	52.8
	2	45.3	46.8	48.2	49.6	51.0	52.5	53.9	44.4	45.8	47.3	48.7	50.1	51.5	52.9
	3	45.4	46.8	48.2	49.7	51.1	52.5	54.0	44.5	45.9	47.3	48.7	50.2	51.6	53.0
	4	45.4	46.9	48.3	49.7	51.2	52.6	54.1	44.6	46.0	47.4	48.8	50.2	51.7	53.1
	5	45.5	46.9	48.4	49.8	51.3	52.7	54.1	44.6	46.1	47.5	48.9	50.3	51.7	53.1
	6	45.5	47.0	48.4	49.9	51.3	52.8	54.2	44.7	46.1	47.5	49.0	50.4	51.8	53.2
	7	45.6	47.0	48.5	49.9	51.4	52.8	54.3	44.8	46.2	47.6	49.0	50.4	51.9	53.3
	8	45.6	47.1	48.5	50.0	51.4	52.9	54.3	44.8	46.3	47.7	49.1	50.5	51.9	53.3
	9	45.7	47.1	48.6	50.1	51.5	53.0	54.4	44.9	46.3	47.7	49.2	50.6	52.0	53.4
	10	45.7	47.2	48.7	50.1	51.6	53.0	54.5	45.0	46.4	47.8	49.2	50.6	52.1	53.5
	11	45.8	47.2	48.7	50.2	51.6	53.1	54.5	45.0	46.4	47.9	49.3	50.7	52.1	53.5
4	0	45.8	47.3	48.7	50.2	51.7	53.1	54.6	45.1	46.5	47.9	49.3	50.8	52.2	53.6
	1	45.9	47.3	48.8	50.3	51.7	53.2	54.7	45.1	46.5	48.0	49.4	50.8	52.2	53.6
	2	45.9	47.4	48.8	50.3	51.8	53.2	54.7	45.2	46.6	48.0	49.4	50.9	52.3	53.7
	3	45.9	47.4	48.9	50.4	51.8	53.3	54.8	45.2	46.7	48.1	49.5	50.9	52.3	53.8
	4	46.0	47.5	48.9	50.4	51.9	53.4	54.8	45.3	46.7	48.1	49.5	51.0	52.4	53.8
	5	46.0	47.5	49.0	50.4	51.9	53.4	54.9	45.3	46.8	48.2	49.6	51.0	52.4	53.9
	6	46.1	47.5	49.0	50.5	52.0	53.5	54.9	45.4	46.8	48.2	49.6	51.1	52.5	53.9
	7	46.1	47.6	49.1	50.5	52.0	53.5	55.0	45.4	46.9	48.3	49.7	51.1	52.5	54.0
	8	46.1	47.6	49.1	50.6	52.1	53.5	55.0	45.5	46.9	48.3	49.7	51.2	52.6	54.0
	9	46.2	47.6	49.1	50.6	52.1	53.6	55.1	45.5	46.9	48.4	49.8	51.2	52.6	54.1
	10	46.2	47.7	49.2	50.7	52.1	53.6	55.1	45.6	47.0	48.4	49.8	51.3	52.7	54.1
	11	46.2	47.7	49.2	50.7	52.2	53.7	55.2	45.6	47.0	48.5	49.9	51.3	52.7	54.1
5	60	46.3	47.7	49.2	50.7	52.2	53.7	55.2	45.7	47.1	48.5	49.9	51.3	52.8	54.2

**Table 7** Weight (kg) for length (cm) for boys and girls between 0–2 years (WHO reference data) percentiles and Z (SD) scores (cm)

Length (cm)	Boys									Length (cm)	Girls								
	Percentiles			Standard deviation (SD) Z score							Percentiles			Standard deviation (SD) Z score					
	3rd	50th	97th	-3SD	-2SD	-1SD	+1SD	+2SD	+3SD		3rd	50th	97th	-3SD	-2SD	-1SD	+1SD	+2SD	+3SD
45.0	2.1	2.4	2.9	1.9	2.0	2.2	2.7	3.0	3.3	45.0	2.1	2.5	2.9	1.9	2.1	2.3	2.7	3.0	3.3
45.5	2.1	2.5	3.0	1.9	2.1	2.3	2.8	3.1	3.4	45.5	2.2	2.5	3.0	2.0	2.1	2.3	2.8	3.1	3.4
46.0	2.2	2.6	3.1	2.0	2.2	2.4	2.9	3.1	3.5	46.0	2.2	2.6	3.1	2.0	2.2	2.4	2.9	3.2	3.5
46.5	2.3	2.7	3.2	2.1	2.3	2.5	3.0	3.2	3.6	46.5	2.3	2.7	3.2	2.1	2.3	2.5	3.0	3.3	3.6
47.0	2.4	2.8	3.3	2.1	2.3	2.5	3.0	3.3	3.7	47.0	2.4	2.8	3.3	2.2	2.4	2.6	3.1	3.4	3.7
47.5	2.4	2.9	3.4	2.2	2.4	2.6	3.1	3.4	3.8	47.5	2.4	2.9	3.4	2.2	2.4	2.6	3.2	3.5	3.8
48.0	2.5	2.9	3.5	2.3	2.5	2.7	3.2	3.6	3.9	48.0	2.5	3.0	3.5	2.3	2.5	2.7	3.3	3.6	4.0
48.5	2.6	3.0	3.6	2.3	2.6	2.8	3.3	3.7	4.0	48.5	2.6	3.1	3.7	2.4	2.6	2.8	3.4	3.7	4.1
49.0	2.7	3.1	3.7	2.4	2.6	2.9	3.4	3.8	4.2	49.0	2.7	3.2	3.8	2.4	2.6	2.9	3.5	3.8	4.4
49.5	2.7	3.2	3.8	2.5	2.7	3.0	3.5	3.9	4.3	49.5	2.8	3.3	3.9	2.5	2.7	3.0	3.6	3.9	4.3
50.0	2.8	3.3	4.0	2.6	2.8	3.0	3.6	4.0	4.4	50.0	2.8	3.4	4.0	2.6	2.8	3.1	3.7	4.0	4.5
50.5	2.9	3.4	4.1	2.7	2.9	3.1	3.8	4.1	4.5	50.5	2.9	3.5	4.1	2.7	2.9	3.2	3.8	4.2	4.6
51.0	3.0	3.5	4.2	2.7	3.0	3.2	3.9	4.2	4.7	51.0	3.0	3.6	4.3	2.8	3.0	3.3	3.9	4.3	4.8
51.5	3.1	3.6	4.3	2.8	3.1	3.3	4.0	4.4	4.8	51.5	3.1	3.7	4.4	2.8	3.1	3.4	4.0	4.4	4.9
52.0	3.2	3.8	4.5	2.9	3.2	3.5	4.1	4.5	5.0	52.0	3.2	3.8	4.5	2.9	3.2	3.5	4.2	4.6	5.1
52.5	3.3	3.9	4.6	3.0	3.3	3.6	4.2	4.6	5.1	52.5	3.3	3.9	4.7	3.0	3.3	3.6	4.3	4.7	5.2
53.0	3.4	4.0	4.7	3.1	3.4	3.7	4.4	4.8	5.3	53.0	3.4	4.0	4.8	3.1	3.4	3.7	4.4	4.9	5.4
53.5	3.5	4.1	4.9	3.2	3.5	3.8	4.5	4.9	5.4	53.5	3.5	4.2	5.0	3.2	3.5	3.8	4.6	5.0	5.5
54.0	3.6	4.3	5.0	3.3	3.6	3.9	4.7	5.1	5.6	54.0	3.6	4.3	5.1	3.3	3.6	3.9	4.7	5.2	5.7
54.5	3.8	4.4	5.2	3.4	3.7	4.0	4.8	5.3	5.8	54.5	3.7	4.4	5.3	3.4	3.7	4.0	4.8	5.3	5.9
55.0	3.9	4.5	5.4	3.6	3.8	4.2	5.0	5.4	6.0	55.0	3.9	4.5	5.4	3.5	3.8	4.2	5.0	5.5	6.1
55.5	4.0	4.7	5.5	3.7	4.0	4.3	5.1	5.6	6.1	55.5	4.0	4.7	5.6	3.6	3.9	4.3	5.1	5.7	6.3
56.0	4.1	4.8	5.7	3.8	4.1	4.4	5.3	5.8	6.3	56.0	4.1	4.8	5.8	3.7	4.0	4.4	5.3	5.8	6.4
56.5	4.3	5.0	5.9	3.9	4.2	4.6	5.4	5.9	6.5	56.5	4.2	5.0	5.9	3.8	4.1	4.5	5.4	6.0	6.6
57.0	4.4	5.1	6.0	4.0	4.3	4.7	5.6	6.1	6.7	57.0	4.3	5.1	6.1	3.9	4.3	4.6	5.6	6.1	6.8
57.5	4.5	5.3	6.2	4.1	4.5	4.9	5.7	6.3	6.9	57.5	4.4	5.2	6.2	4.0	4.4	4.8	5.7	6.3	7.0
58.0	4.6	5.4	6.4	4.3	4.6	5.0	5.9	6.4	7.1	58.0	4.5	5.4	6.4	4.1	4.5	4.9	5.9	6.5	7.1
58.5	4.8	5.6	6.5	4.4	4.7	5.1	6.1	6.6	7.2	58.5	4.6	5.5	6.5	4.2	4.6	5.0	6.0	6.6	7.3
59.0	4.9	5.7	6.7	4.5	4.8	5.3	6.2	6.8	7.4	59.0	4.8	5.6	6.7	4.3	4.7	5.1	6.2	6.8	7.5
59.5	5.0	5.9	6.9	4.6	5.0	5.4	6.4	7.0	7.6	59.5	4.9	5.7	6.9	4.4	4.8	5.3	6.3	6.9	7.7
60.0	5.1	6.0	7.0	4.7	5.1	5.5	6.5	7.1	7.8	60.0	5.0	5.9	7.0	4.5	4.9	5.4	6.4	7.1	7.8
60.5	5.3	6.1	7.2	4.8	5.2	5.6	6.7	7.3	8.0	60.5	5.1	6.0	7.2	4.6	5.0	5.5	6.6	7.3	8.0
61.0	5.4	6.3	7.4	4.9	5.3	5.8	6.8	7.4	8.1	61.0	5.2	6.1	7.3	4.7	5.1	5.6	6.7	7.4	8.2
61.5	5.5	6.4	7.5	5.0	5.4	5.9	7.0	7.6	8.3	61.5	5.3	6.3	7.5	4.8	5.2	5.7	6.9	7.6	8.4
62.0	5.6	6.5	7.7	5.1	5.6	6.0	7.1	7.7	8.5	62.0	5.4	6.4	7.6	4.9	5.3	5.8	7.0	7.7	8.5
62.5	5.7	6.7	7.8	5.2	5.7	6.1	7.2	7.9	8.6	62.5	5.5	6.5	7.8	5.0	5.4	5.9	7.1	7.8	8.7
63.0	5.8	6.8	8.0	5.3	5.8	6.2	7.4	8.0	8.8	63.0	5.6	6.6	7.9	5.1	5.5	6.0	7.3	8.0	8.8
63.5	5.9	6.9	8.1	5.4	5.9	6.4	7.5	8.2	8.9	63.5	5.7	6.7	8.0	5.2	5.6	6.2	7.4	8.1	9.0
64.0	6.0	7.0	8.2	5.5	6.0	6.5	7.6	8.3	9.1	64.0	5.8	6.9	8.2	5.3	5.7	6.3	7.5	8.3	9.1
64.5	6.1	7.1	8.4	5.6	6.1	6.6	7.8	8.5	9.3	64.5	5.9	7.0	8.3	5.4	5.8	6.4	7.6	8.4	9.3
65.0	6.3	7.3	8.5	5.7	6.2	6.7	7.9	8.6	9.4	65.0	6.0	7.1	8.5	5.5	5.9	6.5	7.8	8.6	9.5
65.5	6.4	7.4	8.7	5.8	6.3	6.8	8.0	8.7	9.6	65.5	6.1	7.2	8.6	5.5	6.0	6.6	7.9	8.7	9.6
66.0	6.5	7.5	8.8	5.9	6.4	6.9	8.2	8.9	9.7	66.0	6.2	7.3	8.7	5.6	6.1	6.7	8.0	8.8	9.8
66.5	6.6	7.6	8.9	6.0	6.5	7.0	8.3	9.0	9.9	66.5	6.3	7.4	8.9	5.7	6.2	6.8	8.1	9.0	9.9
67.0	6.7	7.7	9.1	6.1	6.6	7.1	8.4	9.2	10.0	67.0	6.4	7.5	9.0	5.8	6.3	6.9	8.3	9.1	10.0
67.5	6.8	7.9	9.2	6.2	6.7	7.2	8.5	9.3	10.2	67.5	6.5	7.6	9.1	5.9	6.4	7.0	8.4	9.2	10.2
68.0	6.9	8.0	9.3	6.3	6.8	7.3	8.7	9.4	10.3	68.0	6.6	7.7	9.2	6.0	6.5	7.1	8.5	9.4	10.3
68.5	7.0	8.1	9.5	6.4	6.9	7.5	8.8	9.6	10.5	68.5	6.7	7.9	9.4	6.1	6.6	7.2	8.6	9.5	10.5
69.0	7.1	8.2	9.6	6.5	7.0	7.6	8.9	9.7	10.6	69.0	6.7	8.0	9.5	6.1	6.7	7.3	8.7	9.6	10.6
69.5	7.1	8.3	9.7	6.6	7.1	7.7	9.0	9.8	10.8	69.5	6.8	8.1	9.6	6.2	6.8	7.4	8.8	9.7	10.7
70.0	7.2	8.4	9.9	6.6	7.2	7.8	9.2	10.0	10.9	70.0	6.9	8.2	9.7	6.3	6.9	7.5	9.0	9.9	10.9
70.5	7.3	8.5	10.0	6.7	7.3	7.9	9.3	10.1	11.1	70.5	7.0	8.3	9.9	6.4	6.9	7.6	9.1	10.0	11.0
71.0	7.4	8.6	10.1	6.8	7.4	8.0	9.4	10.2	11.2	71.0	7.1	8.4	10.0	6.5	7.0	7.7	9.2	10.1	11.1
71.5	7.5	8.8	10.3	6.9	7.5	8.1	9.5	10.4	11.3	71.5	7.2	8.5	10.1	6.5	7.1	7.7	9.3	10.2	11.3
72.0	7.6	8.9	10.4	7.0	7.6	8.2	9.6	10.5	11.5	72.0	7.3	8.6	10.2	6.6	7.2	7.8	9.4	10.3	11.4
72.5	7.7	9.0	10.5	7.1	7.6	8.3	9.8	10.6	11.6	72.5	7.4	8.7	10.3	6.7	7.3	7.9	9.5	10.5	11.5
73.0	7.8	9.1	10.7	7.2	7.7	8.4	9.9	10.8	11.8	73.0	7.4	8.8	10.4	6.8	7.4	8.0	9.6	10.6	11.7
73.5	7.9	9.2	10.8	7.2	7.8	8.5	10.0	10.9	11.9	73.5	7.5	8.9	10.6	6.9	7.4	8.1	9.7	10.7	11.8
74.0	8.0	9.3	10.9	7.3	7.9	8.6	10.1	11.0	12.1	74.0	7.6	9.0	10.7	6.9	7.5	8.2	9.8	10.8	11.9
74.5	8.1	9.4	11.0	7.4	8.0	8.7	10.2	11.2	12.2	74.5	7.7	9.1	10.8	7.0	7.6	8.3	9.9	10.9	12.0
75.0	8.2	9.5	11.2	7.5	8.1	8.8	10.3	11.3	12.3	75.0	7.8	9.1	10.9	7.1	7.7	8.4	10.0	111	

Contd...

Contd...

Length (cm)	Boys										Length (cm)	Girls									
	Percentiles			Standard deviation (SD) Z score								Percentiles			Standard deviation (SD) Z score						
	3rd	50th	97th	-3SD	-2SD	-1SD	+1SD	+2SD	+3SD	3rd		50th	97th	-3SD	-2SD	-1SD	+1SD	+2SD	+3SD		
77.5	8.6	10.0	11.7	7.9	8.5	9.2	10.9	11.9	13.0	77.5	8.2	9.6	11.4	7.4	8.1	8.8	10.5	11.6	12.8		
78.0	8.7	10.1	11.8	7.9	8.6	9.3	11.0	12.0	13.1	78.0	8.2	9.7	11.5	7.5	8.2	8.9	10.6	11.7	12.9		
78.5	8.7	10.2	12.0	8.0	8.7	9.4	11.1	12.1	13.2	78.5	8.3	9.8	11.7	7.6	8.2	9.0	10.7	11.8	13.0		
79.0	8.8	10.3	12.1	8.1	8.7	9.5	11.2	12.2	13.3	79.0	8.4	9.9	11.8	7.7	8.3	9.1	10.8	11.9	13.1		
79.5	8.9	10.4	12.2	8.2	8.8	9.5	11.3	12.3	13.4	79.5	8.5	10.0	11.9	7.7	8.4	9.1	10.9	12.0	13.3		
80.0	9.0	10.4	12.3	8.2	8.9	9.6	11.4	12.4	13.6	80.0	8.6	10.1	12.0	7.8	8.5	9.2	11.0	12.1	13.4		
80.5	9.1	10.5	12.4	8.3	9.0	9.7	11.5	12.5	13.7	80.5	8.7	10.2	12.1	7.9	8.6	9.3	11.2	12.3	13.5		
81.0	9.1	10.6	12.5	8.4	9.1	9.8	11.6	12.6	13.8	81.0	8.8	10.3	12.2	8.0	8.7	9.4	11.3	12.4	13.7		
81.5	9.2	10.7	12.6	8.5	9.1	9.9	11.7	12.7	13.9	81.5	8.8	10.4	12.4	8.1	8.8	9.5	11.4	12.5	13.8		
82.0	9.3	10.8	12.7	8.5	9.2	10.0	11.8	12.8	14.0	82.0	8.9	10.5	12.5	8.1	8.8	9.6	11.5	12.6	13.9		
82.5	9.4	10.9	12.8	8.6	9.3	10.1	11.9	13.0	14.2	82.5	9.0	10.6	12.6	8.2	8.9	9.7	11.6	12.8	14.1		
83.0	9.5	11.0	13.0	8.7	9.4	10.2	12.0	13.1	14.3	83.0	9.1	10.7	12.8	8.3	9.0	9.8	11.8	12.9	14.2		
83.5	9.6	11.2	13.1	8.8	9.5	10.3	12.1	13.2	14.4	83.5	9.2	10.9	12.9	8.4	9.1	9.9	11.9	13.1	14.4		
84.0	9.7	11.3	13.2	8.9	9.6	10.4	12.2	13.3	14.6	84.0	9.3	11.0	13.1	8.5	9.2	10.1	12.0	13.2	14.5		
84.5	9.8	11.4	13.3	9.0	9.7	10.5	12.4	13.5	14.7	84.5	9.4	11.1	13.2	8.6	9.3	10.2	12.1	13.3	14.7		
85.0	9.9	11.5	13.5	9.1	9.8	10.6	12.5	13.6	14.9	85.0	9.5	11.2	13.3	8.7	9.4	10.3	12.3	13.5	14.9		
85.5	10.0	11.6	13.6	9.2	9.9	10.7	12.6	13.7	15.0	85.5	9.6	11.3	13.5	8.8	9.5	10.4	12.4	13.6	15.0		
86.0	10.1	11.7	13.7	9.3	10.0	10.8	12.8	13.9	15.2	86.0	9.8	11.5	13.6	8.9	9.7	10.5	12.6	13.8	15.2		
86.5	10.2	11.9	13.9	9.4	10.1	11.0	12.9	14.0	15.3	86.5	9.9	11.6	13.8	9.0	9.8	10.6	12.7	13.9	15.4		
87.0	10.3	12.0	14.0	9.5	10.2	11.1	13.0	14.2	15.5	87.0	10.0	11.7	13.9	9.1	9.9	10.7	12.8	14.1	15.5		
87.5	10.4	12.1	14.2	9.6	10.4	11.2	13.2	14.3	15.6	87.5	10.1	11.8	14.1	9.2	10.0	10.9	13.0	14.2	15.7		
88.0	10.6	12.2	14.3	9.7	10.5	11.3	13.3	14.5	15.8	88.0	10.2	12.0	14.2	9.3	10.1	11.0	13.1	14.4	15.9		
88.5	10.7	12.4	14.4	9.8	10.6	11.4	13.4	14.6	15.9	88.5	10.3	12.1	14.4	9.4	10.2	11.1	13.2	14.5	16.0		
89.0	10.8	12.5	14.6	9.9	10.7	11.5	13.5	14.7	16.1	89.0	10.4	12.2	14.5	9.5	10.3	11.2	13.4	14.7	16.2		
89.5	10.9	12.6	14.7	10.0	10.8	11.6	13.7	14.9	16.2	89.5	10.5	12.3	14.7	9.6	10.4	11.3	13.5	14.8	16.4		
90.0	11.0	12.7	14.9	10.1	10.9	11.8	13.8	15.0	16.4	90.0	10.6	12.5	14.8	9.7	10.5	11.4	13.7	15.0	16.5		
90.5	11.1	12.8	15.0	10.2	11.0	11.9	13.9	15.1	16.5	90.5	10.7	12.6	15.0	9.8	10.6	11.5	13.8	15.1	16.7		
91.0	11.2	13.0	15.1	10.3	11.1	12.0	14.1	15.3	16.7	91.0	10.8	12.7	15.1	9.9	10.7	11.7	13.9	15.3	16.9		
91.5	11.3	13.1	15.3	10.4	11.2	12.1	14.2	15.4	16.8	91.5	10.9	12.8	15.3	10.0	10.8	11.8	14.1	15.5	17.0		
92.0	11.4	13.2	15.4	10.5	11.3	12.2	14.3	15.6	17.0	92.0	11.0	13.0	15.4	10.1	10.9	11.9	14.2	15.6	17.2		
92.5	11.5	13.3	15.5	10.6	11.4	12.3	14.4	15.7	17.1	92.5	11.1	13.1	15.6	10.1	11.0	12.0	14.3	15.8	17.4		
93.0	11.6	13.4	15.7	10.7	11.5	12.4	14.6	15.8	17.3	93.0	11.2	13.2	15.7	10.2	11.1	12.1	14.5	15.9	17.5		
93.5	11.7	13.5	15.8	10.7	11.6	12.5	14.7	16.0	17.4	93.5	11.3	13.3	15.9	10.3	11.2	12.2	14.6	16.1	17.7		
94.0	11.8	13.7	16.0	10.8	11.7	12.6	14.8	16.1	17.6	94.0	11.4	13.5	16.0	10.4	11.3	12.3	14.7	16.2	17.9		
94.5	11.9	13.8	16.1	10.9	11.8	12.7	14.9	16.3	17.7	94.5	11.5	13.6	16.2	10.5	11.4	12.4	14.9	16.4	18.0		
95.0	12.0	13.9	16.2	11.0	11.9	12.8	15.1	16.4	17.9	95.0	11.6	13.7	16.3	10.6	11.5	12.6	15.0	16.5	18.2		
95.5	12.1	14.0	16.4	11.1	12.0	12.9	15.2	16.5	18.0	95.5	11.8	13.8	16.5	10.7	11.6	12.7	15.2	16.7	18.4		
96.0	12.2	14.1	16.5	11.2	12.1	13.1	15.3	16.7	18.2	96.0	11.9	14.0	16.6	10.8	11.7	12.8	15.3	16.8	18.6		
96.5	12.3	14.3	16.7	11.3	12.2	13.2	15.5	16.8	18.4	96.5	12.0	14.1	16.8	10.9	11.8	12.9	15.4	17.0	18.7		
97.0	12.4	14.4	16.8	11.4	12.3	13.3	15.6	17.0	18.5	97.0	12.1	14.2	16.9	11.0	12.0	13.0	15.6	17.1	18.9		
97.5	12.5	14.5	17.0	11.5	12.4	13.4	15.7	17.1	18.7	97.5	12.2	14.4	17.1	11.1	12.1	13.1	15.7	17.3	19.1		
98.0	12.6	14.6	17.1	11.6	12.5	13.5	15.9	17.3	18.9	98.0	12.3	14.5	17.3	11.2	12.2	13.3	15.9	17.5	19.3		
98.5	12.7	14.8	17.3	11.7	12.6	13.6	16.0	17.5	19.1	98.5	12.4	14.6	17.4	11.3	12.3	13.4	16.0	17.6	19.5		
99.0	12.8	14.9	17.4	11.8	12.7	13.7	16.2	17.6	19.2	99.0	12.5	14.8	17.6	11.4	12.4	13.5	16.2	17.8	19.6		
99.5	12.9	15.0	17.6	11.9	12.8	13.9	16.3	17.8	19.4	99.5	12.6	14.9	17.8	11.5	12.5	13.6	16.3	18.0	19.8		
100.0	13.0	15.2	17.8	12.0	12.9	14.0	16.5	18.0	19.6	100.0	12.7	15.0	17.9	11.6	12.6	13.7	16.5	18.1	20.0		
100.5	13.2	15.3	17.9	12.1	13.0	14.1	16.6	18.1	19.8	100.5	12.9	15.2	18.1	11.7	12.7	13.9	16.6	18.3	20.2		
101.0	13.3	15.4	18.1	12.2	13.2	14.2	16.8	18.3	20.0	101.0	13.0	15.3	18.3	11.8	12.8	14.0	16.8	18.5	20.4		
101.5	13.4	15.6	18.3	12.3	13.3	14.4	16.9	18.5	20.2	101.5	13.1	15.5	18.5	11.9	13.0	14.1	17.0	18.7	20.6		
102.0	13.5	15.7	18.5	12.4	13.4	14.5	17.1	18.7	20.4	102.0	13.2	15.6	18.6	12.0	13.1	14.3	17.1	18.9	20.8		
102.5	13.6	15.9	18.6	12.5	13.5	14.6	17.3	18.8	20.6	102.5	13.3	15.8	18.8	12.1	13.2	14.4	17.3	19.0	21.0		
103.0	13.8	16.0	18.8	12.6	13.6	14.8	17.4	19.0	20.8	103.0	13.5	15.9	19.0	12.3	13.3	14.5	17.5	19.2	21.3		
103.5	13.9	16.2	19.0	12.7	13.7	14.9	17.6	19.2	21.0	103.5	13.6	16.1	19.2	12.4	13.5	14.7	17.6	19.4	21.5		
104.0	14.0	16.3	19.2	12.8	13.9	15.0	17.8	19.4	21.2	104.0	13.7	16.2	19.4	12.5	13.6	14.8	17.8	19.6	21.7		
104.5	14.1	16.5	19.4	12.9	14.0	15.2	17.9	19.6	21.5	104.5	13.9	16.4	19.6	12.6	13.7	15.0	18.0	19.8	21.9		
105.0	14.2	16.6	19.6	13.0	14.1	15.3	18.1</														

**Table 8** Weight (kg) for Height (cm) for boys and girls between 2–5 years (WHO reference data) percentiles and Z (SD) scores

Boys										Girls									
Height	Percentiles			Standard deviation (SD) Z score						Height	Percentiles			Standard deviation (SD) Z score					
	3rd	50th	97th	-3SD	-2SD	-1SD	+1SD	+2SD	+3SD		3rd	50th	97th	-3SD	-2SD	-1SD	+1SD	+2SD	+3SD
65.0	6.4	7.4	8.7	5.9	6.3	6.9	8.1	8.8	9.6	65.0	6.1	7.2	8.6	5.6	6.1	6.6	7.9	8.7	9.7
65.5	6.5	7.6	8.9	6.0	6.4	7.0	8.2	8.9	9.8	65.5	6.2	7.4	8.8	5.7	6.2	6.7	8.1	8.9	9.8
66.0	6.6	7.7	9.0	6.1	6.5	7.1	8.3	9.1	9.9	66.0	6.3	7.5	8.9	5.8	6.3	6.8	8.2	9.0	10.0
66.5	6.7	7.8	9.1	6.1	6.6	7.2	8.5	9.2	10.1	66.5	6.4	7.6	9.0	5.8	6.4	6.9	8.3	9.1	10.1
67.0	6.8	7.9	9.3	6.2	6.7	7.3	8.6	9.4	10.2	67.0	6.5	7.7	9.2	5.9	6.4	7.0	8.4	9.3	10.2
67.5	6.9	8.0	9.4	6.3	6.8	7.4	8.7	9.5	10.4	67.5	6.6	7.8	9.3	6.0	6.5	7.1	8.5	9.4	10.4
68.0	7.0	8.1	9.5	6.4	6.9	7.5	8.8	9.6	10.5	68.0	6.7	7.9	9.4	6.1	6.6	7.2	8.7	9.5	10.5
68.5	7.1	8.2	9.7	6.5	7.0	7.6	9.0	9.8	10.7	68.5	6.8	8.0	9.5	6.2	6.7	7.3	8.8	9.7	10.7
69.0	7.2	8.4	9.8	6.6	7.1	7.7	9.1	9.9	10.8	69.0	6.9	8.1	9.7	6.3	6.8	7.4	8.9	9.8	10.8
69.5	7.3	8.5	9.9	6.7	7.2	7.8	9.2	10.0	11.0	69.5	7.0	8.2	9.8	6.3	6.9	7.5	9.0	9.9	10.9
70.0	7.4	8.6	10.1	6.8	7.3	7.9	9.3	10.2	11.1	70.0	7.0	8.3	9.9	6.4	7.0	7.6	9.1	10.0	11.1
70.5	7.5	8.7	10.2	6.9	7.4	8.0	9.5	10.3	11.3	70.5	7.1	8.4	10.0	6.5	7.1	7.7	9.2	10.1	11.2
71.0	7.6	8.8	10.3	6.9	7.5	8.1	9.6	10.4	11.4	71.0	7.2	8.5	10.1	6.6	7.1	7.8	9.3	10.3	11.3
71.5	7.7	8.9	10.5	7.0	7.6	8.2	9.7	10.6	11.6	71.5	7.3	8.6	10.3	6.7	7.2	7.9	9.4	10.4	11.5
72.0	7.8	9.0	10.6	7.1	7.7	8.3	9.8	10.7	11.7	72.0	7.4	8.7	10.4	6.7	7.3	8.0	9.5	10.5	11.6
72.5	7.8	9.1	10.7	7.2	7.8	8.4	9.9	10.8	11.8	72.5	7.5	8.8	10.5	6.8	7.4	8.1	9.7	10.6	11.7
73.0	7.9	9.2	10.8	7.3	7.9	8.5	10.0	11.0	12.0	73.0	7.6	8.9	10.6	6.9	7.5	8.1	9.8	10.7	11.8
73.5	8.0	9.3	11.0	7.4	7.9	8.6	10.2	11.1	12.1	73.5	7.6	9.0	10.7	7.0	7.6	8.2	9.9	10.8	12.0
74.0	8.1	9.4	11.1	7.4	8.0	8.7	10.3	11.2	12.2	74.0	7.7	9.1	10.8	7.0	7.6	8.3	10.0	11.0	12.1
74.5	8.2	9.5	11.2	7.5	8.1	8.8	10.4	11.3	12.4	74.5	7.8	9.2	10.9	7.1	7.7	8.4	10.1	11.1	12.2
75.0	8.3	9.6	11.3	7.6	8.2	8.9	10.5	11.4	12.5	75.0	7.9	9.3	11.1	7.2	7.8	8.5	10.2	11.2	12.3
75.5	8.4	9.7	11.4	7.7	8.3	9.0	10.6	11.6	12.6	75.5	8.0	9.4	11.2	7.2	7.9	8.6	10.3	11.3	12.5
76.0	8.5	9.8	11.6	7.7	8.4	9.1	10.7	11.7	12.8	76.0	8.0	9.5	11.3	7.3	8.0	8.7	10.4	11.4	12.6
76.5	8.5	9.9	11.7	7.8	8.5	9.2	10.8	11.8	12.9	76.5	8.1	9.6	11.4	7.4	8.0	8.7	10.5	11.5	12.7
77.0	8.6	10.0	11.8	7.9	8.5	9.2	10.9	11.9	13.0	77.0	8.2	9.6	11.5	7.5	8.1	8.8	10.6	11.6	12.8
77.5	8.7	10.1	11.9	8.0	8.6	9.3	11.0	12.0	13.1	77.5	8.3	9.7	11.6	7.5	8.2	8.9	10.7	11.7	12.9
78.0	8.8	10.2	12.0	8.0	8.7	9.4	11.1	12.1	13.3	78.0	8.4	9.8	11.7	7.6	8.3	9.0	10.8	11.8	13.1
78.5	8.8	10.3	12.1	8.1	8.8	9.5	11.2	12.2	13.4	78.5	8.4	9.9	11.8	7.7	8.4	9.1	10.9	12.0	13.2
79.0	8.9	10.4	12.2	8.2	8.8	9.6	11.3	12.3	13.5	79.0	8.5	10.0	11.9	7.8	8.4	9.2	11.0	12.1	13.3
79.5	9.0	10.5	12.3	8.3	8.9	9.7	11.4	12.4	13.6	79.5	8.6	10.1	12.1	7.8	8.5	9.3	11.1	12.2	13.4
80.0	9.1	10.6	12.4	8.3	9.0	9.7	11.5	12.6	13.7	80.0	8.7	10.2	12.2	7.9	8.6	9.4	11.2	12.3	13.6
80.5	9.2	10.7	12.5	8.4	9.1	9.8	11.6	12.7	13.8	80.5	8.8	10.3	12.3	8.0	8.7	9.5	11.3	12.4	13.7
81.0	9.3	10.8	12.6	8.5	9.2	9.9	11.7	12.8	14.0	81.0	8.9	10.4	12.4	8.1	8.8	9.6	11.4	12.6	13.9
81.5	9.3	10.9	12.8	8.6	9.3	10.0	11.8	12.9	14.1	81.5	9.0	10.6	12.6	8.2	8.9	9.7	11.6	12.7	14.0
82.0	9.4	11.0	12.9	8.7	9.3	10.1	11.9	13.0	14.2	82.0	9.1	10.7	12.7	8.3	9.0	9.8	11.7	12.8	14.1
82.5	9.5	11.1	13.0	8.7	9.4	10.2	12.1	13.1	14.4	82.5	9.2	10.8	12.8	8.4	9.1	9.9	11.8	13.0	14.3
83.0	9.6	11.2	13.1	8.8	9.5	10.3	12.2	13.3	14.5	83.0	9.3	10.9	13.0	8.5	9.2	10.0	11.9	13.1	14.5
83.5	9.7	11.3	13.3	8.9	9.6	10.4	12.3	13.4	14.6	83.5	9.4	11.0	13.1	8.5	9.3	10.1	12.1	13.3	14.6
84.0	9.8	11.4	13.4	9.0	9.7	10.5	12.4	13.5	14.8	84.0	9.5	11.1	13.3	8.6	9.4	10.2	12.2	13.4	14.8
84.5	9.9	11.5	13.5	9.1	9.9	10.7	12.5	13.7	14.9	84.5	9.6	11.3	13.4	8.7	9.5	10.3	12.3	13.5	14.9
85.0	10.1	11.7	13.7	9.2	10.0	10.8	12.7	13.8	15.1	85.0	9.7	11.4	13.5	8.8	9.6	10.4	12.5	13.7	15.1
85.5	10.2	11.8	13.8	9.3	10.1	10.9	12.8	13.9	15.2	85.5	9.8	11.5	13.7	8.9	9.7	10.6	12.6	13.8	15.3
86.0	10.3	11.9	13.9	9.4	10.2	11.0	12.9	14.1	15.4	86.0	9.9	11.6	13.8	9.0	9.8	10.7	12.7	14.0	15.4
86.5	10.4	12.0	14.1	9.5	10.3	11.1	13.1	14.2	15.5	86.5	10.0	11.8	14.0	9.1	9.9	10.8	12.9	14.2	15.6
87.0	10.5	12.2	14.2	9.6	10.4	11.2	13.2	14.4	15.7	87.0	10.1	11.9	14.1	9.2	10.0	10.9	13.0	14.3	15.8
87.5	10.6	12.3	14.4	9.7	10.5	11.3	13.3	14.5	15.8	87.5	10.2	12.0	14.3	9.3	10.1	11.0	13.2	14.5	15.9
88.0	10.7	12.4	14.5	9.8	10.6	11.5	13.5	14.7	16.0	88.0	10.3	12.1	14.4	9.4	10.2	11.1	13.3	14.6	16.1
88.5	10.8	12.5	14.6	9.9	10.7	11.6	13.6	14.8	16.1	88.5	10.4	12.3	14.6	9.5	10.3	11.2	13.4	14.8	16.3
89.0	10.9	12.6	14.8	10.0	10.8	11.7	13.7	14.9	16.3	89.0	10.5	12.4	14.7	9.6	10.4	11.4	13.6	14.9	16.4
89.5	11.0	12.8	14.9	10.1	10.9	11.8	13.9	15.1	16.4	89.5	10.6	12.5	14.9	9.7	10.5	11.5	13.7	15.1	16.6
90.0	11.1	12.9	15.1	10.2	11.0	11.9	14.0	15.2	16.6	90.0	10.8	12.6	15.0	9.8	10.6	11.6	13.8	15.2	16.8
90.5	11.2	13.0	15.2	10.3	11.1	12.0	14.1	15.3	16.7	90.5	10.9	12.8	15.2	9.9	10.7	11.7	14.0	15.4	16.9
91.0	11.3	13.1	15.3	10.4	11.2	12.1	14.2	15.5	16.9	91.0	11.0	12.9	15.3	10.0	10.9	11.8	14.1	15.5	17.1
91.5	11.4	13.2	15.5	10.5	11.3	12.2	14.4	15.6	17.0	91.5	11.1	13.0	15.5	10.1	11.0	11.9	14.3	15.7	17.3
92.0	11.5	13.4	15.6	10.6	11.4	12.3	14.5	15.8	17.2	92.0	11.2	13.1	15.6	10.2	11.1	12.0	14.4	15.8	17.4

Contd...



Contd...

Boys										Girls									
Height	Percentiles			Standard deviation (SD) Z score						Height	Percentiles			Standard deviation (SD) Z score					
	3rd	50th	97th	-3SD	-2SD	-1SD	+1SD	+2SD	+3SD		3rd	50th	97th	-3SD	-2SD	-1SD	+1SD	+2SD	+3SD
92.5	11.6	13.5	15.7	10.7	11.5	12.4	14.6	15.9	17.3	92.5	11.3	13.3	15.8	10.3	11.2	12.1	14.5	16.0	17.6
93.0	11.7	13.6	15.9	10.8	11.6	12.6	14.7	16.0	17.5	93.0	11.4	13.4	15.9	10.4	11.3	12.3	14.7	16.1	17.8
93.5	11.8	13.7	16.0	10.9	11.7	12.7	14.9	16.2	17.6	93.5	11.5	13.5	16.1	10.5	11.4	12.4	14.8	16.3	17.9
94.0	11.9	13.8	16.1	11.0	11.8	12.8	15.0	16.3	17.8	94.0	11.6	13.6	16.2	10.6	11.5	12.5	14.9	16.4	18.1
94.5	12.0	13.9	16.3	11.1	11.9	12.9	15.1	16.5	17.9	94.5	11.7	13.8	16.4	10.7	11.6	12.6	15.1	16.6	18.3
95.0	12.1	14.1	16.4	11.1	12.0	13.0	15.3	16.6	18.1	95.0	11.8	13.9	16.5	10.8	11.7	12.7	15.2	16.7	18.5
95.5	12.2	14.2	16.6	11.2	12.1	13.1	15.4	16.7	18.3	95.5	11.9	14.0	16.7	10.8	11.8	12.8	15.4	16.9	18.6
96.0	12.3	14.3	16.7	11.3	12.2	13.2	15.5	16.9	18.4	96.0	12.0	14.1	16.9	10.9	11.9	12.9	15.5	17.0	18.8
96.5	12.4	14.4	16.9	11.4	12.3	13.3	15.7	17.0	18.6	96.5	12.1	14.3	17.0	11.0	12.0	13.1	15.6	17.2	19.0
97.0	12.5	14.6	17.0	11.5	12.4	13.4	15.8	17.2	18.8	97.0	12.2	14.4	17.2	11.1	12.1	13.2	15.8	17.4	19.2
97.5	12.7	14.7	17.2	11.6	12.5	13.6	15.9	17.4	18.9	97.5	12.3	14.5	17.3	11.2	12.2	13.3	15.9	17.5	19.3
98.0	12.8	14.8	17.3	11.7	12.6	13.7	16.1	17.5	19.1	98.0	12.4	14.7	17.5	11.3	12.3	13.4	16.1	17.7	19.5
98.5	12.9	14.9	17.5	11.8	12.8	13.8	16.2	17.7	19.3	98.5	12.6	14.8	17.7	11.4	12.4	13.5	16.2	17.9	19.7
99.0	13.0	15.1	17.7	11.9	12.9	13.9	16.4	17.9	19.5	99.0	12.7	14.9	17.8	11.5	12.5	13.7	16.4	18.0	19.9
99.5	13.1	15.2	17.8	12.0	13.0	14.0	16.5	18.0	19.7	99.5	12.8	15.1	18.0	11.6	12.7	13.8	16.5	18.2	20.1
100.0	13.2	15.4	18.0	12.1	13.1	14.2	16.7	18.2	19.9	100.0	12.9	15.2	18.2	11.7	12.8	13.9	16.7	18.4	20.3
100.5	13.3	15.5	18.2	12.2	13.2	14.3	16.9	18.4	20.1	100.5	13.0	15.4	18.3	11.9	12.9	14.1	16.9	18.6	20.5
101.0	13.4	15.6	18.4	12.3	13.3	14.4	17.0	18.5	20.3	101.0	13.1	15.5	18.5	12.0	13.0	14.2	17.0	18.7	20.7
101.5	13.6	15.8	18.5	12.4	13.4	14.5	17.2	18.7	20.5	101.5	13.3	15.7	18.7	12.1	13.1	14.3	17.2	18.9	20.9
102.0	13.7	15.9	18.7	12.5	13.6	14.7	17.3	18.9	20.7	102.0	13.4	15.8	18.9	12.2	13.3	14.5	17.4	19.1	21.1
102.5	13.8	16.1	18.9	12.6	13.7	14.8	17.5	19.1	20.9	102.5	13.5	16.0	19.1	12.3	13.4	14.6	17.5	19.3	21.4
103.0	13.9	16.2	19.1	12.8	13.8	14.9	17.7	19.3	21.1	103.0	13.6	16.1	19.3	12.4	13.5	14.7	17.7	19.5	21.6
103.5	14.0	16.4	19.3	12.9	13.9	15.1	17.8	19.5	21.3	103.5	13.8	16.3	19.5	12.5	13.6	14.9	17.9	19.7	21.8
104.0	14.2	16.5	19.5	13.0	14.0	15.2	18.0	19.7	21.6	104.0	13.9	16.4	19.7	12.6	13.8	15.0	18.1	19.9	22.0
104.5	14.3	16.7	19.7	13.1	14.2	15.4	18.2	19.9	21.8	104.5	14.0	16.6	19.9	12.8	13.9	15.2	18.2	20.1	22.3
105.0	14.4	16.8	19.9	13.2	14.3	15.5	18.4	20.1	22.0	105.0	14.2	16.8	20.1	12.9	14.0	15.3	18.4	20.3	22.5
105.5	14.5	17.0	20.1	13.3	14.4	15.6	18.5	20.3	22.2	105.5	14.3	16.9	20.3	13.0	14.2	15.5	18.6	20.5	22.7
106.0	14.7	17.2	20.3	13.4	14.5	15.8	18.7	20.5	22.5	106.0	14.5	17.1	20.5	13.1	14.3	15.6	18.8	20.8	23.0
106.5	14.8	17.3	20.5	13.5	14.7	15.9	18.9	20.7	22.7	106.5	14.6	17.3	20.7	13.3	14.5	15.8	19.0	21.0	23.2
107.0	14.9	17.5	20.7	13.7	14.8	16.1	19.1	20.9	22.9	107.0	14.7	17.5	21.0	13.4	14.6	15.9	19.2	21.2	23.5
107.5	15.1	17.7	20.9	13.8	14.9	16.2	19.3	21.1	23.2	107.5	14.9	17.7	21.2	13.5	14.7	16.1	19.4	21.4	23.7
108.0	15.2	17.8	21.1	13.9	15.1	16.4	19.5	21.3	23.4	108.0	15.0	17.8	21.4	13.7	14.9	16.3	19.6	21.7	24.0
108.5	15.3	18.0	21.3	14.0	15.2	16.5	19.7	21.5	23.7	108.5	15.2	18.0	21.6	13.8	15.0	16.4	19.8	21.9	24.3
109.0	15.5	18.2	21.5	14.1	15.3	16.7	19.8	21.8	23.9	109.0	15.4	18.2	21.9	13.9	15.2	16.6	20.0	22.1	24.5
109.5	15.6	18.3	21.7	14.3	15.5	16.8	20.0	22.0	24.2	109.5	15.5	18.4	22.1	14.1	15.4	16.8	20.3	22.4	24.8
110.0	15.8	18.5	22.0	14.4	15.6	17.0	20.2	22.2	24.4	110.0	15.7	18.6	22.4	14.2	15.5	17.0	20.5	22.6	25.1
110.5	15.9	18.7	22.2	14.5	15.8	17.1	20.4	22.4	24.7	110.5	15.8	18.8	22.6	14.4	15.7	17.1	20.7	22.9	25.4
111.0	16.1	18.9	22.4	14.6	15.9	17.3	20.7	22.7	25.0	111.0	16.0	19.0	22.8	14.5	15.8	17.3	20.9	23.1	25.7
111.5	16.2	19.1	22.6	14.8	16.0	17.5	20.9	22.9	25.2	111.5	16.2	19.2	23.1	14.7	16.0	17.5	21.2	23.4	26.0
112.0	16.3	19.2	22.9	14.9	16.2	17.6	21.1	23.1	25.5	112.0	16.3	19.4	23.4	14.8	16.2	17.7	21.4	23.6	26.2
112.5	16.5	19.4	23.1	15.0	16.3	17.8	21.3	23.4	25.8	112.5	16.5	19.6	23.6	15.0	16.3	17.9	21.6	23.9	26.5
113.0	16.6	19.6	23.4	15.2	16.5	18.0	21.5	23.6	26.0	113.0	16.7	19.8	23.9	15.1	16.5	18.0	21.8	24.2	26.8
113.5	16.8	19.8	23.6	15.3	16.6	18.1	21.7	23.9	26.3	113.5	16.8	20.0	24.1	15.3	16.7	18.2	22.1	24.4	27.1
114.0	17.0	20.0	23.8	15.4	16.8	18.3	21.9	24.1	26.6	114.0	17.0	20.2	24.4	15.4	16.8	18.4	22.3	24.7	27.4
114.5	17.1	20.2	24.1	15.6	16.9	18.5	22.1	24.4	26.9	114.5	17.2	20.5	24.7	15.6	17.0	18.6	22.6	25.0	27.8
115.0	17.3	20.4	24.3	15.7	17.1	18.6	22.4	24.6	27.2	115.0	17.3	20.7	24.9	15.7	17.2	18.8	22.8	25.2	28.1
115.5	17.4	20.6	24.6	15.8	17.2	18.8	22.6	24.9	27.5	115.5	17.5	20.9	25.2	15.9	17.3	19.0	23.0	25.5	28.4
116.0	17.6	20.8	24.8	16.0	17.4	19.0	22.8	25.1	27.8	116.0	17.7	21.1	25.5	16.0	17.5	19.2	23.3	25.8	28.7
116.5	17.7	21.0	25.1	16.1	17.5	19.2	23.0	25.4	28.0	116.5	17.9	21.3	25.7	16.2	17.7	19.4	23.5	26.1	29.0
117.0	17.9	21.2	25.3	16.2	17.7	19.3	23.3	25.6	28.3	117.0	18.0	21.5	26.0	16.3	17.8	19.6	23.8	26.3	29.3
117.5	18.0	21.4	25.6	16.4	17.9	19.5	23.5	25.9	28.6	117.5	18.2	21.7	26.3	16.5	18.0	19.8	24.0	26.6	29.6
118.0	18.2	21.6	25.8	16.5	18.0	19.7	23.7	26.1	28.9	118.0	18.4	22.0	26.5	16.6	18.2	19.9	24.2	26.9	29.9
118.5	18.4	21.8	26.1	16.7	18.2	19.9	23.9	26.4	29.2	118.5	18.6	22.2	26.8	16.8	18.4	20.1	24.5	27.2	30.3
119.0	18.5	22.0	26.3	16.8	18.3	20.0	24.1	26.6	29.5	119.0	18.7	22.4	27.1	16.9	18.5	20.3	24.7	27.4	30.6
119.5	18.7	22.2	26.6	16.9	18.5	20.2	24.4	26.9	29.8	119.5	18.9	22.6	27.4	17.1	18.7	20.5	25.0	27.7	30.9
120.0	18.8	22.4	26.8	17.1	18.6	20.4	24.6	27.2	30.1	120.0	19.1	22.8	27.6	17.3	18.9	20.7	25.2	28.0	31.2

**Table 9** Body mass index (kg/m<sup>2</sup>) for boys 0–5 years (WHO standards)

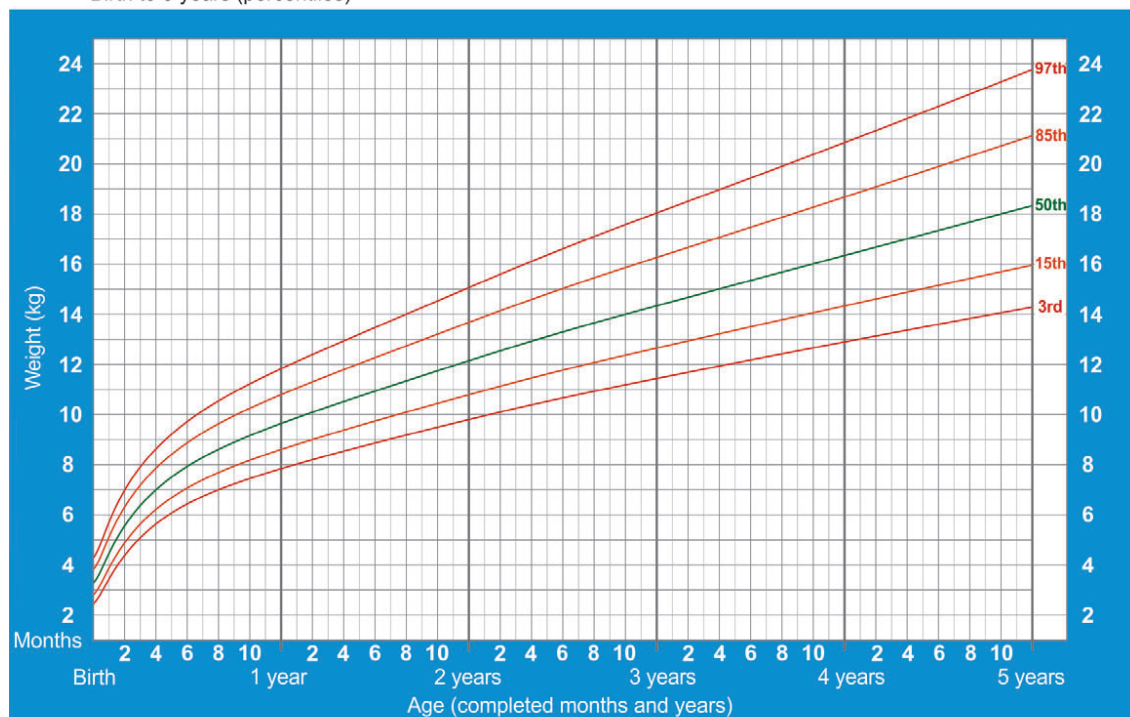
Years	Months	Percentiles					Standard deviation (SD) Z score					
		5th	15th	50th	85th	95th	–3Z	–2Z	–1Z	+1Z	+2Z	+3Z
1	0	11.5	12.2	13.4	14.8	15.8	10.2	11.1	12.2	14.8	16.3	18.1
	1	12.8	13.6	14.9	16.4	17.3	11.3	12.4	13.6	16.3	17.8	19.4
	2	14.1	14.9	16.3	17.8	18.8	12.5	13.7	15.0	17.8	19.4	21.1
	3	14.7	15.5	16.9	18.5	19.4	13.1	14.3	15.5	18.4	20.0	21.8
	4	15.0	15.7	17.2	18.7	19.7	13.4	14.5	15.8	18.7	20.3	22.1
	5	15.1	15.9	17.3	18.9	19.8	13.5	14.7	15.9	18.8	20.5	22.3
	6	15.2	15.9	17.3	18.9	19.9	13.6	14.7	16.0	18.8	20.5	22.3
	7	15.2	15.9	17.3	18.9	19.9	13.7	14.8	16.0	18.8	20.5	22.3
	8	15.1	15.9	17.3	18.8	19.8	13.6	14.7	15.9	18.7	20.4	22.2
	9	15.1	15.8	17.2	18.7	19.7	13.6	14.7	15.8	18.6	20.3	22.1
	10	15.0	15.7	17.0	18.6	19.5	13.5	14.6	15.7	18.5	20.1	22.0
2	11	14.9	15.6	16.9	18.4	19.4	13.4	14.5	15.6	18.4	20.0	21.8
	0	14.8	15.5	16.8	18.3	19.2	13.4	14.4	15.5	18.2	19.8	21.6
	1	14.7	15.4	16.7	18.1	19.1	13.3	14.3	15.4	18.1	19.7	21.5
	2	14.6	15.3	16.6	18.0	18.9	13.2	14.2	15.3	18.0	19.5	21.3
	3	14.5	15.2	16.4	17.9	18.8	13.1	14.1	15.2	17.8	19.4	21.2
	4	14.4	15.1	16.3	17.8	18.7	13.1	14.0	15.1	17.7	19.3	21.0
	5	14.3	15.0	16.2	17.6	18.6	13.0	13.9	15.0	17.6	19.1	20.9
	6	14.2	14.9	16.1	17.5	18.5	12.9	13.9	14.9	17.5	19.0	20.8
	7	14.2	14.8	16.1	17.4	18.4	12.9	13.8	14.9	17.4	18.9	20.7
	8	14.1	14.8	16.0	17.4	18.3	12.8	13.7	14.8	17.3	18.8	20.6
	9	14.1	14.7	15.9	17.3	18.2	12.8	13.7	14.7	17.2	18.7	20.5
3	10	14.0	14.6	15.8	17.2	18.1	12.7	13.6	14.7	17.2	18.7	20.4
	11	14.0	14.6	15.8	17.1	18.0	12.7	13.6	14.6	17.1	18.6	20.3
	0	13.9	14.5	15.7	17.1	18.0	12.7	13.6	14.6	17.0	18.5	20.3
BMI by height												
4	0	14.2	14.8	16.0	17.4	18.3	12.9	13.8	14.8	17.3	18.9	20.6
	1	14.1	14.8	16.0	17.4	18.3	12.8	13.8	14.8	17.3	18.8	20.5
	2	14.1	14.7	15.9	17.3	18.2	12.8	13.7	14.8	17.3	18.8	20.5
	3	14.0	14.7	15.9	17.3	18.2	12.7	13.7	14.7	17.2	18.7	20.4
	4	14.0	14.7	15.9	17.2	18.1	12.7	13.6	14.7	17.2	18.7	20.4
	5	14.0	14.6	15.8	17.2	18.1	12.7	13.6	14.7	17.1	18.6	20.3
	6	13.9	14.6	15.8	17.2	18.0	12.6	13.6	14.6	17.1	18.6	20.2
	7	13.9	14.5	15.8	17.1	18.0	12.6	13.5	14.6	17.1	18.5	20.2
	8	13.9	14.5	15.7	17.1	18.0	12.5	13.5	14.6	17.0	18.5	20.1
	9	13.8	14.5	15.7	17.0	17.9	12.5	13.5	14.5	17.0	18.5	20.1
	10	13.8	14.4	15.7	17.0	17.9	12.5	13.4	14.5	17.0	18.4	20.0
5	11	13.8	14.4	15.6	17.0	17.9	12.4	13.4	14.5	16.9	18.4	20.0
	0	13.7	14.4	15.6	17.0	17.8	12.4	13.4	14.4	16.9	18.4	20.0
	1	13.7	14.4	15.6	16.9	17.8	12.4	13.3	14.4	16.9	18.3	19.9
	2	13.7	14.3	15.5	16.9	17.8	12.3	13.3	14.4	16.8	18.3	19.9
	3	13.6	14.3	15.5	16.9	17.7	12.3	13.3	14.3	16.8	18.3	19.9
	4	13.6	14.3	15.5	16.8	17.7	12.3	13.2	14.3	16.8	18.2	19.9
	5	13.6	14.2	15.5	16.8	17.7	12.2	13.2	14.3	16.8	18.2	19.9
	6	13.6	14.2	15.4	16.8	17.7	12.2	13.2	14.3	16.8	18.2	19.8
	7	13.5	14.2	15.4	16.8	17.7	12.2	13.2	14.2	16.7	18.2	19.8
	8	13.5	14.2	15.4	16.8	17.7	12.2	13.1	14.2	16.7	18.2	19.8
	9	13.5	14.2	15.4	16.8	17.6	12.2	13.1	14.2	16.7	18.2	19.8
6	10	13.5	14.1	15.4	16.7	17.6	12.1	13.1	14.2	16.7	18.2	19.8
	11	13.5	14.1	15.3	16.7	17.6	12.1	13.1	14.2	16.7	18.2	19.9
	0	13.4	14.1	15.3	16.7	17.6	12.1	13.1	14.1	16.7	18.2	19.9
	1	13.4	14.1	15.3	16.7	17.6	12.1	13.0	14.1	16.7	18.2	19.9
	2	13.4	14.1	15.3	16.7	17.6	12.1	13.0	14.1	16.7	18.2	19.9
	3	13.4	14.0	15.3	16.7	17.6	12.1	13.0	14.1	16.6	18.2	19.9
	4	13.4	14.0	15.3	16.7	17.6	12.0	13.0	14.1	16.6	18.2	19.9
	5	13.3	14.0	15.3	16.7	17.6	12.0	13.0	14.1	16.6	18.2	20.0
	6	13.3	14.0	15.3	16.7	17.6	12.0	13.0	14.0	16.6	18.2	20.0
	7	13.3	14.0	15.2	16.7	17.6	12.0	13.0	14.0	16.6	18.2	20.0
	8	13.3	14.0	15.2	16.7	17.6	12.0	12.9	14.0	16.6	18.2	20.1
7	9	13.3	14.0	15.2	16.7	17.6	12.0	12.9	14.0	16.6	18.2	20.1
	10	13.3	13.9	15.2	16.7	17.6	12.0	12.9	14.0	16.6	18.3	20.2
	11	13.3	13.9	15.2	16.7	17.7	12.0	12.9	14.0	16.6	18.3	20.2
8	0	13.3	13.9	15.2	16.7	17.7	12.0	12.9	14.0	16.6	18.3	20.3

**Table 10** Body mass index (kg/m<sup>2</sup>) for girls 0–5 years (WHO standards)

Years	Months	Percentiles					Standard deviation (SD) Z score					
		5th	15th	50th	85th	95th	−3Z	−2Z	−1Z	+1Z	+2Z	+3Z
	0	11.5	12.1	13.3	14.7	15.8	10.2	11.1	12.2	14.8	16.3	18.1
	1	12.4	13.2	14.6	16.1	17.3	11.3	12.4	13.6	16.3	17.8	19.4
	2	13.5	14.3	15.8	17.4	18.8	12.5	13.7	15.0	17.8	19.4	21.1
	3	14.0	14.9	16.4	18.0	19.4	13.1	14.3	15.5	18.4	20.0	21.8
	4	14.3	15.2	16.7	18.3	19.7	13.4	14.5	15.8	18.7	20.3	22.1
	5	14.5	15.3	16.8	18.5	19.8	13.5	14.7	15.9	18.8	20.5	22.3
	6	14.6	15.4	16.9	18.6	19.9	13.6	14.7	16.0	18.8	20.5	22.3
	7	14.6	15.4	16.9	18.6	19.9	13.7	14.8	16.0	18.8	20.5	22.3
	8	14.6	15.4	16.8	18.5	19.8	13.6	14.7	15.9	18.7	20.4	22.2
	9	14.5	15.3	16.7	18.4	19.7	13.6	14.7	15.8	18.6	20.3	22.1
	10	14.4	15.2	16.6	18.2	19.5	13.5	14.6	15.7	18.5	20.1	22.0
	11	14.3	15.1	16.5	18.1	19.4	13.4	14.5	15.6	18.4	20.0	21.8
1	0	14.2	15.0	16.4	17.9	19.2	13.4	14.4	15.5	18.2	19.8	21.6
1	1	14.1	14.8	16.2	17.8	19.1	13.3	14.3	15.4	18.1	19.7	21.5
1	2	14.0	14.7	16.1	17.7	18.9	13.2	14.2	15.3	18.0	19.5	21.3
1	3	13.9	14.6	16.0	17.5	18.8	13.1	14.1	15.2	17.8	19.4	21.2
1	4	13.8	14.6	15.9	17.4	18.7	13.1	14.0	15.1	17.7	19.3	21.0
1	5	13.8	14.5	15.8	17.3	18.6	13.0	13.9	15.0	17.6	19.1	20.9
1	6	13.7	14.4	15.7	17.2	18.5	12.9	13.9	14.9	17.5	19.0	20.8
1	7	13.6	14.3	15.7	17.2	18.4	12.9	13.8	14.9	17.4	18.9	20.7
1	8	13.6	14.3	15.6	17.1	18.3	12.8	13.7	14.8	17.3	18.8	20.6
1	9	13.6	14.2	15.5	17.0	18.2	12.8	13.7	14.7	17.2	18.7	20.5
1	10	13.5	14.2	15.5	17.0	18.1	12.7	13.6	14.7	17.2	18.7	20.4
1	11	13.5	14.2	15.4	16.9	18.0	12.7	13.6	14.6	17.1	18.6	20.3
2	0	13.5	14.1	15.4	16.9	18.0	12.7	13.6	14.6	17.0	18.5	20.3
<b>BMI by height</b>												
2	0	13.7	14.4	15.7	17.2	18.1	12.4	13.3	14.4	17.1	18.7	20.6
2	1	13.7	14.4	15.7	17.1	18.1	12.4	13.3	14.4	17.1	18.7	20.6
2	2	13.7	14.4	15.6	17.1	18.1	12.3	13.3	14.4	17.0	18.7	20.6
2	3	13.7	14.3	15.6	17.1	18.0	12.3	13.3	14.4	17.0	18.6	20.5
2	4	13.6	14.3	15.6	17.0	18.0	12.3	13.3	14.3	17.0	18.6	20.5
2	5	13.6	14.3	15.6	17.0	18.0	12.3	13.2	14.3	17.0	18.6	20.4
2	6	13.6	14.3	15.5	17.0	17.9	12.3	13.2	14.3	16.9	18.5	20.4
2	7	13.6	14.2	15.5	17.0	17.9	12.2	13.2	14.3	16.9	18.5	20.4
2	8	13.5	14.2	15.5	16.9	17.9	12.2	13.2	14.3	16.9	18.5	20.4
2	9	13.5	14.2	15.5	16.9	17.9	12.2	13.1	14.2	16.9	18.5	20.3
2	10	13.5	14.2	15.4	16.9	17.9	12.2	13.1	14.2	16.8	18.5	20.3
2	11	13.5	14.1	15.4	16.9	17.8	12.1	13.1	14.2	16.8	18.4	20.3
3	0	13.5	14.1	15.4	16.9	17.8	12.1	13.1	14.2	16.8	18.4	20.3
3	1	13.4	14.1	15.4	16.8	17.8	12.1	13.1	14.1	16.8	18.4	20.3
3	2	13.4	14.1	15.4	16.8	17.8	12.1	13.0	14.1	16.8	18.4	20.3
3	3	13.4	14.1	15.3	16.8	17.8	12.0	13.0	14.1	16.8	18.4	20.3
3	4	13.4	14.0	15.3	16.8	17.8	12.0	13.0	14.1	16.8	18.4	20.3
3	5	13.3	14.0	15.3	16.8	17.8	12.0	13.0	14.1	16.8	18.4	20.4
3	6	13.3	14.0	15.3	16.8	17.8	12.0	12.9	14.0	16.8	18.4	20.4
3	7	13.3	14.0	15.3	16.8	17.8	11.9	12.9	14.0	16.8	18.4	20.4
3	8	13.3	14.0	15.3	16.8	17.8	11.9	12.9	14.0	16.8	18.5	20.4
3	9	13.3	14.0	15.3	16.8	17.8	11.9	12.9	14.0	16.8	18.5	20.5
3	10	13.2	13.9	15.3	16.8	17.8	11.9	12.9	14.0	16.8	18.5	20.5
3	11	13.2	13.9	15.3	16.8	17.9	11.8	12.8	14.0	16.8	18.5	20.5
4	0	13.2	13.9	15.3	16.8	17.9	11.8	12.8	14.0	16.8	18.5	20.6
4	1	13.2	13.9	15.3	16.8	17.9	11.8	12.8	13.9	16.8	18.5	20.6
4	2	13.2	13.9	15.3	16.8	17.9	11.8	12.8	13.9	16.8	18.6	20.7
4	3	13.2	13.9	15.3	16.8	17.9	11.8	12.8	13.9	16.8	18.6	20.7
4	4	13.1	13.9	15.2	16.9	17.9	11.7	12.8	13.9	16.8	18.6	20.7
4	5	13.1	13.9	15.3	16.9	17.9	11.7	12.7	13.9	16.8	18.6	20.8
4	6	13.1	13.9	15.3	16.9	18.0	11.7	12.7	13.9	16.8	18.7	20.8
4	7	13.1	13.9	15.3	16.9	18.0	11.7	12.7	13.9	16.8	18.7	20.9
4	8	13.1	13.8	15.3	16.9	18.0	11.7	12.7	13.9	16.8	18.7	20.9
4	9	13.1	13.8	15.3	16.9	18.0	11.7	12.7	13.9	16.9	18.7	21.0
4	10	13.1	13.8	15.3	16.9	18.0	11.7	12.7	13.9	16.9	18.8	21.0
4	11	13.1	13.8	15.3	16.9	18.1	11.6	12.7	13.9	16.9	18.8	21.0
5	0	13.1	13.8	15.3	17.0	18.1	11.6	12.7	13.9	16.9	18.8	21.1

## Weight-for-age BOYS

Birth to 5 years (percentiles)

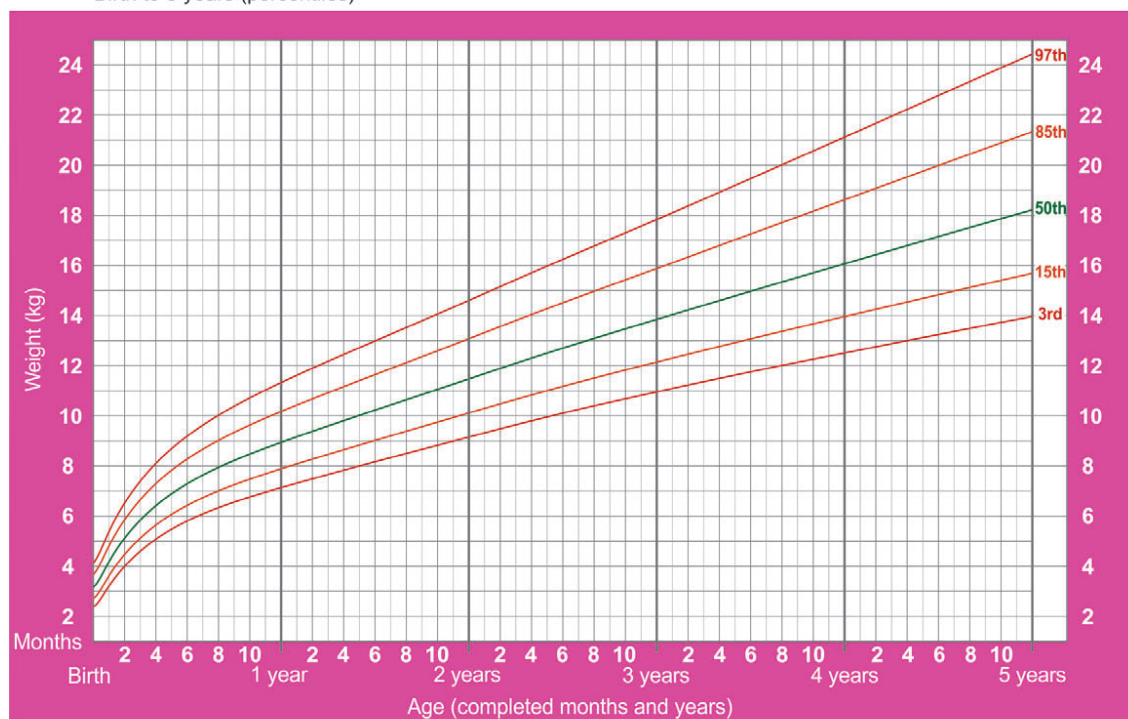


WHO Child Growth Standards

**Figure 7** Weight for age chart [World Health Organization (WHO)] for boys 0–5 years

## Weight-for-age GIRLS

Birth to 5 years (percentiles)

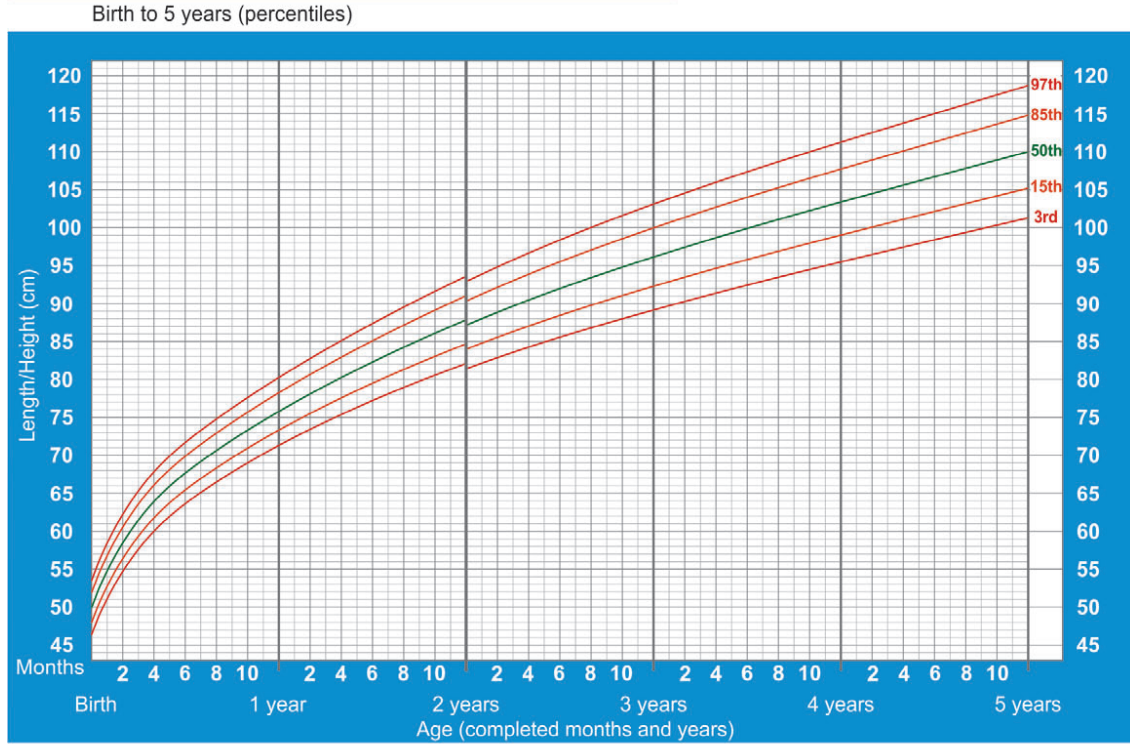


WHO Child Growth Standards

**Figure 8** Weight for age chart [World Health Organization (WHO)] for girls 0–5 years

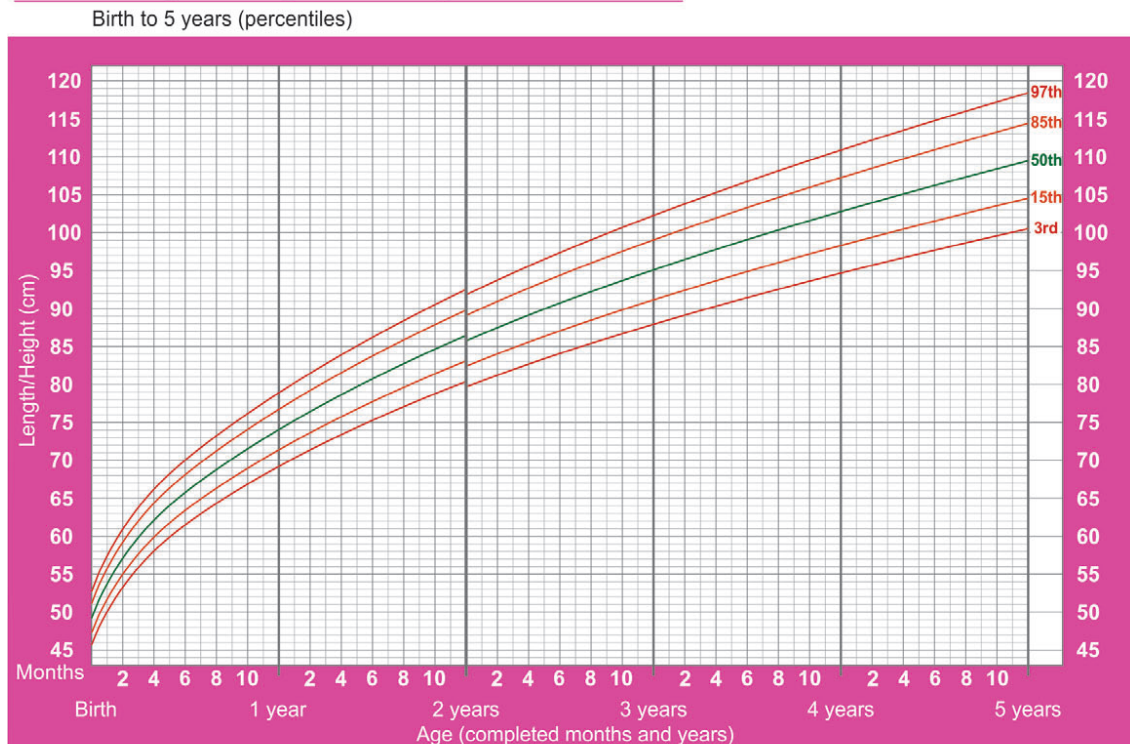


## Length/height-for-age BOYS



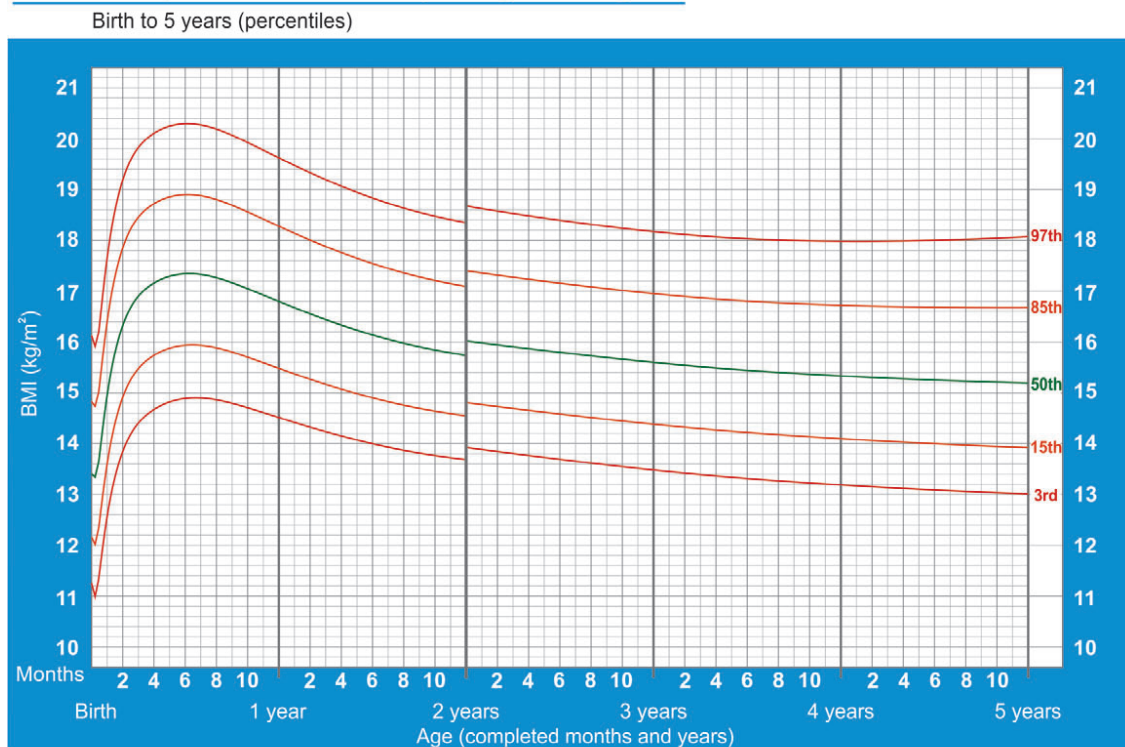
**Figure 9** Length/height for age chart [World Health Organization (WHO)] for boys 0–5 years

## Length/height-for-age GIRLS



**Figure 10** Length/height for age chart [World Health Organization (WHO)] for girls 0–5 years

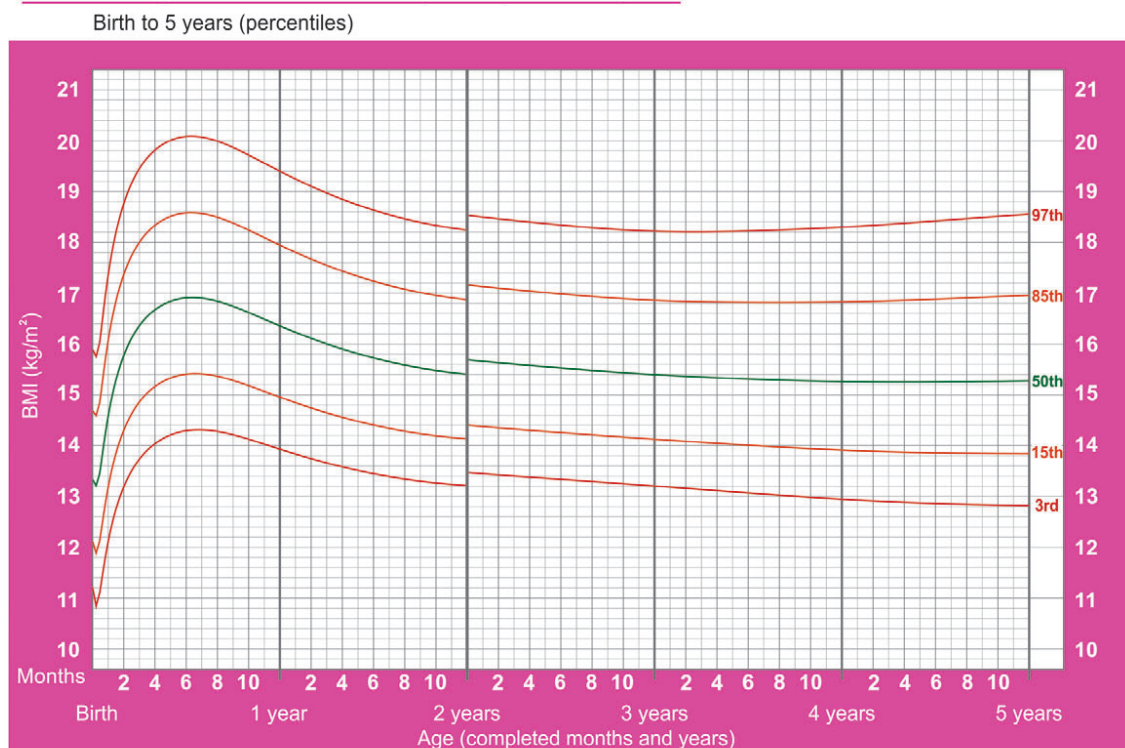
## Body Mass Index (BMI)-for-age BOYS



WHO Child Growth Standards

**Figure 11** Body mass index (BMI) for age chart [World Health Organization (WHO)] for boys 0–5 years

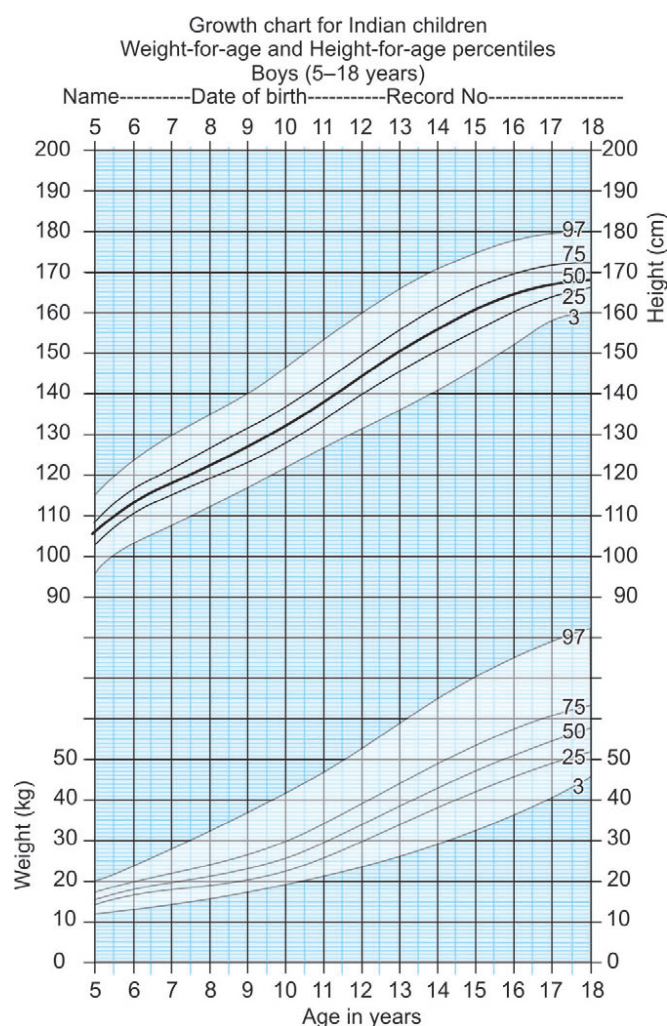
## Body Mass Index (BMI)-for-age GIRLS



WHO Child Growth Standards

**Figure 12** Body mass index (BMI) for age chart [World Health Organization (WHO)] for girls 0–5 years





**Figure 13** Growth chart for Indian boys aged 5–18 years

Source: Based on Agarwal DK, Agarwal KN, Upadhyay SK, et al. Physical and sexual growth pattern of affluent Indian children from 5 to 18 years of age. *Indian Pediatr.* 1992;29:1203-82.

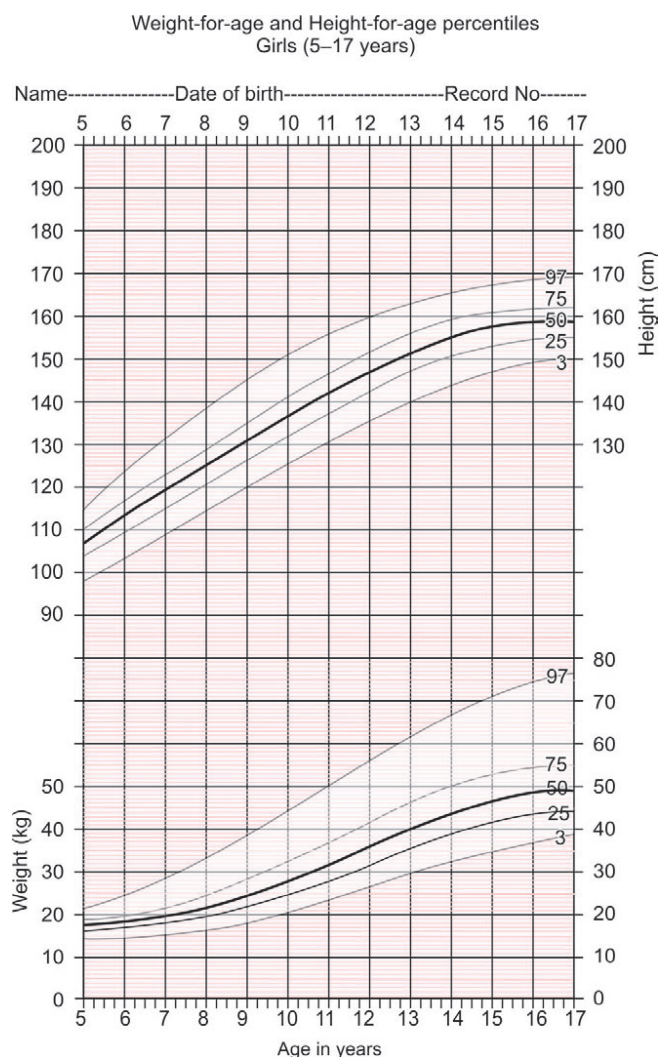
and various computerized programs are available for this purpose. WHO gives a freely downloadable anthropometric calculator at its website for calculation of Z-scores based on WHO reference ([www.who.int/childgrowth/software/en/](http://www.who.int/childgrowth/software/en/)).

Another way to compare anthropometric measurements of a child with reference data would be as a *percentage of the median value*. For height, a value less than 90% of the median value is considered as short stature and for weight values less than 80% are considered as underweight. These percentage cut-offs roughly correspond to  $-2$  SDS. Both SDS and percentage of median can be used for generating summary statistics like mean and standard deviations in population based studies, and thus have an advantage over using percentile based comparison.

## Interpretation of Growth Parameters

### Weight for Age

Weight for age is a measure of weight of a child compared to the weight of children of the same age and gender from a reference population. A child whose weight for age is below  $-2$  Z-score is underweight and below  $-3$  Z-score is severely underweight.



**Figure 14** Growth chart for Indian girls aged 5–17 years

Source: Based on Agarwal DK, Agarwal KN, Upadhyay SK, et al. Physical and sexual growth pattern of affluent Indian children from 5 to 18 years of age. *Indian Pediatr.* 1992;29:1203-82.

### Weight for Length/Height

Weight for length/height is a measure of weight compared to the weight of children of the same gender and length/height from a reference population. It is an indicator of acute malnutrition independent of age. A child whose weight for length/height is below  $-2$  Z-score is wasted and below  $-3$  Z-score is severely wasted. WHO and CDC weight for length/height standards are available for children.

### Height/Length for Age

Height/length for age is a measure of length/height compared to the length/height of children of the same age and gender from a reference population. It is an indicator of chronic malnutrition/short stature. A child whose length/height for age is below  $-2$  Z-score is stunted and below  $-3$  Z-score is severely stunted. A height of less than  $-2$  SDS is also the conventionally accepted definition of short stature.

### Body Mass Index

Body mass index (BMI) is used to assess the nutritional status of children more than 5 years of age instead of weight for length.

**Table 11** Height percentiles of Indian boys 5–18 years age

Age (Years)	N	Mean	SE	Percentiles						
				3rd	5th	10th	25th	50th	75th	97th
5.0	450	107.1	0.22	97.9	99.1	100.4	103.8	106.7	109.9	116.4
5.5	277	110.4	0.30	100.7	101.9	103.6	107.2	109.9	113.3	119.5
6.0	175	113.7	0.41	103.7	105.5	106.9	112.0	114.2	118.0	125.9
6.5	128	117.5	0.49	106.1	107.5	109.6	113.5	117.3	120.7	128.4
7.0	235	118.6	0.36	108.5	109.8	112.0	115.9	119.7	123.0	130.8
7.5	213	121.6	0.40	110.9	111.3	114.2	117.8	121.6	125.2	133.2
8.0	295	124.1	0.32	113.3	114.0	116.3	119.7	123.6	127.4	135.5
8.5	275	126.4	0.37	115.2	116.2	118.6	121.9	125.7	129.8	138.5
9.0	338	130.4	0.34	118.0	118.5	120.9	124.2	128.2	132.5	141.4
9.5	348	131.5	0.35	120.3	120.9	123.4	126.7	130.8	135.3	144.5
10.0	425	134.7	0.31	122.7	123.4	125.9	129.4	133.6	138.3	147.7
10.5	621	137.6	0.26	125.1	125.9	128.6	132.2	136.6	141.5	151.0
11.0	621	139.6	0.28	127.5	128.5	131.2	135.6	139.6	144.7	154.3
11.5	761	142.3	0.26	129.9	131.1	133.9	138.0	142.7	147.9	157.5
12.0	755	144.7	0.28	132.4	133.8	136.6	141.0	145.8	151.1	160.8
12.5	889	147.9	0.27	134.9	136.5	139.3	143.9	148.9	154.2	163.9
13.0	771	150.3	0.29	137.4	139.2	142.0	146.8	152.0	157.3	166.9
13.5	829	154.9	0.28	140.0	141.8	144.7	149.7	154.9	160.2	169.7
14.0	754	158.0	0.29	142.6	144.5	147.4	152.4	157.6	162.9	172.3
14.5	743	161.4	0.27	145.2	147.2	149.9	155.0	160.2	165.4	174.7
15.0	628	164.3	0.27	148.0	149.8	152.4	157.4	162.5	167.7	176.8
15.5	528	165.5	0.28	150.8	152.4	154.9	159.6	164.6	169.6	178.5
16.0	461	167.1	0.29	153.6	154.9	157.9	161.6	166.3	171.2	179.8
16.5	393	167.9	0.32	156.6	157.4	159.4	163.3	167.7	172.4	180.7
17.0	288	168.6	0.36	159.6	159.8	161.5	165.0	168.7	173.1	181.2
17.5	177	169.4	0.42	162.7	163.1	163.4	167.5	169.3	173.4	181.1
18.0	87	168.9	0.60	161.0	163.5	164.0	168.8	169.8	173.4	181.6

Abbreviations: N, number of subjects; SE, standard error.

Source: Agarwal DK, Agarwal KN, Upadhyay SK, et al. Physical and sexual growth pattern of affluent Indian children from 5 to 18 years of age. *Indian Pediatr.* 1992;29:1203-82; Reproduced with permission.

BMI is kilograms (kg) of body weight per height in meters squared ( $\text{m}^2$ ), i.e.  $[\text{BMI} = \text{weight in kg}/(\text{height in m})^2]$ . A BMI of  $18.5\text{--}24.99 \text{ kg/m}^2$ , is considered normal for adults. Adults are defined as underweight if their BMI is  $< 18.5 \text{ kg/m}^2$ , overweight if it is between  $25 \text{ kg/m}^2$  and  $29.9 \text{ kg/m}^2$  and obese if more than or equal to  $30 \text{ kg/m}^2$ . For children, there is no absolute BMI cut-off as BMI values change with age. Age and gender-specific BMI percentile curves are available in all reference data sets in common clinical use. Children with BMI less than 5th percentile are classified as underweight. The definitions of childhood overweight and obesity are BMI above or equal to the 85th and 95th percentile, respectively. In the recent Indian reference charts (Marwaha RK et al. 2011, Khadilkar VV et al. 2009), the 85th and 95th percentile for BMI at age 18 years in boys exceeded the adult BMI cut-off values for overweight and obesity of 25 and 30 respectively. As proposed by International Obesity Task Force (IOTF), Khadilkar VV et al. have published cross-sectional age and gender-specific BMI cut-offs for Indian

children linked to proposed Asian adult cut-offs of 23 and  $28 \text{ kg/m}^2$  for the assessment of risk of overweight and obesity (2012). These lower BMI cut-offs of 23 and  $28 \text{ kg/m}^2$  have been suggested for overweight and obesity, respectively for Asian adults, as they are more prone to adiposity and central obesity at a lower BMI than their western counterparts.

### Waist Circumference

Specific ethnic cut-off levels of waist circumference are available for screening for obesity related complications. These correspond to values greater than 80–88 cm, in Indian women and men, respectively. Waist circumference reference charts for Indian children (Khadilkar VV et al., 2014—multicentric data from five cities in different zones of India; and Kuriyan R et al., 2011—from Bengaluru) are available. The authors have recommended a cut-off value more than or equal to 70th percentile and more than or equal to 75th centile, respectively, for diagnosing obesity and screening for metabolic syndrome (Tables 17 and 18).



**Table 12** Height percentiles of Indian girls 5–17 years age

Age (Years)	N	Mean	SE	Percentiles						
				3rd	5th	10th	25th	50th	75th	97th
5.0	381	106.0	0.23	97.2	98.6	100.3	103.1	106.0	108.8	113.8
5.5	245	109.4	0.28	99.6	100.0	103.5	105.0	108.1	112.0	116.4
6.0	241	113.0	0.35	102.1	104.5	106.1	108.8	112.5	115.9	123.3
6.5	251	115.4	0.32	104.5	107.0	108.4	111.1	114.9	118.4	126.0
7.0	294	118.2	0.35	107.1	109.4	110.7	113.7	117.4	121.3	129.3
7.5	319	120.2	0.31	109.7	111.6	113.1	116.4	120.3	124.4	132.8
8.0	328	122.7	0.32	112.3	113.9	115.5	119.3	123.2	127.5	136.4
8.5	349	126.2	0.33	115.0	116.2	118.1	122.2	126.2	130.7	139.8
9.0	399	128.6	0.32	117.8	118.8	120.9	125.1	129.2	133.8	143.1
9.5	429	131.9	0.32	120.6	121.4	123.6	128.0	132.3	136.9	146.2
10.0	487	134.8	0.31	123.4	124.1	126.5	130.8	135.2	139.8	149.0
10.5	452	137.9	0.34	126.1	126.9	129.3	133.7	138.1	142.7	151.7
11.0	503	141.3	0.32	128.8	129.7	132.1	136.4	140.9	145.4	154.2
11.5	490	144.3	0.31	131.4	132.4	134.8	139.0	143.5	147.9	156.5
12.0	435	146.7	0.32	133.9	135.0	137.4	141.5	146.0	150.3	158.5
12.5	489	149.9	0.28	136.3	137.5	139.8	143.8	148.3	152.5	160.4
13.0	455	151.4	0.28	138.5	139.8	142.1	145.9	150.4	154.4	162.1
13.5	456	153.2	0.28	140.6	141.9	144.1	147.8	152.2	156.2	163.5
14.0	391	153.6	0.29	142.4	143.8	145.9	149.4	153.8	157.6	164.7
14.5	350	154.8	0.30	144.1	145.4	147.4	150.8	155.1	158.8	165.8
15.0	291	155.0	0.33	145.5	146.6	148.6	151.8	156.0	159.7	166.5
15.5	204	155.4	0.39	146.6	147.5	149.3	152.6	156.6	160.4	167.4
16.0	176	155.1	0.38	147.5	148.0	149.7	152.9	156.8	160.4	167.4
16.5	182	156.0	0.38	148.0	148.1	149.7	152.9	156.5	160.5	167.6
17.0	116	157.1	0.55	148.3	148.5	149.8	153.0	157.0	160.5	168.0

Abbreviations: N, number of subjects; SE, standard error.

Source: Agarwal DK, Agarwal KN, Upadhyay SK, et al. Physical and sexual growth pattern of affluent Indian children from 5 to 18 years of age. Indian Pediatr. 1992;29:1203-82; Reproduced with permission.

## GROWTH MONITORING: LONGITUDINAL ASSESSMENT OF GROWTH

One-time assessment of growth parameters gives information on how the child is at that particular time, without any relation to what he/she has been like in past. It thus has limited scope for interpretation. Growth is best evaluated longitudinally by measuring and recording on a growth chart, serial recordings of anthropometric parameters. Growth monitoring consists of regularly measuring anthropometric parameters (weight and length/height) in a child and recording them on a growth chart. An accurately maintained growth record is a very sensitive indicator of growth abnormalities. It helps in diagnosing ill health or nutritional imbalance, as well as monitoring response to remedial interventions. Growth monitoring is a potent tool used in primary health-care for identifying malnourished children and their response to nutritional interventions. In case of well babies, growth monitoring may help to reassure and educate the mother about feeding practices.

The growth curve of most normal children would fall between 3rd and 97th centile lines and would be parallel to these lines. The particular centile line followed by the child is determined by his/her genetic potential. This is determined by the *mid-parental height* (MPH). MPH is the average of the parents height and is calculated by the following formula

$$\text{MPH for boys (in cm)} = \frac{\text{Father's height} + \text{Mother's height} + 13}{2}$$

$$\text{MPH for girls (in cm)} = \frac{\text{Father's height} + \text{Mother's height} - 13}{2}$$

The MPH is plotted on the child's growth chart at 18 years of age. If the child's growth curve is extrapolated to 18 years of age, it should ideally lie  $\pm 2\text{SD}$  of the MPH (this is approximately  $\pm 8\text{ cm}$ ). **Figure 15** shows a child growing normally parallel to the centile lines with the extrapolated height at 18 years within the limits of his MPH. A child whose growth is clearly out of the MPH range, even though it might still be within 3rd and 97th centiles, needs careful evaluation. Also, since children

**Table 13** Weight percentiles of Indian boys 5–18 years age

Age (Years)	N	Mean	SE	Percentiles						
				3rd	5th	10th	25th	50th	75th	97th
5.0	450	17.4	0.10	13.8	14.3	14.9	16.0	17.1	18.4	21.5
5.5	277	18.4	0.12	14.5	15.0	15.8	17.0	18.1	19.5	22.7
6.0	175	19.2	0.20	15.2	15.7	16.2	18.0	19.0	20.7	25.4
6.5	128	20.6	0.25	15.7	16.4	17.4	18.6	20.0	21.9	27.7
7.0	235	21.0	0.21	16.2	16.9	18.2	19.4	21.0	22.9	29.7
7.5	213	22.4	0.24	16.8	17.5	18.7	20.0	22.0	23.9	31.6
8.0	295	23.5	0.22	17.5	18.0	19.1	20.7	22.6	25.0	33.5
8.5	275	24.5	0.27	18.2	18.6	19.7	21.3	23.5	26.3	35.5
9.0	338	26.5	0.26	19.2	19.4	20.3	22.0	24.4	27.7	37.7
9.5	348	26.8	0.26	19.9	20.2	21.2	22.9	25.6	29.4	40.1
10.0	425	28.7	0.26	20.9	21.2	22.3	24.1	27.0	31.3	42.7
10.5	612	30.8	0.25	21.9	22.3	23.5	25.5	28.7	33.4	45.4
11.0	621	31.9	0.27	22.9	23.5	24.9	27.1	30.6	35.6	48.2
11.5	761	33.8	0.27	24.1	24.9	26.3	28.9	32.7	37.9	51.1
12.0	755	35.4	0.25	25.3	26.3	27.9	30.7	34.8	40.3	54.1
12.5	889	37.9	0.28	26.7	27.8	29.6	32.7	37.1	42.7	57.1
13.0	771	39.4	0.32	28.1	29.3	31.3	34.7	39.4	45.1	60.0
13.5	829	43.2	0.33	29.6	31.0	33.1	36.8	41.8	47.6	63.0
14.0	754	44.7	0.34	31.2	32.7	34.9	38.8	44.1	50.0	65.9
14.5	743	48.1	0.35	32.9	34.5	36.7	40.9	46.3	52.4	68.7
15.0	628	51.0	0.37	34.6	36.3	38.6	42.8	48.5	54.6	71.4
15.5	528	52.4	0.43	36.5	38.1	40.3	44.7	50.5	56.8	73.9
16.0	461	55.0	0.49	38.5	40.0	42.1	46.5	52.4	58.8	76.3
16.5	393	54.9	0.47	40.6	41.9	43.8	48.1	54.0	60.6	78.5
17.0	288	56.6	0.55	42.8	43.9	45.9	50.0	55.5	62.3	80.5
17.5	177	56.9	0.66	45.2	45.8	46.9	52.0	57.2	63.7	82.2
18.0	87	59.7	1.20	47.6	47.8	48.3	54.0	58.6	64.9	83.6

Abbreviations: N, number of subjects; SE, standard error.

Source: Agarwal DK, Agarwal KN, Upadhyay SK, et al. Physical and sexual growth pattern of affluent Indian children from 5 to 18 years of age. Indian Pediatr. 1992;29:1203-82; Reproduced with permission.

**Table 14** Weight percentiles of Indian girls 5–17 years age

Age (Years)	N	Mean	SE	Percentiles						
				3rd	5th	10th	25th	50th	75th	97th
5.0	381	17.0	0.11	13.6	13.8	14.6	15.6	16.8	18.2	21.1
5.5	245	17.9	0.13	14.0	14.7	15.2	16.0	17.4	18.8	22.2
6.0	241	18.7	0.19	14.1	15.2	15.7	16.4	17.8	19.2	23.7
6.5	251	19.6	0.20	14.4	15.5	16.1	16.9	18.3	19.9	25.4
7.0	294	20.5	0.20	14.8	15.8	16.4	17.3	19.0	20.9	27.5
7.5	319	21.7	0.24	15.3	16.2	16.9	18.0	19.9	22.2	29.8
8.0	328	23.0	0.24	15.9	16.4	17.2	18.7	20.8	23.6	32.3
8.5	349	24.9	0.28	16.4	16.8	17.8	19.6	22.0	25.3	34.9
9.0	399	25.8	0.26	17.1	17.6	18.7	20.7	23.5	27.2	37.7
9.5	429	27.5	0.29	18.3	18.5	19.7	22.1	25.1	29.3	40.5
10.0	487	29.6	0.31	19.5	19.7	21.0	23.6	26.9	31.4	43.4
10.5	452	31.9	0.34	20.9	21.0	22.4	25.3	28.9	33.7	46.4
11.0	503	34.3	0.36	22.3	22.4	24.0	27.1	30.9	36.0	49.3
11.5	490	36.8	0.37	23.7	24.0	25.6	28.9	32.9	38.4	52.2
12.0	435	38.7	0.41	25.1	25.6	27.3	30.8	35.0	40.7	55.1
12.5	489	41.9	0.40	26.5	27.2	29.0	32.6	37.1	42.9	57.9
13.0	455	42.6	0.40	27.9	28.9	30.7	34.5	39.1	45.1	60.7
13.5	456	45.2	0.44	29.3	30.6	32.4	36.2	41.0	47.1	63.2
14.0	391	45.7	0.45	30.7	32.1	34.0	37.8	42.7	48.9	65.7
14.5	350	46.6	0.45	32.1	33.6	35.5	39.3	44.3	50.5	67.9
15.0	291	48.0	0.54	33.4	35.0	36.9	40.6	45.7	51.8	70.0
15.5	204	48.9	0.64	34.6	36.2	38.2	41.7	46.8	52.9	71.8
16.0	176	49.2	0.69	35.7	37.3	39.3	42.5	47.7	53.6	73.3
16.5	182	49.6	0.62	36.7	38.1	40.1	43.0	48.2	54.0	74.6
17.0	116	49.0	0.72	37.6	38.7	40.7	43.3	48.4	53.9	75.6

Abbreviations: N, number of subjects; SE, standard error.

Source: Agarwal DK, Agarwal KN, Upadhyay SK, et al. Physical and sexual growth pattern of affluent Indian children from 5 to 18 years of age. Indian Pediatr. 1992;29:1203-82; Reproduced with permission.

**Table 15** Body mass index (BMI) percentiles of Indian boys 5–18 years age

Age (Years)	N	Mean	SD	Percentiles							
				5	10	25	50	75	85	95	
5	97	14.4	1.31	12.4	12.8	13.5	14.4	15.0	15.6	17.0	
6	358	14.8	1.34	13.0	13.4	13.9	14.7	15.4	15.9	17.8	
7	501	15.0	1.57	13.0	13.5	14.0	14.8	15.7	16.4	18.8	
8	585	15.2	1.83	12.9	13.3	14.0	14.8	15.9	17.0	19.7	
9	701	15.6	2.09	12.9	13.4	14.2	15.1	16.4	17.3	21.0	
10	1135	16.1	2.42	13.2	13.6	14.5	15.4	17.0	18.5	22.1	
11	1476	16.6	2.71	13.3	13.8	14.7	15.8	17.6	19.1	23.4	
12	1652	17.1	2.72	13.6	14.2	15.2	16.4	18.3	19.8	23.8	
13	1591	17.7	3.03	14.0	14.5	15.5	17.1	19.0	20.4	25.3	
14	1433	18.2	2.90	14.5	15.1	16.3	17.7	19.6	21.1	25.3	
15	1093	19.2	3.12	15.4	15.9	16.9	18.4	20.5	22.0	27.3	
16	771	19.7	3.09	15.8	16.5	17.4	19.1	21.1	22.7	27.6	
17	361	20.1	2.83	16.3	16.9	17.8	19.7	21.5	24.4	26.8	
18	87	20.4	3.36	15.7	16.8	17.8	20.0	22.5	23.6	28.0	

Abbreviations: N, number of subjects; SD, standard deviation.

Source: Agarwal KN, Saxena A, Bansal AK, Agarwal DK. Physical growth assessment in adolescence. Indian Pediatr. 2001;38:1217-35; Reproduced with permission.

**Table 16** Body mass index (BMI) percentiles of Indian girls 5–18 years age

Age (Years)	N	Mean	SD	Percentiles							
				5	10	25	50	75	85	95	
5	254	14.4	1.5	12.3	12.7	13.5	14.3	15.2	15.7	18.3	
6	449	14.5	1.7	12.4	12.9	13.5	14.3	15.3	16.0	18.8	
7	596	15.0	1.9	12.5	12.9	13.5	14.6	15.7	16.6	19.7	
8	640	15.7	2.32	12.8	13.2	13.9	14.9	16.5	18.0	21.4	
9	784	15.7	2.5	12.5	13.1	14.0	15.1	16.8	18.0	21.7	
10	933	16.7	6.6	13.0	13.6	14.6	16.1	18.2	19.9	23.2	
11	906	17.5	3.1	13.5	14.1	15.2	16.9	19.0	20.6	24.5	
12	893	18.4	3.2	13.9	14.6	15.9	17.8	20.1	21.9	25.7	
13	782	19.2	3.6	14.6	15.3	16.7	18.6	21.0	22.6	27.1	
14	627	19.7	3.2	15.4	16.0	17.3	19.0	21.4	23.0	27.4	
15	383	20.0	3.3	15.9	16.5	17.7	19.3	22.0	23.6	27.7	
16	270	20.5	3.2	15.9	16.6	18.1	20.0	22.4	23.7	27.4	
17	119	20.3	3.1	16.6	16.9	18.3	20.1	22.0	23.0	25.9	
18	27	20.9	3.2	16.9	17.9	18.3	20.0	23.0	23.2	-	

Abbreviations: N, number of subjects; SD, standard deviation.

Source: Agarwal KN, Saxena A, Bansal AK, Agarwal DK. Physical growth assessment in adolescence. Indian Pediatr. 2001;38:1217-35; Reproduced with permission.

**Table 17** Waist circumference percentile values in Indian boys and girls

Age (Years)	Waist circumference percentile								
	5th	10th	15th	25th	50th	75th	85th	90th	95th
<i>Boys</i>									
2+	41.9	42.9	43.5	44.6	46.8	49.3	50.8	51.9	53.7
3+	43.3	44.4	45.1	46.3	48.7	51.5	53.1	54.3	56.3
4+	45.1	46.2	47.1	48.4	51.1	54.2	56.0	57.4	59.6
5+	46.9	48.2	49.1	50.5	53.5	57.0	59.1	60.6	63.1
6+	48.8	50.2	51.2	52.8	56.1	59.9	62.2	64.0	66.7
7+	50.7	52.2	53.3	55.1	58.7	62.9	65.5	67.4	70.5
8+	52.6	54.3	55.5	57.4	61.3	66.0	68.8	70.9	74.3
9+	54.7	56.5	57.8	59.9	64.2	69.2	72.3	74.6	78.2
10+	57.0	59.0	60.4	62.6	67.3	72.7	76.0	78.4	82.3
11+	59.3	61.5	63.0	65.4	70.4	76.2	79.7	82.3	86.4
12+	61.5	63.8	65.4	68.0	73.3	79.4	83.1	85.8	90.1
13+	63.4	65.8	67.6	70.3	75.8	82.2	86.0	88.8	93.2
14+	64.9	67.5	69.3	72.2	78.0	84.5	88.4	91.2	95.6
15+	66.2	68.9	70.8	73.8	79.8	86.5	90.4	93.2	97.6
16+	67.4	70.2	72.1	75.2	81.3	88.1	92.1	94.9	99.2
17+	68.4	71.3	73.3	76.5	82.7	89.6	93.5	96.3	100.6
<i>Girls</i>									
2+	41.6	42.6	43.3	44.5	46.9	49.9	51.8	53.2	55.7
3+	42.5	43.5	44.3	45.5	48.0	51.1	53.1	54.6	57.2
4+	44.7	45.8	46.6	48.0	50.8	54.2	56.4	58.1	60.9
5+	46.8	48.1	49.0	50.4	53.5	57.3	59.8	61.6	64.7
6+	48.8	50.1	51.1	52.7	56.1	60.3	62.9	64.9	68.3
7+	50.6	52.1	53.2	55.0	58.7	63.2	66.0	68.1	71.7
8+	52.4	54.1	55.3	57.2	61.2	66.0	69.0	71.3	74.9
9+	54.5	56.3	57.6	59.7	64.0	69.1	72.3	74.6	78.4
10+	56.8	58.8	60.3	62.5	67.2	72.6	75.9	78.3	82.2
11+	59.3	61.5	63.1	65.5	70.5	76.2	79.6	82.1	86.0
12+	61.7	64.0	65.7	68.3	73.5	79.5	83.0	85.5	89.5
13+	63.6	66.1	67.9	70.6	76.1	82.2	85.7	88.3	92.2
14+	65.0	67.6	69.5	72.3	78.0	84.2	87.8	90.3	94.2
15+	66.0	68.7	70.6	73.5	79.3	85.6	89.1	91.6	95.4
16+	66.6	69.5	71.4	74.4	80.3	86.5	90.1	92.5	96.3
17+	67.1	70.1	72.1	75.2	81.1	87.4	90.9	93.3	96.9

Source: Khadilkar A, Ekbote V, Chiplonkar S, et al. Waist circumference percentiles in 2–18 year old Indian Children. J Pediatr. 2014;164(6):1358-62; Reprinted with permission from Elsevier.

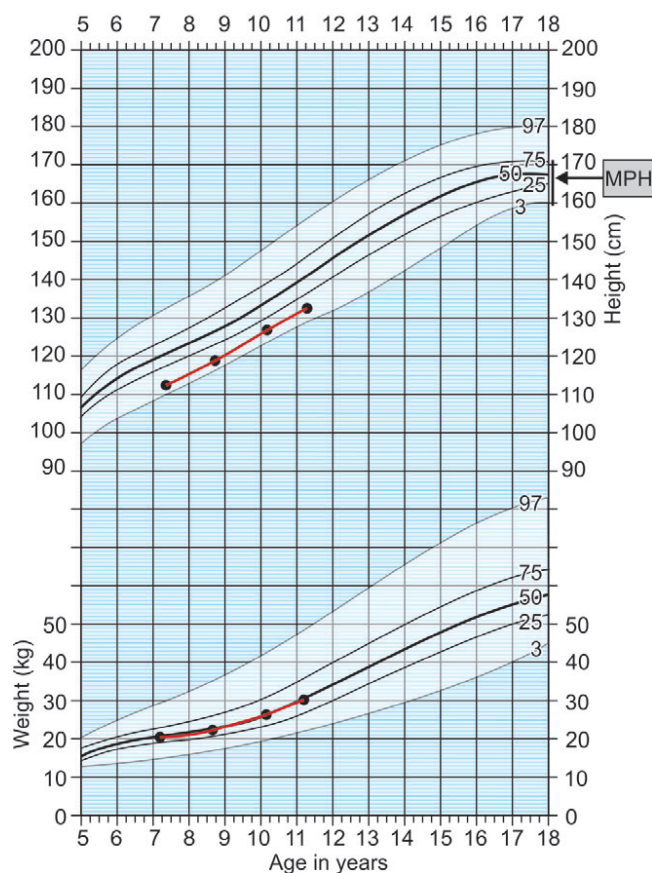
**Table 18** Waist circumference (WC) cut-off values for metabolic syndrome risk in Indian boys and girls

Age (Years)	70th percentile (cm)	
	Boys	Girls
2+	48.8	49.1
3+	50.8	50.4
4+	53.4	53.4
5+	56.1	56.4
6+	59.0	59.3
7+	61.9	62.1
8+	64.9	64.9
9+	68.0	67.9
10+	71.4	71.3
11+	74.9	74.8
12+	78.0	78.1
13+	80.7	80.8
14+	83.0	82.7
15+	84.9	84.1
16+	86.5	85.1
17+	87.9	85.9

Source: Khadilkar A, Ekbote V, Chiplonkar S, et al. Waist circumference percentiles in 2–18 year old Indian Children. *J Pediatr*. 2014;164(6):1358-62; Reprinted with permission from Elsevier.

Weight-for-age and Height-for-percentiles Boys (5–18 years)

Name-----Date of birth-----Record No-----



**Figure 15** Growth chart of an 11.5-year-old boy showing height growth parallel to and in between the 3rd and 25th centile lines and weight along the 50th centile. Mid-parental height (MPH) and target range for height is shown at 18 years of age. When the boy's growth curve is extrapolated to 18 years, the height is within  $\pm 8$  cm (target range) of the MPH

normally grow parallel to their respective centile lines, crossing over of two major centile lines, especially between the age of 2 years and the onset of puberty, i.e. roughly 10 years of age, is considered abnormal and may point to a pathological diagnosis or nutritional problems.

### IN A NUTSHELL

1. It is recommended that the World Health Organization (WHO) growth charts (0–60 months), which are based on growth of exclusively breastfed babies and depict the best physiological growth standards from birth to 5 years of age, be used to record and monitor growth in young children. Use of local reference charts is preferred for children beyond 5 years.
2. Anthropometric measurements from an individual child can be compared with standard reference growth charts or tables with the help of percentile values, standard deviation scores or percentage of the median.
3. Growth monitoring, that comprises of regularly measuring anthropometric parameters (weight and length/height) in a child and recording them on a growth chart, is a potent tool for diagnosing growth faltering and nutritional problems as well as monitoring response to therapeutic interventions.

Recently, Indian Academy of Pediatrics has developed new growth reference data and charts for Indian children more than five years of age while endorsing use of WHO growth charts for younger children. The new data set had been developed by collating data from multiple studies from different parts of the country. New IAP guidelines incorporating this information were published in January 2015, while this book was in press, these can be accessed from the website of IAP.

### MORE ON THIS TOPIC

- Agarwal DK, Agarwal KN, Upadhyay SK, et al. Physical and sexual growth pattern of affluent Indian children from 5 to 18 years of age. *Indian Pediatr*. 1992;29:1203-82.
- Agarwal KN, Saxena A, Bansal AK, Agarwal DK. Physical growth assessment in adolescence. *Indian Pediatr*. 2001;38:1217-35.
- Bhatia V. Growth charts suitable for Indian children-an unending saga? *Indian J Pediatr*. 2012;79:943-4.
- Khadilkar VV, Khadilkar AV, Borade AB, Chiplonkar SA. Body mass index cut-offs for screening for childhood overweight and obesity in Indian children. *Indian Pediatr*. 2012;49:29-34.
- Khadilkar VV, Khadilkar AV, Cole TJ, Sayyad MG. Cross-sectional growth curves for height, weight and body mass index for affluent Indian children, 2007. *Indian Pediatr*. 2009;46:477-89.
- Khadilkar A, Ekbote V, Chiplonkar S, et al. Waist circumference percentiles in 2–18 year old Indian Children. *J Pediatr*. 2014;164(6):1358-62.
- Kuriyan R, Thomas T, Lokesh DP, et al. Waist circumference and waist for height percentiles in urban South Indian children aged 3–16 years. *Indian Pediatr*. 2011;48(10):765-71.
- Marwaha RK, Tandon N, Ganie MA, et al. Nationwide reference data for height, weight and body mass index of Indian school children. *Natl Med J India*. 2011;24:269-77.
- Moon JS. Reappraisal of regional growth charts in the era of WHO Growth Standards. *Pediatr Gastroenterol Hepatol Nutr*. 2013;16:137-42.



## Chapter 19.4

### Dental Development and Anomalies

Sunanda Roychoudhury, Shakil Ahmed Nagori,  
Ajoy Roychoudhury

#### DEVELOPMENT OF THE DENTITION

The development of the dentition includes the processes of tooth eruption and of the development of occlusion posteruption. Three distinct phases of tooth development can be recognized that ultimately lead to the establishment of the full dentition. First, there is a phase termed the *pre-eruptive phase*, which starts with the initiation of tooth development and ends with the completion of the crown. Second, there is the *phase of tooth eruption* (pre-functional phase), which begins once the roots commence to form. Third, after the teeth have emerged into the oral cavity, there is a protracted phase concerned with the development, and maintenance, of occlusion (the *functional phase*).

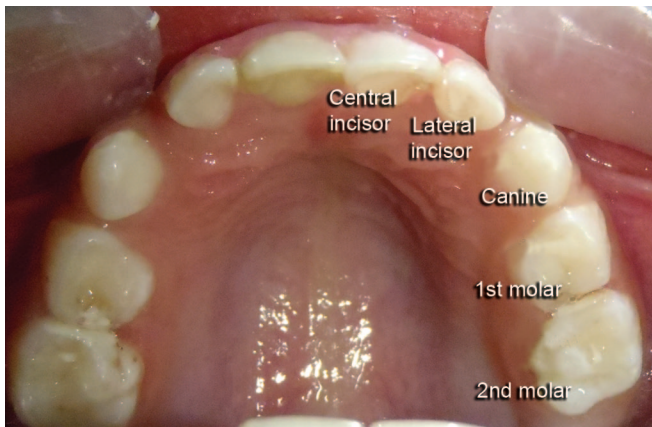
The human dentition is usually categorized as being primary, mixed (transitional), and permanent dentition. The transition from the primary/deciduous dentition to the permanent dentition is of particular interest because of changes that may herald the onset of malocclusion and provide for its interception and correction.

#### Pre-Dentition Period

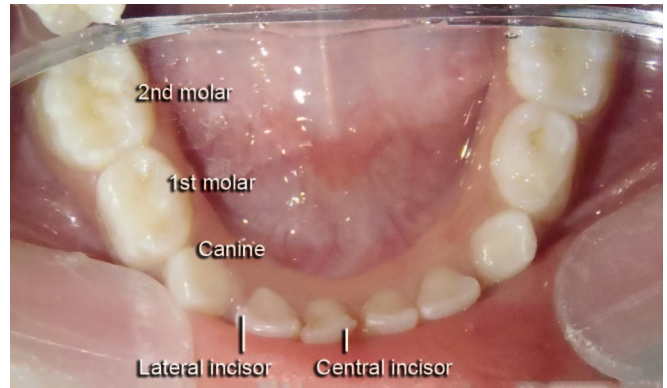
This is from birth to 6 months. At this stage, the infant is edentulous. Both jaws undergo rapid growth; the growth is in three planes of space: (1) downward, (2) forward, and (3) laterally. Forward growth for the mandible is greater. Occasionally, there may be a neonatal tooth present at birth. It is a supernumerary tooth and is often lost soon after birth. At birth, one would often see bulges in the developing alveoli preceding eruption of the deciduous teeth.

#### Deciduous Dentition Period

The deciduous teeth start to erupt at the age of 6 months and the deciduous dentition is completed by the age of approximately 2½ years (**Figs 1 and 2**). The jaws continue to increase in size at all points until about 1 year. After this, growth of the arches is in the form of lengthening at their posterior (distal) ends. Also, there is slightly more forward growth of the mandible than the maxilla.



**Figure 1** Maxillary deciduous dentition



**Figure 2** Mandibular deciduous dentition

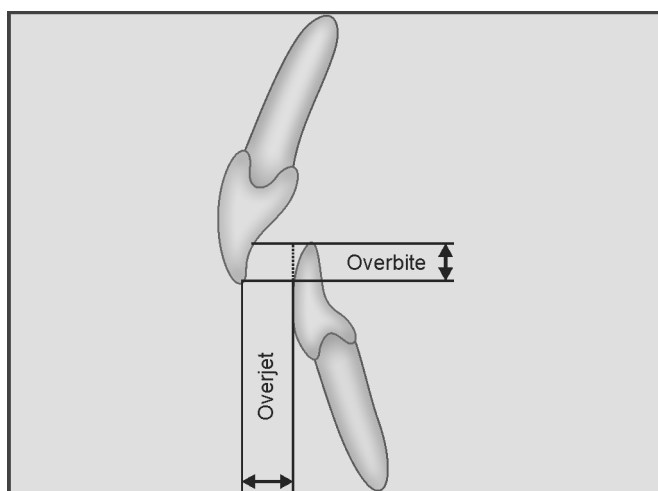
**Table 1** Development of deciduous dentition

Tooth	First evidence of calcification (months in utero)	Crown completed (months)	Eruption (months)	Root completed (years)
<i>Maxillary</i>				
Central incisor	3–4	4	7	1½–2
Lateral incisor	4½	5	8	1½–2
Canine	5	9	16–20	1½–3
First molar	5	6	12–16	2–2½
Second molar	6–7	10–12	21–30	3
<i>Mandibular</i>				
Central incisor	4½	4	6½	1½–2
Lateral incisor	4½	4	7	1½–2
Canine	5	9	16–20	1½–3
First molar	5	6	12–16	2–2½
Second molar	6	10–12	21–30	3

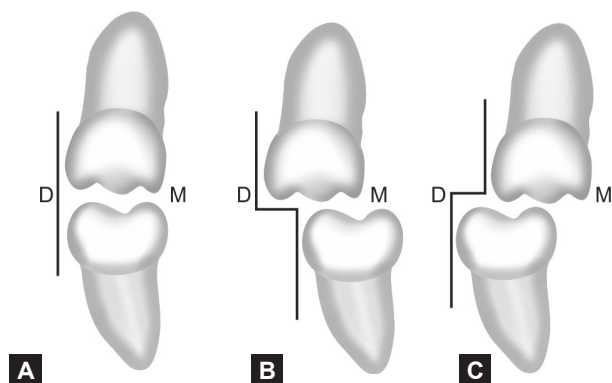
Many early developmental events take place in this period; the tooth buds anticipate the ultimate occlusal pattern. Mandibular teeth tend to erupt first. The pattern for the deciduous incisors is usually in this distinctive order: mandibular central; maxillary central incisors; and then all four lateral incisors. By 1 year, the deciduous molars begin to erupt. The eruption pattern for the deciduous dentition is described in **Table 1**. If deciduous teeth are retained too long, one must consider ankylosed teeth or missing or impacted teeth.

#### Occlusal Changes in the Deciduous Dentition

The term *occlusion* is used to describe the relationship of maxillary and mandibular teeth with each other. Broadly it is used to describe anterior relationship, i.e., the relationship of incisors and canines or posterior relation which is the relationship of molars. The incisor relationship in any dentition is usually described by the terms *overjet* and *overbite* (**Fig. 3**). Overjet is the anteroposterior overlap while overbite is the vertical overlap between incisor teeth. In the deciduous dentition, overjet and overbite are minimal and often decrease with age due to the gradual wear and tear of teeth. The molar relationship describes the relation of second deciduous molars with each other. In normal molar relation of deciduous dentition, the distal surfaces of maxillary and mandibular second deciduous molars are in one plane when both the teeth are occluded (**Figs 4A to C**). Other relations described are the mesial



**Figure 3** Vertical overlap between incisors is termed as overbite while horizontal overlap is termed as overjet



**Figures 4A to 4C** Occlusal relationship in deciduous dentition (D, distal surface; M, mesial surface). (A) Flush terminal plane; (B) Mesial step; (C) Distal step

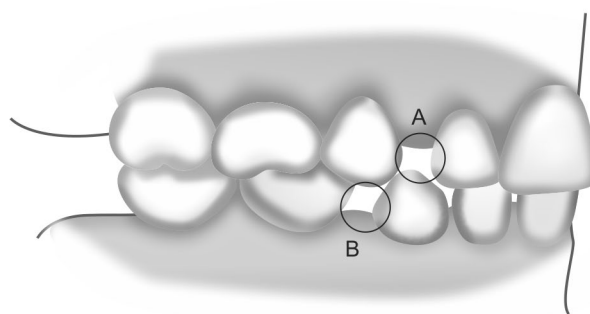
step or distal step. In a mesial step molar relation, the distal surface of mandibular second deciduous molar is mesial to its maxillary counterpart. Such type of primary dentition predisposes to a “class III malocclusion” in the permanent dentition. The other type is the distal step molar relationship. In this case, the distal surface of mandibular second deciduous molar is distal to its maxillary counterpart. Such type of primary dentition predisposes to a “class II malocclusion” in the permanent dentition.

Spacing between teeth is a common feature of deciduous dentition (**Fig. 5**). This is because the permanent teeth which would be finally occupying the space in the arches are larger in size than primary teeth.

### Mixed Dentition Period

The mixed dentition period begins with the eruption of the first permanent molars distal to the second deciduous molars at around 6 years of age and ends when the last deciduous tooth is lost. It is an important phase in the life of the child as the deciduous dentition is completely replaced by the permanent dentition.

The deciduous incisors, canines and molars are replaced by the permanent incisors, canines and premolars respectively. The permanent molars do not replace any deciduous tooth and erupt distal to the deciduous dentition (**Fig. 6**). The first permanent molars initially articulate or occlude in an *end-on* relationship after eruption. In the mixed dentition, the deciduous second molars



**Figure 5** Primate spacing in deciduous dentition. (A) Maxillary primate space mesial to canine; (B) Mandibular primate space distal to canine



**Figure 6** Radiograph of a patient in mixed dentition stage. The permanent incisors and 1st molars have completely erupted. Canines and premolars are yet to erupt. 2nd and 3rd molars are seen developing distal to 1st molars

have a special importance for the integrity of the permanent dentition. Consider this: The first permanent molars at age 6 years erupt distal to the second deciduous molars. Permanent posterior teeth exhibit physiological mesial drift, i.e., the tendency of the tooth to drift mesially when space is available. If the deciduous second molars are lost prematurely, the first permanent molars drift anteriorly and block out the second premolars. This would hinder its eruption and result in an impacted second permanent premolar.

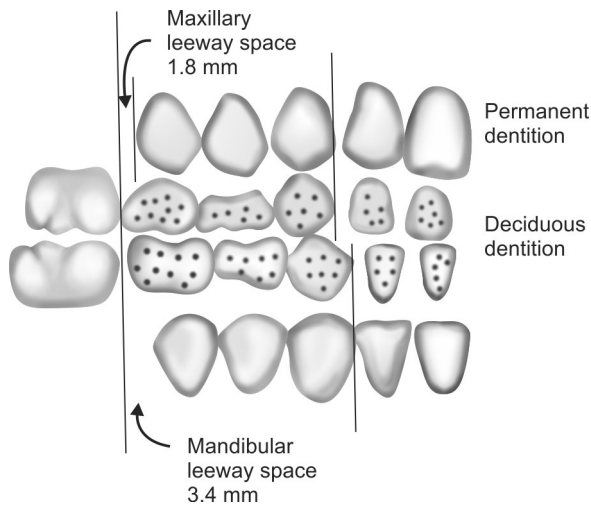
The deciduous anterior-incisors and canines are narrower than their permanent successors mesiodistally. The deciduous molars are wider than their permanent successors mesiodistally. This size difference has clinical significance. The difference is called the leeway space (**Fig. 7**).

Another feature which may be seen in a developing dentition is the flaring of permanent central incisors after eruption. This is called the “ugly duckling stage” (**Figs 8A and B**). This occurs due to late eruption of the permanent canines in the permanent dentition. While the central incisors erupt vertically the developing canine exerts pressure on the roots of the central and lateral incisors causing a typical flaring. This feature usually resolves when the canines have erupted into the arch.

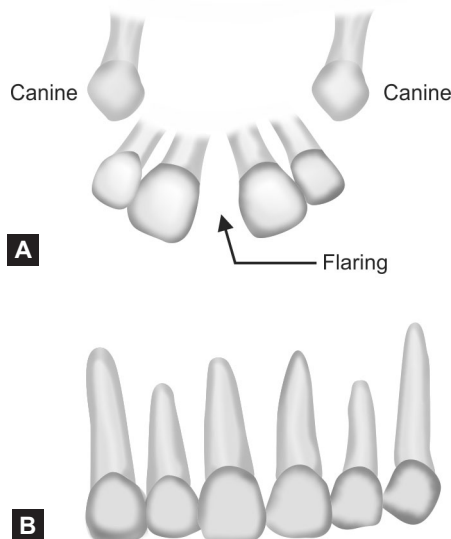
### Permanent Dentition Period

The permanent dentition consisting of 32 teeth is completed from 18 years to 25 years of age if the third molars are included. The chronology of eruption of permanent teeth is given in **Table 2**. Maxillary/mandibular occlusal relationships are established when the last of the deciduous teeth are lost. The incisor relationship in a normal fully developed permanent dentition usually results

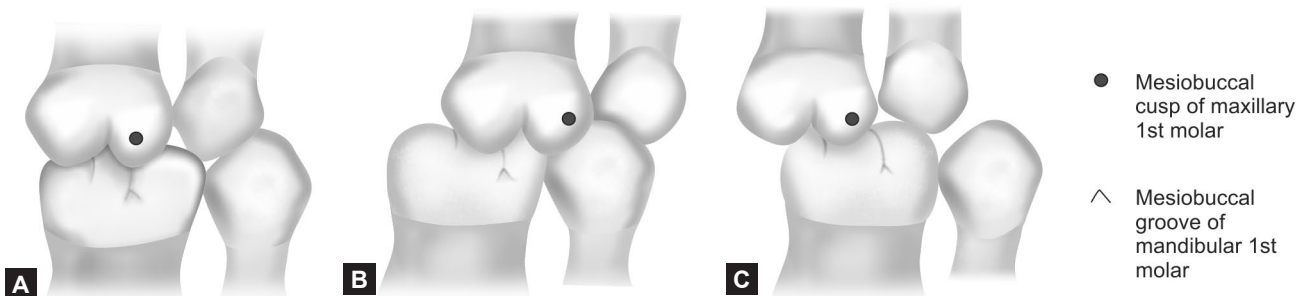
in a 2 mm overjet and overbite. A normal molar relationship is characterized by the occluding of mesiobuccal cusp of the first permanent maxillary molar in the mesiobuccal groove of the first permanent mandibular molar. This is known as the Angle's



**Figure 7** Illustration of leeway space in maxillary and mandibular arches



**Figures 8A and B** Ugly duckling stage. (A) Flaring of maxillary central incisors seen due to eruption of canines; (B) This stage resolves spontaneously with complete eruption of canines



**Figures 9A to C** Angle's molar relationship in permanent dentition. (A) Class I molar relationship; (B) Class II molar relationship; (C) Class III molar relationship

**Table 2** Development of permanent dentition

Tooth	First evidence of calcification	Crown completed (months)	Eruption (months)	Root completed (years)
<i>Maxillary</i>				
Central incisor	3–4 months	4–5	7–8	10
Lateral incisor	10–12 months	4–5	8–9	11
Canine	4–5 months	6–7	11–12	13–15
First premolar	1½–1¾ years	5–6	10–11	12–13
Second premolar	2–2½ years	6–7	10–12	12–14
First molar	Birth	2½–3	6–7	9–10
Second molar	2½–3 years	7–8	12–13	14–16
Third molar	7–9 years	12–16	17–21	18–25
<i>Mandibular</i>				
Central incisor	3–4 months	4–5	7–8	10
Lateral incisor	3–4 months	4–5	8–9	11
Canine	4–5 months	6–7	11–12	13–15
First premolar	1¾–3 years	5–6	10–11	12–13
Second premolar	1¼–2½ years	6–7	10–12	12–14
First molar	Birth	2½–3	6–7	9–10
Second molar	2½–3 years	7–8	12–13	14–16
Third molar	8–10 years	12–16	17–21	18–25

Class I molar relation. If the maxillary cusp occludes anterior to the mesiobuccal groove it results in a Class II molar relationship while if it occludes posterior to the mesiobuccal groove a Class III molar relationship is seen (**Figs 9A to C**). The maxillary teeth are also seen to be more buccal of the mandibular teeth. This maxillary overhang provides protection from check biting during mastication.

## OCCUSION AND MALOCCLUSION

Various changes occur during dental and facial development starting from birth to the age of 18 years. What may be normal at one stage of development can be abnormal at another stage. At birth there are no teeth present and the gum pads meet only in the posterior region. This anterior space between the gum pads facilitates the process of suckling where in the tongue positions itself. The mandible is small in comparison to the maxilla. The mandible at this stage thrusts forwards with every act of suckling. The first teeth erupt at the age of 6–7 months and the deciduous dentition is completely erupted by the age of 2 years. There are



various typical features of deciduous dentition, which are normal for that stage.

- Generalized space between teeth
- Primate or anthropoid spaces
- Deep bite/edge to edge bite of incisors
- Upright incisors
- Flush terminal plane of molars.

Once permanent teeth start to erupt at the age of 6 years the spacing between teeth gradually disappears as the larger anterior permanent teeth replace the smaller deciduous anterior teeth. By 12 years all the deciduous teeth are replaced by their permanent successors. At 12 years there are 28 teeth present, 14 in each jaw. The teeth of maxilla and mandible meet each other in a cusp-fossa relationship. *This is referred to as occlusion.* Normal occlusion is when the mesiobuccal cusp of the 1st maxillary permanent molar occludes with the mesial groove of the mandibular 1st permanent molar (Class I molar relation) and all the posterior teeth fit with each other with an overjet and overbite of 2 mm each in the anterior teeth (**Fig. 10**). *Any deviation from the normal occlusion is termed as malocclusion.* The malocclusion can have a dental origin/component or skeletal origin/component or both. Skeletal component is when there is discrepancy between the maxillary and mandibular skeletal size and position.

### Angle's Classification of Malocclusion

#### Angle's Class I Malocclusion

The molar relationship in permanent dentition occlusion is Class I but the rest of the teeth are not in normal alignment. There could

be crowding or spacing or rotation of individual teeth. There could also be anterior or posterior open bite or increased overjet or proclination of teeth. The face in Class I malocclusion is in balance and has pleasing esthetics. The facial profile is straight, the lips are competent and the musculature is relaxed. The maxilla and mandible are normal in size and position. This malocclusion is mainly dental in origin (**Figs 11A to D**).

#### Angle's Class II Malocclusion

The maxillary 1st permanent molar is more anterior to the mandibular 1st permanent molar. The distobuccal cusp of the maxillary molar occludes with the mesial groove of mandibular 1st molar. There is an increased overjet and deep over bite (**Figs 12A to D**). The maxilla and mandible are not in normal relation to each other. The maxilla may be prognathic or mandible may be retrognathic or there may be combination of both. The facial profile is convex. The midface is prominent, chin is retrusive. The lips may be incompetent. There is strain in musculature of face. The upper lip may be hypotonic, the lower lip may be thick, everted and redundant. There may be a lip trap present, where the lower lip rests behind the upper anterior teeth. The mentolabial sulcus is deep. In addition to dental malocclusion there is a skeletal component present in malocclusion. This type of malocclusion should be treated at an early age.

#### Angle's Class III Malocclusion

The maxillary 1st permanent molar is posterior to the mandibular 1st permanent molar. The mesiobuccal cusp of the maxillary 1st molar occludes with the distal groove of the mandibular



**Figure 10** 1st maxillary permanent molar occludes with the mesial groove of the mandibular 1st permanent molar (Class I molar relation) and all the posterior teeth fit with each other with an overjet and overbite of 2 mm each in the anterior teeth

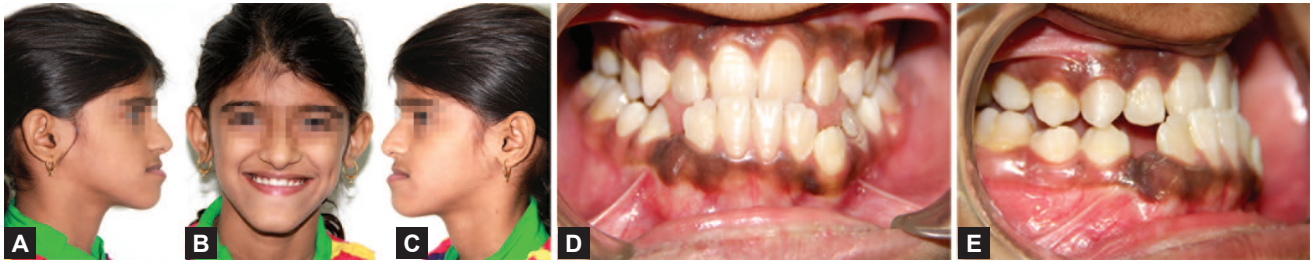


**Figures 11A to D** Skeletal Class I malocclusion. (A and B) Straight profile; lips competent; (C and D) Angle Class I molar relation with normal overjet and overbite with mild crowding





**Figures 12A to D** Skeletal Class II malocclusion. (A and B) Retrognathic mandible, convex facial profile, incompetent lips, lip trap, deep mentolabial sulcus; (C and D) Proclined incisors, increased overjet and overbite, Class II molar relation



**Figures 13A to E** Skeletal Class III malocclusion. (A to C) Prognathic mandible, concave profile, chin protruding, midface flatness; (D and E) Reverse overjet and overbite, Class III molar relation

1st permanent molar. There is reverse overjet and underbite. The maxilla and mandible are not in harmony with each other. Either the maxilla is retrognathic or mandible prognathic or there is a combination of both. The facial profile is concave, the midface being flat and the chin is protruding. The profile of face makes individuals very conscious of their appearance (**Figs 13A to E**). This malocclusion also has skeletal component in addition to the dental component.

## Treatment of Malocclusion

### Deciduous Dentition Phase

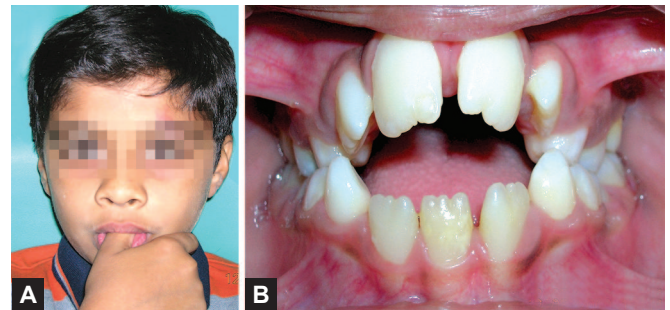
Very few conditions require orthodontic treatment in this phase. Class III malocclusion where there is cross bite of anterior or posterior teeth can lead to restriction of normal growth of maxilla and hence aggravate the malocclusion. Such malocclusion should be intercepted and treated when diagnosed. Certain deleterious habits such as prolonged thumb sucking can lead to proclination of teeth and can develop into class II malocclusion. Such habits can also lead to developing of an open bite (**Figs 14A and B**). In this phase, the habits are intercepted by appropriate habit breaking appliances.

### Mixed Dentition Period

The developing malocclusion can be intercepted and treated using oral appliance that take the advantage of the neuromusculature to correct malocclusion and also direct the growth of jaws to favorable direction to minimize malocclusion. These are referred to as myofunctional appliances (**Figs 15A and B**).

### Permanent Dentition

Till the age of 11–12 years in girls and up to 14 years in boys, the myofunctional appliance and the fixed orthodontic braces are used to treat the malocclusion, especially when the skeletal component is also present. The appliance takes the advantage of growth and redirects the deficient or excess mandible or maxilla to normal. The only dental component malocclusion is treated using fixed



**Figures 14A and B** (A) Thumb sucking habit; (B) Open bite, the gap between upper and lower incisors

orthodontic appliances as braces on teeth. The treatment typically requires wearing braces and wires for 18–24 months and retention periods of 12 months or more (**Fig. 16**).

## ANOMALIES OF DENTOFACIAL REGION: DEVELOPMENTAL DISORDERS OF TONGUE

### Macroglossia

Macroglossia or enlarged tongue can be due to a variety of causes. It has been traditionally defined as a resting tongue that protrudes beyond the teeth or alveolar ridge. Broadly it can be classified as true macroglossia or pseudomacroglossia. True macroglossia is either secondary to hyperplasia or hypertrophy of tongue muscles or can be as a result of infiltration by other tissues. Pseudomacroglossia is the relative enlargement of tongue seen due to a small mandible. Some of the causes of macroglossia are specified in **Table 3**.

### Clinical Features

A large tongue is usually obvious in comparison to adjacent structures (**Fig. 17**). The child may show crenations along the lateral border of tongue due to indentations of teeth. Speech can be



**Figures 15A and B** Myofunctional appliance—"Twin Block" consisting of mandibular and maxillary components to be worn accordingly



**Figure 16** Fixed orthodontic appliance

**Table 3** Some causes of macroglossia

<i>Congenital</i>	<i>Acquired</i>
Congenital hypothyroidism	Acromegaly
Down syndrome	Lingual thyroid
Beckwith-Wiedemann syndrome	Amyloidosis
Lymphangiomas	Angioedema
Mucopolysaccharidoses	Tumors infiltrating the tongue
Neurofibromatosis	

affected due to the enlarged size. There may be drooling of saliva, difficulty in swallowing with limited mobility of tongue. Constant protrusion of tongue may lead to ulceration. Dental abnormalities may accompany like anterior open bite. Some patients may present with airway obstruction, noisy breathing, stridor and it may be a cause of obstructive sleep apnea syndrome.

### Diagnosis

Thorough history and physical examination is required, which may allow the recognition of a syndrome of which the enlarged tongue is one component. Thyroid function tests, isotopic imaging of the thyroid gland, chromosomal studies, and urinary mucopolysaccharide assay may be indicated. Computed tomography and magnetic resonance imaging may be useful to delineate soft tissues and to show the extent of tumors and other masses. Microscopic examination of tongue tissue in primary macroglossia may be unhelpful, but biopsy is useful for localized



**Figure 17** Macroglossia in a patient with mucopolysaccharidoses

lesions of the tongue that occur in chronic granulomatous and neoplastic disorders.

### Treatment

Reduction glossectomy is required in cases of true primary macroglossia if it interferes in function. Treatment of other infiltrative tumors requires excision. Goal is to restore tongue size and thereby improve function.

### Tongue-Tie

Ankyloglossia or tongue-tie is the restriction of free tongue movement caused due to attachment of the inferior frenulum to the bottom of the tongue (**Fig. 18**). It has a wide spectrum of presentation ranging from very thin band to fully developed ankyloglossia. Reported incidence of tongue-tie varies from 0.04% to 0.1% and the male:female ratio is 2.6:1.

Limitation of tongue mobility beyond the incisal edges of anterior teeth is the defining feature. Limited tongue movement can lead to breastfeeding problems causing sore nipples, repeated bouts of mastitis, and failure to thrive. Speech defects especially with articulation of sounds like l, r, t, d, n, th, z is seen because pronunciation of these requires opposition of tongue to alveolus or palate. Inability to perform internal oral toilet and inability to lick lips is also seen. It may cause dental anomalies like persistent gap between incisor teeth. Treatment consists of frenulectomy.





**Figure 18** Tongue-tie

### Lingual Thyroid Nodule

Thyroid gland originates from the endodermal tissues in the pharyngeal floor between the tuberculum impar and hypobranchial eminence. The thyroid then descends along a path from the foramen cecum to its final position in front of the trachea. While descending it retains its communication with the foramen cecum which is known as the thyroglossal duct. The duct gradually degenerates in most individuals. The lingual thyroid is an anomalous condition in which thyroid follicles are found in the substance of the tongue possibly from a thyroid anlage which failed to migrate to its normal position. The incidence of lingual thyroid is reported as 1:100,000 with male: female ratio of 1:7.

### Clinical Features

The lingual enlargement is usually seen in the midline, at the base of the tongue. It is usually deeply seated rather than a superficial exophytic lesion. Onset of symptoms is usually early in life and it may present as dysphagia, dyspnea, dysphonia, sleep apnea, and stridor. It may be a cause of respiratory emergency with severe airway obstruction. Patients may show features of hypothyroidism and in some it may be the only thyroid tissue in the body.

### Diagnosis

Neck palpation is necessary to check for normal thyroid tissue. Investigations required are: thyroid function tests (for baseline thyroid function) and technetium scanning (demonstration of thyroid tissue in the tongue and normal thyroid gland). Fine needle aspiration cytology of the mass demonstrates thyroid tissue and may be helpful in differentiating from salivary gland tumors.

### Treatment

Suppressive therapy with exogenous thyroid hormone should be tried first. This often decreases the gland size after which elective surgery can be planned if required. Levothyroxine therapy should be initiated after surgical excision as the lingual thyroid may be the only thyroid tissue in the body.

## DEVELOPMENTAL DISORDERS OF GINGIVA

### Fibromatosis Gingivae

#### (Hereditary Gingival Fibromatosis)

It is a benign, idiopathic condition causing diffuse fibrous overgrowth of gingival tissues. It is usually autosomal dominant and affects males and females equally. The reported incidence is



**Figure 19** Hereditary gingival fibromatosis

of 1:350,000. Gingival fibromatosis may be familial or idiopathic. The familial variation may occur with a number of other inherited syndromes, e.g., Zimmerman Laband syndrome, Cowden syndrome, juvenile hyaline fibromatosis, multiple hamartomas, and tuberous sclerosis.

### Clinical Features

Gingival enlargement is usually slowly progressive, sometimes covering the major parts or even complete tooth surfaces which may project into the vestibule and floor of the mouth (**Fig. 19**). It can interfere with normal mastication and even lip closure that makes speech difficult. The enlarged gingival tissue appears firm and pink and may either be generalized (symmetric) or localized (nodular). Severity varies in patients and it may completely involve the buccal and lingual tissues of both maxillary and mandibular arches. Hereditary gingival fibromatosis (HGF) is seldom present at birth. It usually begins at the time of eruption of permanent dentition but can develop with the eruption of primary dentition. If the enlargement is present before tooth eruption the dense fibrous tissue may interfere with or prevent eruption. The most common effects related to gingival overgrowth are spacing between teeth, malpositioned teeth and prolonged retention of primary teeth.

### Treatment

Surgical removal of excessive tissue and exposure is indicated when it interferes in eruption of teeth and for cosmetic purposes.

## DEVELOPMENTAL DISORDERS OF TEETH

### Anodontia/Hypodontia

Anodontia or congenital absence of teeth may be either total or partial. Total anodontia, i.e., complete absence of dentition is an extremely rare condition which can affect either deciduous or permanent dentition. It usually is seen with a more generalized disorder like hereditary ectodermal dysplasia. Partial anodontia (hypodontia/oligodontia) which involves one or more teeth is common. Mandibular third molars followed by maxillary third molars are the most common missing teeth. Other commonly missing teeth include maxillary lateral incisors and mandibular second premolars. Hypodontia in deciduous dentition is however uncommon. The etiology of single missing tooth is unknown and familial tendency may be seen. Treatment is usually prosthetic replacement for the missing tooth in permanent dentition.

### Supernumerary Teeth

Presence of an *extra-tooth* beyond the normal number of teeth in the dentition is termed as supernumerary tooth. Not unusual these are more common in the permanent dentition. The etiology is unknown. The incidence is around 2.1% in the permanent dentition and 0.8% in the deciduous dentition. These may be single,



**Figure 20** Amelogenesis imperfecta

multiple, unilateral, bilateral affecting either arches. Multiple supernumerary teeth are seen associated with conditions like cleft lip and palate, cleidocranial dysplasia, and Gardener syndrome. Common types of supernumerary tooth include: Mesiodens—a single cone-shaped tooth usually found between or palatal to maxillary central incisors; paramolars—a 4th molar seen distal or buccal to maxillary molars. Treatment is usually extraction.

### Amelogenesis Imperfecta

Dental enamel is a highly mineralized tissue with over 95% of its volume occupied by unusually large, highly organized, hydroxyapatite crystals. Congenital defects of this layer leads to an anomaly known as amelogenesis imperfecta. The reported incidence varies widely from 1:700 to 1:14,000. This congenital anomaly shows autosomal dominant, autosomal recessive, sex-linked and sporadic inheritance patterns. It may as well present as a sporadic case. The structure and clinical appearance of enamel of all or nearly all the teeth is affected in a more or less equal manner. The enamel may be hypoplastic, hypomineralized or both and teeth affected may be discolored, sensitive or prone to disintegration either posteruption (posteruptive breakdown) or pre-eruption (idiopathic resorption) (**Fig. 20**). Extraoral radiographs may reveal the presence of unerupted and sometimes spontaneously resorbing teeth. Intraoral radiographs will reveal the relative contrast between enamel and dentine in cases where mineralization may have been affected. Treatment is limited to improving cosmetic appearance.

### Enamel Hypoplasia

Enamel hypoplasia is defined as an incomplete or defective formation of the organic enamel matrix of the teeth. Broadly, it can be classified as either hereditary (amelogenesis imperfecta) or environmental. Hereditary form involves both deciduous and permanent dentition and is restricted to defects of only the enamel. The environmental form on the other hand involves either dentition and both enamel and dentin are affected. Hypoplasia occurs only if injury occurs during the formative stages of tooth. Once enamel has been formed no such defect is seen. Causes of injury to teeth are listed in **Box 1**.

#### BOX 1 Causes of injury to teeth

- Nutritional deficiencies—vitamin A, C and D
- Exanthematous diseases—measles, chickenpox, scarlet fever
- Congenital syphilis
- Hypocalcemia
- Birth injury, Rh hemolytic disease
- Local infection or trauma
- Chemicals: Tetracycline, Fluorides
- Idiopathic.

Use of tetracycline in childhood can chelate calcium of developing tooth. It becomes incorporated in the enamel resulting



**Figure 21** Yellowish spots of enamel hypoplasia seen on maxillary central incisors

in characteristic staining of teeth. While 1 ppm of fluoride in drinking water is known for its anticariogenic effect on teeth, excessive fluoride in water leads to enamel hypoplasia (enamel mottling). Indian states of Rajasthan and Haryana have high fluoride content in their groundwater hence enamel fluorosis is common in these states. The severity of hypoplasia increases with increase in fluoride content.

### Clinical Features

Hypoplastic teeth depending upon severity show occasional white flecking or spotting of enamel to more white opaque areas covering the entire tooth surface (**Fig. 21**). Severe cases show pitting, brownish staining of the tooth surface and may have a corroded appearance. The affected teeth have high rate of wear and tear and are prone to fractures.

### Treatment

Cosmetic dental treatment is required depending upon involvement.

## DEVELOPMENTAL DISORDERS OF ERUPTION

### Premature Eruption

A wide variation exists in the eruption age of deciduous and permanent teeth and sometimes deciduous teeth that have erupted into the oral cavity are seen in infants at birth. These are natal teeth. Neonatal teeth are those which erupt in the first 30 days of life. The mandibular central incisors are the usual ones to erupt. The etiology of this phenomenon is however unknown.

### Delayed Eruption

Absence of deciduous teeth beyond the maximal limit may result in conditions like rickets, cretinism and cleidocranial dysplasia. It may be completely idiopathic in some cases. Local factors like gingival fibromatosis may also lead to delayed eruption.

### Embedded and Impacted Teeth

Embedded teeth are those which do not erupt due to an inherent lack of eruptive force. Impacted teeth on the other hand are prevented from erupting by a physical barrier in the eruption path. Lack of space due to crowding of dental arches; premature loss of deciduous teeth with subsequent closure of space are some of the common causes of impacted teeth. Mandibular third molars (**Fig. 22**), maxillary third molars and maxillary and mandibular canines (**Fig. 23**) are most commonly impacted. Impacted tooth may cause disruption of eruption paths of adjacent teeth and can lead malocclusion. While impacted third molars other





**Figure 22** Impacted mandibular third molar



**Figure 23** Impacted left mandibular canine



**Figure 24** Mandibular micrognathia secondary to temporomandibular joint ankylosis

deeply impacted teeth are usually extracted, others may require orthodontic treatment for their eruption and repositioning.

## DEVELOPMENTAL DISTURBANCES OF THE JAWS

### Micrognathia

Micrognathia simply means a small jaw (**Fig. 24**). This may involve either the maxilla or mandible. True micrognathia needs to be differentiated from apparent micrognathia where the

defect lies in the position of the jaw rather than in size of the jaw. True micrognathia can be classified as congenital or acquired. Congenital mandibular micrognathia seen in syndromic patients like Pierre Robin sequence, Treacher Collins syndrome, Stickler syndrome, and Nager syndrome or may be seen in rare cases of condylar agenesis. In India and many other developing countries, acquired micrognathia is usually secondary to temporomandibular joint (TMJ) ankylosis. Micrognathia of the maxilla occurs due to deficient maxillary development and is most commonly due to cleft lip/palate. It may also be seen in patients with achondroplasia, Crouzon syndrome, etc.

### Clinical Features

The mandible appears to be repositioned relative to the maxilla in cases of mandibular micrognathia. In severe cases, bird-face deformity may be seen.

- In cases of maxillary retrognathia, the middle-third of the face appears retracted.
- Mandibular micrognathia cases may be associated with obstructive sleep apnea syndrome. The retruded mandible results in retroglossal airway obstruction which may result in desaturation episodes in the patient. Snoring and excessive day time sleepiness are characteristics signs of obstructive sleep apnea.
- Maxillary retraction may result in airway obstruction at the level of nasal passage. Speech may be affected.

### Temporomandibular Joint Ankylosis

Temporomandibular joint ankylosis is the most common cause of acquired mandibular micrognathia in India. It results due to fibrous or bony union of the mandibular condyle to the glenoid fossa. Other causes include *trauma*: direct or indirect injury to the mandibular condyles; *infections*: otitis media, mastoiditis, parotitis; *birth injury*: forceps delivery resulting in injury to mandibular condyles; and *others*: rheumatoid arthritis, infectious arthritis, Marie-Strumpell disease.

### Clinical Features

Condition occurs at any age but most cases are seen in children. Patient with fibrous ankylosis usually has some amount albeit decreased mouth opening. In complete ankylosis however the mouth opening is nil. In unilateral ankylosis, the chin is deviated to the affected side and face appears asymmetric. There is flattening on the nonaffected side with soft tissue fullness on the affected side. The movement of the condyle on the affected side is not palpable. Malocclusion may be present. In bilateral ankylosis, the chin is retruded with a characteristic convex profile. Condylar movements are not palpable bilaterally. Patients may have poor oral hygiene and multiple carious teeth due to limited mouth opening. Nutrition may be hampered in long standing cases.

### Radiographic Features

Abnormal or irregular shaped condyle with radiopacity filling the joint space is evident on orthopantomogram.

### Treatment

Treatment of TMJ bony ankylosis is surgical. Arthroplasty of the affected joint is carried out to provide a sufficient gap between the two bony surfaces. In case there is concomitant underdevelopment of the jaw, distraction osteogenesis for lengthening of the mandible can be performed.

### Macrognathia

Macrognathia means large jaws. Sometimes, increase in the size of the jaws is not in proportion to the growth of the entire



**Figure 25** Macrognathia of maxilla secondary to fibrous dysplasia

skeleton. Macrognathia may be associated with certain conditions, such as Paget's disease, acromegaly, and fibrous dysplasia of the jaws (**Fig. 25**). It is a rare condition in children. One condition which is frequently seen is mandibular prognathism. In many cases mandibular prognathism is due to disparity in the size of the maxilla in relation to mandible or due to excessive condylar growth.

### *Treatment*

Treatment depends on the underlying cause. In case of fibrous dysplasia, surgical contouring is performed only after the completion of growth. Mandibular prognathism can be treated by growth modulation and orthodontic correction of the malocclusion if diagnosed at an early age.

### IN A NUTSHELL

1. Three distinct phases of tooth development are recognized namely: deciduous dentition, mixed dentition, permanent dentition.
2. Deciduous dentition stage is between 6 months and 6 years of age, mixed dentition from 6 years to 12 years and permanent dentition from 12 years onwards.
3. Mixed dentition stage is of particular interest as it may herald the onset of malocclusion and provide for its interception and correction.
4. Eruptions times of teeth vary with individuals and close follow-up with dentists is essential to intercept any developing anomalies.
5. Malocclusions should be treated for esthetic and functional reasons.
6. Tongue-tie is a common anomaly in children which may affect speech development and cause dental spacing. It is treated by frenulectomy.
7. White chalky spots on dentition are usually a sign of enamel hypoplasia, a very common condition due to high fluoride content in drinking water.
8. Micrognathia is mostly acquired and secondary to temporomandibular joint ankylosis. Bird facies due to small mandible, convex profile are usual features of mandibular micrognathia.
9. Obstructive sleep apnea is seen in a certain cohort of children suffering from temporomandibular joint ankylosis and extreme micrognathia.

### MORE ON THIS TOPIC

- Development of face and oral cavity. In: Kumar GS (Ed). Orban's Oral Histology and Embryology. 13<sup>th</sup> ed. New Delhi: Elsevier; 2011. pp. 5-24.
- Gupta SK, Saxena P, Jain S, Deshraj J. Prevalence and distribution of selected developmental dental anomalies in an Indian population. J Oral Sci. 2011;53:231-8.
- Guttal KS, Naikmasur VG, Bhargava P, Bathi RJ. Frequency of developmental dental anomalies in the Indian population. Eur J Dent. 2010;4:263-9.
- Rajendran R, Sivapathasundharam B. Shafer's Textbook of Oral Pathology. 7<sup>th</sup> ed. New Delhi: Elsevier; 2012.

## Chapter 19.5

# Bone Age and Predicted Final Height

*M Vijayakumar, Anju Seth*

In normal children, there is an orderly and predictable sequence of appearance and development of epiphyseal centers in growing bones, which can be readily observed on a radiograph. This has enabled generation of standards for bone maturation at different ages during childhood and adolescence for both genders. Comparison of skeletal maturity of an individual with these age and gender-related standards forms the basis of bone age (BA) assessment. Importance of BA lies in the fact that it is a better indicator of biological maturity as compared to the chronological age (CA), and many parameters including height velocity, menarche, accrual of muscle mass and bone mineral density correlate better with BA than CA. Assessment of BA is thus an important tool in evaluation of various types of growth, endocrine and genetic disorders and to assess the impact of treatment in these conditions.

### BONE DEVELOPMENT

Flat bones like carpal bones develop from a single primary center. In contrast, long bones like radius and ulna and short bones like metacarpals have a primary center which will develop into the diaphysis and a secondary center that appears at the end of the bone which forms the epiphysis. The part of diaphysis that lies close to the epiphysis is the metaphysis. Growth of the bone ceases and final adult stature is attained when osseous structures of metaphysis and epiphysis fuse.

The process of bone calcification begins as early as 8th week of intrauterine period. By 13th week of fetal life, most of the primary centers of long bones are well developed into diaphysis which gets completely ossified at birth. Epiphysis for calcaneus and talus appear by 6 months in utero and that of cuboid by birth. Ossification of distal femoral epiphysis begins by 38 weeks in utero and that of proximal tibial epiphysis by 40 weeks of gestation. Ossification center of head of femur appears by 1 year of life. Many factors may influence the normal maturational pattern of bones. These include genetic factors, hormones (thyroxine, growth hormone and sex steroids) and nutrition.

### ASSESSMENT OF SKELETAL MATURITY

Radiographs of entire skeleton may appear a logical tool to assess BA, but are neither practical nor, fortunately required. For clinical purposes, beyond the neonatal period, radiograph of the left hand and wrist is adequate, and is commonly employed for BA assessment since changes associated with progressive skeletal maturity are reasonably reflected in a radiograph of the hand.

### Normal Sequence of Skeletal Development Observed on a Radiograph of Hand

First ossification center that appears in the X-ray of hand and wrist is that of capitate, closely followed by hamate at 3 months of age. At about 1 year in girls and 1½ years in boys, ossification center in the distal epiphysis of radius appears. Between 1 year and 3 years of age ossification centers of metacarpals and phalanges develop.

Boys tend to lag behind girls by 6 months during this period. The third carpal bone (triquetral) develops by 2 years in girls and 6 months later in boys. Subsequently, ossification centers of other carpal bones appear in the following order:

- Lunate (3 years in girls, 6 months later in boys)
- Trapezium (4 years in girls, 6 months later in boys)
- Trapezoid (5 years in girls, 6 years in boys)
- Scaphoid (6 years in girls, 7 years in boys).

Distal epiphysis of ulna also appears during this period (5 years in girls, 6 years in boys). During early puberty, pisiform (9 years in girls, 10 years in boys) and sesamoid in the tendon of abductor pollicis appear (11 years in girls, 12 years in boys). During this period epiphysis of metacarpals and phalanges continue to grow and their width become more than the metaphysis. As the puberty advances, progressive fusion of epiphysis to metaphysis occurs in the long bones, which begin in the phalanges and metacarpals. Epiphyseal fusion of ulna followed by radius occurs at 15–17 years in girls and 17–19 years in boys.

### Obtaining a Radiograph for Bone Age Assessment

Correct positioning of the hand and wrist while obtaining the radiograph is important since incorrect positioning may give an inaccurate image of the bone's shape and obscure the new changes that have occurred in it during maturation. The hand should be placed with palm facing downwards in contact with the cassette. Axis of the forearm should be in direct line with the axis of the middle finger. Upper arm and forearm should be in the same horizontal plane. Fingers should not be touching each other and thumb should be placed at an angle of 30 degrees with the first finger. X-ray tube should be kept half way between the tip of the fingers and distal end of the radius (above the head of third metacarpal). Tube film distance should be 30 inches.

### Methods for Assessment of Skeletal Age

Bone age is assessed by comparing the degree of maturation of various epiphyses in the X-ray of the hand with age-related standards. As the age advances, so does the variability in time of appearance and fusion of centers. Thus, mere assessment of appearance and fusion of centers is a crude method of BA assessment and has limited clinical utility. In clinical practice, Greulich and Pyle (GP) atlas, based on visual evaluation of skeletal development of left hand and wrist, is a commonly used method for assessment of BA. This method was introduced in 1950 and remains the most widely used method even now. Tanner Whitehouse method (TW) is the other frequently used method. In this electronic era, attempts are also being made to develop digital methods to assess the bone age quickly and accurately. In all methods, different reference standards exist for boys and girls.

### Greulich and Pyle Atlas

This atlas is divided into two separate set of X-rays, one for boys and the other for girls. Each part contains radiographs of left hand arranged in chronological order. BA of a given child is assessed by comparing his/her radiograph with the standards given in the atlas. To begin with, the X-ray is compared with the X-ray picture of the same age and gender given in the atlas. If it does not match correctly, comparison is made with the radiographs preceding or following that radiograph till the closest match is achieved. If none of the X-rays in the atlas correlate with the given X-ray, BA is interpreted as the picture to which it closely resembles. If the X-ray falls in between two pictures in the atlas, the age is interpreted to be between the ages of the standards it closely resembles.



### Tanner and Whitehouse Method

This method is based on individual bone's stages of maturity. Recently the updated version, TW3 is in use. Here, 20 regions of interest (ROI) in different bones are considered for BA calculation. Each ROI is divided into discrete stages depending on their development and each stage is given a letter (A, B, C, D, E, F, G, H and I). A numerical score is assigned to each stage. By adding the scores of each ROI a maturity score is obtained. This score is compared with the provided charts (separate for boys and girls) and BA is determined. Though time consuming, TW method gives a more objective assessment of BA as compared to GP atlas where there are more chances of interobserver variation in interpretation. Further, TW3 can differentiate BA up to 1/10th of a year; while GP atlas gives a rough approximation with interval of 6–12 months between standards. TW3 method is thus more sensitive in following small changes in BA.

### Computer-assisted Skeletal Age Scores

Recently, various computer-assisted techniques for BA assessment have been developed. In these methods, the hand radiograph is digitized, bone by bone. Each digitized information is analyzed by comparing with digitized images of standard stages (A to I) and the closest match is found. The actual rating is done by the computer. Commonly used methods are computer-assisted skeletal age score (CASAS) and BoneXpert.

### Clinical Applications

Bone age assessment provides important clues in diagnosis of various growth disorders. Degree of delay in BA may reflect duration of disease process. BA helps in predicting adult height and to monitor growth potential over time, especially if a treatment to modify growth/puberty is being given. BA is delayed in short stature due to chronic systemic diseases, malnutrition, constitutional delay in growth and puberty (CDGP), and various endocrine disorders including growth hormone deficiency and hypothyroidism. It is not generally delayed in skeletal dysplasia since epiphyseal maturation in these disorders remains unaffected. BA is advanced in congenital adrenal hyperplasia, precocious puberty and in overgrowth syndromes like Beckwith-Wiedemann syndrome.

### Short Stature

Bone age is an important tool in the diagnosis of short stature. Familial short stature is characterized by BA corresponding to CA or delayed by less than a year. Mild delay (up to 2 years) is commonly seen in malnutrition, systemic diseases and idiopathic short stature. In constitutional delay in growth and puberty (CDGP), BA is usually delayed by 2–3 years though it correlates well with height and age. Endocrine disorders like hypopituitarism and hypothyroidism, on the other hand, are characterized by marked delay in BA, even more than that expected for height. BA is also useful for assessing response to treatment in these disorders, e.g., during growth hormone therapy. If increment in height during treatment is larger than increment in BA, it predicts improved prognosis for final stature.

### Pubertal Disorders

Exposure to sex hormones accelerates bone maturation. BA is delayed in almost all cases with delayed puberty, while precocious puberty is characterized by marked BA advancement. In normal pubertal variants like premature thelarche and adrenarche, BA advancement is minimal. Serial BA assessment, at least once every year, is recommended during follow-up evaluation of subjects receiving gonadotropin-releasing hormone analog

therapy for precocious puberty to assess improvement in predicted height, and to help decide duration of therapy. Slowing of bone maturation on therapy is a sign of adequacy of treatment.

### Congenital Adrenal Hyperplasia

Adrenal androgens have a marked stimulatory effect on bone maturation. This accelerated bone maturation eventually leads to premature closure of sutures resulting in final short stature. BA assessment is an important component of follow-up evaluation of children with congenital adrenal hyperplasia (CAH). This helps in titrating the dose of corticosteroids and prediction of final adult height. Inadequate drug dosage results in rapid advancement of BA age due to unsuppressed sex steroid production.

### PREDICTION OF ADULT HEIGHT

In a normal individual, there is a direct relation between degree of skeletal maturation and time of epiphyseal closure, an event that marks attainment of adult stature. Therefore, there is a significant correlation between BA and the proportion of final stature achieved. More delayed the BA for CA, longer the time before epiphyseal fusion. On the other hand, if the BA is advanced, epiphyseal fusion and attainment of final stature would occur earlier than at the expected CA. Expected adult height can be predicted from a child's height at a particular age and his skeletal age at the time of obtaining the height. Various methods have been developed to assess this, like those by Bayley-Pinneau, Roche, or TW.

The method formulated by Nancy Bayley and Samuel Pinneau is based on GP atlas. Here height of the child at maturity is taken as 100% and the average percent of mature height (PMH) for various bone ages are precalculated and presented as separate charts for boys and girls. Mature height is calculated by dividing the child's height by the percentage of mature height which corresponds to his/her BA. Prediction is generally more accurate if the difference between BA and CA is not much.

In the method formulated by JM Tanner and RH Whitehouse, coefficients of height, age and BA are presented for boys and girls of different chronological ages. Accurate height and CA are recorded and BA is calculated by TW3. Predicted adult height can be derived from the following formula:

$$\text{Predicted adult height} = (\text{Height coefficient} \times \text{present height in cm}) + (\text{Age coefficient} \times \text{chronological age}) + (\text{Bone age coefficient} \times \text{Bone age in years}) + \text{constant}$$

There are separate charts for boys and girls. It should be realized that regardless of method used, height predictions are not totally accurate and of limited clinical use in children with growth disorders. One of the main sources of inaccuracy is impreciseness in BA assessment. A small difference in BA estimation can lead to a marked difference in predicted height. Their main clinical application remains in assessing short-term response to various growth modifying therapies.

### IN A NUTSHELL

1. Bone age is a better indicator of biological maturity as compared to the chronological age.
2. Assessment of bone age is an important tool in evaluation of growth, endocrine and genetic disorders and to assess the impact of treatment in these conditions.
3. It also helps in predicting adult stature of a child.
4. Bone age is assessed by comparing the degree of maturation of various epiphyses in the X-ray of the hand with age-related standards. Common methods in clinical use include Greulich and Pyle atlas and Tanner and Whitehouse method.



## MORE ON THIS TOPIC

- Gilsanz V, Ratib O. Hand bone age-a digital atlas of bone age maturity. Berlin Heidelberg: Springer-Verlag; 2005.
- Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrists. 2<sup>nd</sup> ed. Stanford, California: Stanford University Press; 1971.
- Martin DD, Wit JM, Hochberg Z. The use of bone age in clinical practice (Part 1). *Horm Res Paediatr*. 2011;76:1-9.
- Martin DD, Wit JM, Hochberg Z. The use of bone age in clinical practice (Part 2). *Horm Res Paediatr*. 2011;76:10-6.
- Niemeijer M, van Ginneken B, Maas CA, et al. Assessing the skeletal age from a hand radiograph: automating the Tanner-Whitehouse method. *Medical Imaging*. 2003;503:1-6.
- Tanner JM, Goldstein JRH. Assessment of skeletal maturity and prediction of adult height (TW3 method). USA: WB Saunders; 2001.

## Chapter 19.6

# Failure to Thrive

Sudha Rao Chandrashekhar

Although regular assessment of growth and monitoring of growth parameters are important aspects of child health surveillance programs, detecting deviations from normal especially in infants and young children is a major challenge to practicing pediatrician and primary care physicians. Divergence from normal may occur at any age, in any of the parameters and in any direction. Hence routine measurement and maintaining a longitudinal record of growth parameters especially weight, length/height and head circumference in all children especially in early childhood, forms the biological basis of early detection of any abnormality.

Failure to thrive (FTT) is a description of any condition associated with inadequate growth or inability to maintain adequate growth especially in early childhood, commonly in the first 2 years of life due to lack of sufficient *usable* nutrition contributed by biological, environmental and psychosocial factors. Thus FTT is not a diagnosis by itself but is a sign that has multiple etiologies with long-term effects on stature, development and cognitive functions.

### DEFINITION

In routine practice, FTT is best defined as poor physical growth diagnosed by observation over a period of time using reference growth charts. Although anthropometric criteria form the basis of defining FTT, there is no consensus on the definition. Use of a single parameter like weight has been shown to have low positive predictive value for true undernutrition. It is thus suggested to use more than one criterion to define FTT.

FTT can be defined if any of the following criteria are met on multiple occasions on follow-up:

- Weight for age less than 5th percentile
- Weight deceleration crossing two major percentile lines
- Weight velocity less than 5th percentile
- Weight less than 75% of median weight for age
- Weight less than 75% of median weight for length
- Length for age less than 5th percentile
- Body mass index (BMI) less than 5th percentile for age and gender.

In any nutritional deficiency state, weight gets affected earlier and to a greater extent as compared to linear growth or growth of head circumference which get affected with severe or prolonged nutritional deprivation.

As weight is accepted as the simplest and most reasonable marker of FTT, the condition has been now renamed as *weight faltering*. FTT/weight faltering is commonly defined as weight less than 5th percentile for age on two or more occasions and/or weight crosses two major percentile lines over time. Weight faltering is again a description of a growth pattern rather than a disorder. If we look at normal growth pattern 5% of all children will fulfil the above criteria of weight faltering and thus may be labeled FTT causing not only anxiety amongst parents and caretakers but also initiating interventions where none may be required for most children.

### ASSESSMENT OF GROWTH

Accurate measurement of weight and height/length, head circumference on multiple visits and plotting on standardized growth curve is essential for defining FTT.

The technique of measurement of the various anthropometric parameters and their interpretation using an appropriate growth reference has been already described in the chapter 19.3 on assessment of physical growth. In children born premature, the anthropometric parameters should be plotted at corrected chronological age, calculated as postnatal age at examination minus number of weeks born premature. For example, a baby born at 32 weeks gestational age is 8 weeks premature (40–32) and at 9 months of chronological age the corrected age would be 7 months (9–2 months). There is no consensus as to how long to correct for the prematurity as the catch-up growth is dependent on degree of prematurity, chronological age at assessment, genetic potential, ethnicity, etc. Most experts prefer to correct for prematurity till 18 months of age for head circumference, 24 months of age for weight and 40 months of age for stature. It is expected that more premature a baby, the catch-up growth would continue for a longer period of time. In UK, it is accepted to correct for prematurity all the three parameters namely weight, height/length and head circumference till 2 years of chronological age for children born before 32 weeks of gestation and until 12 months of chronological age for babies born between 32 weeks and 36 weeks gestation. Despite correction for prematurity when a child remains small, assessment of velocity of growth for corrected age or weight for length/height helps as they would be as per normal reference standard. The expected rate of daily weight gain at different ages is given in **Table 1**.

Another aspect of growth in infancy which confounds the definition of FTT is the normal variation in growth seen in the first 2 years of life. Some children may show a *catch-down* in growth as per their genetic potential, in the first 2 years of life. Although they initially shift major percentile lines in terms of weight and/or length, they continue to show a normal growth velocity subsequently. Babies born to short parents, large for gestational age newborns and those with constitutional delay, may show this physiological downward deviation from their birth centile. Thus, interpretation of growth in these children should be done on a longitudinal basis and in the correct perspective.

**Table 1** Expected daily weight gain at different ages

Age	Expected daily weight gain (g/day)
0–3 months	26–31
3–6 months	17–18
6–9 months	12–13
9–12 months	9–13
1–3 years	7–9

### EPIDEMIOLOGY

The prevalence of FTT is dependent on the definition, the reference standard used, the population studied, the demography of the population sample whether rural or urban and whether studied in in-hospital setting or primary care setting.

Nearly 80% of children with FTT present in the first 18 months of life. In the US, FTT is seen in 5–10% of children in primary care setting and 3–5% of children in hospital setting. In India as per the National Family Health Survey-3 (NFHS-3, 2005–2006) using World Health Organization growth standards, 22.9% children under 3 years are wasted with a higher prevalence in rural (24.1%) as compared to urban (19.1%) areas. There seems to be an increase in number of children who are wasted as compared to NFHS-2 (1998–1999) where 19.7% children under 3 years were reported as wasted.

Failure to assess growth parameters, incorrect measuring technique and faulty plotting or interpretation may lead to failure to correctly detect FTT in many children. In a study from UK, 54% children with FTT were undiagnosed by the primary care physicians and a diagnosis was delayed in 41% due to incorrect plotting of growth parameters. In some population series, nearly 33% children with FTT were undiagnosed. This is usually due to poor physician awareness, motivation and lack of time to assess growth parameters in a busy clinic.

## ETIOLOGY

The etiology is multifactorial with interplay of biological, environmental and psychosocial effects. The traditional etiological classification of FTT as organic or nonorganic is no longer exclusive as there is often a significant overlap between the two conditions and they may coexist. A child with an organ system disease as a cause of FTT could have an associated psychological affecter caused by poor parenting due to stress. As the underlying pathology is nutritional deficiency, it is prudent to classify FTT based on calorie deficit as due to inadequate intake, improper or poor absorption, and increased requirement due either to increased metabolism or defective utilization (**Table 2**).

Inadequate calorie intake is the most common cause of FTT. In Indian scenario poor calorie intake is often due to lack of availability of nutrients due to poor purchasing capacity or inadequate knowledge of appropriate feeding. Organic causes that limit the food intake while increasing the caloric requirement, especially recurrent respiratory infection, recurrent diarrhea, infections like tuberculosis and human immunodeficiency virus (HIV) are important contributors to causation of FTT.

*Environmental enteropathy* (tropical enteropathy), a recently recognized entity causing FTT is caused by poor hygiene and sanitation. In the presence of unhygienic environment, there is a constant orofecal contamination leading to repeated episodes of diarrhea which is sometimes self-limiting. Repeated gastrointestinal (GI) infection leads to mucosal inflammation and structural changes in small intestine resulting in mucosal disruption causing malabsorption, altered mucosal immunity causing repeated infections—a vicious cycle leading to malnutrition and FTT. In a study from Vellore, environmental enteropathy was found in babies as young as 8 weeks of age.

Psychosocial causes of FTT are also increasingly recognized in Indian scenario. Poor parenting skills, lack of knowledge of calorie rich diets, single parent, stress of living, substance abuse (alcohol, tobacco and drugs) and child abuse are not uncommon especially in urban population.

**Table 2** Etiology of failure to thrive

<i>Inadequate calorie intake</i>	<i>Inadequate calorie absorption</i>
<b>Poor feeding</b> Breastfeeding problems Incorrect formula/top milk feeds Inadequate number of feedings per day Underfeeding (lack of food/lack of knowledge) Difficulty/delayed weaning Food faddism Misreading signals of satiety/hunger Coercive feeding Autonomy struggle Highly distractible child/environment Neglect, abuse, parental mental illness <i>Neurological dysfunction:</i> Oromotor dysfunction, sensory based feeding disorder, autism, swallowing difficulty Gastroesophageal reflux disease (GERD)	<b>Malabsorption syndromes</b> Chronic diarrhea Frequent vomiting Environmental enteropathy Celiac disease Cystic fibrosis Pancreatic insufficiency Protein-losing enteropathy Chronic liver disease Short gut syndrome Inborn errors of metabolism
<b>Psychosocial causes</b> Poverty Social isolation, stresses in life Single parent, poor parenting skills, parental cognitive problems Substance abuse, physical abuse Psychopathy Poor child-parent interactions	<b>Food allergy/intolerance</b> Milk protein allergy
	<b>Intestinal parasites</b>
<i>Excess calorie expenditure due to increased requirement*</i>	<i>Excess calorie expenditure due to defective utilization*</i>
<b>Systemic illnesses</b> <i>Cardiac:</i> Cyanotic/acyanotic heart disease, congestive cardiac failure, vascular anomalies <i>Pulmonary:</i> Chronic lung disease, severe asthma, chronic respiratory failure, hypoxia <i>Renal:</i> Chronic renal failure, renal tubular acidosis <i>Endocrine:</i> Hyperthyroidism, diabetes mellitus, diabetes insipidus, adrenal insufficiency, growth hormone deficiency <i>Infections:</i> Tuberculosis, human immunodeficiency virus (HIV), congenital infections <i>Others:</i> Malignancy, systemic inflammatory disorders	<b>Chromosomal disorders</b> Trisomy 13, 21, 18 <b>Dysmorphic/Genetic syndromes</b> Russell-Silver syndrome Seckel syndrome Prader-Willi syndrome <b>Storage disorders</b> Glycogen storage disorder <b>Inborn errors of metabolism</b> Aminoacidopathies Recurrent hypoglycemia Organic acidemia

\*Failure to thrive (FTT) usually manifests by 8 weeks of age

## CLINICAL FEATURES

The clinical presentation of FTT depends on the age at onset, associated symptoms, severity of malnutrition and the degree of impairment of growth parameters. The correlation of deceleration of weight as compared to length/height and head circumference gives a possible etiological clue. Children with nutritional deficiency initially have poor weight velocity followed by slow deceleration of height velocity and then poor head growth as compared to children with normal variants where the velocity of growth will be normal.

Children with systemic illnesses causing FTT may manifest as early as 8 weeks of age depending upon age at onset of illness and have more severe weight deficit as compared to children with behavioral difficulties leading to poor feeding who may present late. Presence of associated symptoms like respiratory distress, cyanosis, recurrent diarrhea, vomiting, jaundice and food allergy is suggestive of an underlying illness. In children with FTT due to organic causes, presence of dysmorphic features, anomalies like cleft lip or palate, cyanosis, respiratory distress, cardiac murmurs, developmental delay and tone abnormalities should be evaluated. Some conditions such as food allergies, chronic renal insufficiencies and celiac disease can have subtle presentation and need careful evaluation of growth over multiple visits.

The assessment of severity of FTT is helpful for effective intervention. The severity of FTT can be assessed by various methods (**Table 3**). Gomez method based on child's weight as a percentage of median weight expected for age is a commonly used tool to classify severity of FTT. Wellcome method uses the child's height as percentage of expected median height for age and child's weight as a percentage of median weight for a child of his/her height. McLaren method assesses severity of malnutrition by using ratio of present weight to height as compared to median weight:height ratio for age. Besides anthropometric characteristics, children with FTT may have associated recurrent infections of respiratory, GI tracts, skin involvement in the form of dermatitis, impetigo, alopecia, associated loss of subcutaneous fat and muscle mass and features of vitamin deficiencies. Signs of neglect in the form of poor personal hygiene, uncut nails, diaper rash, dirty and soiled clothing and body louse may also be seen.

Features of abuse should be actively looked for. A child abuse is suspected if features suggestive of problems are seen in five or more organ systems, presence of five or more food allergies and absence of serious congenital anomalies or genetic defects. Presence of unexplained, unusual and multiple injury marks especially of different ages, suggests physical abuse.

## APPROACH TO DIAGNOSIS

A detailed history, thorough physical examination and careful observation of child parent interactions help in making accurate

diagnosis. Evaluation of FTT can be categorized based on the age at onset (**Table 4**).

## History

A careful dietary history is the foremost aspect of evaluation of a child with FTT. Diet assessment for meal content, meal timings, types of food, access to aerated drinks, etc., needs to be recorded. Consumption of a lot of fruit juices not only affects appetite but also does not provide enough calories. Dietary details can be obtained either based on a 3 day diet diary or 24 hours dietary recall. It is also very useful to actually observe the parent child interaction during a feeding session. Important cues like poor latching in breastfed baby, improper preparation of formula milk, gagging, vomiting, rumination, mother's response to baby's signals of satiety/hunger, feeding interactions, coercive feeding, autonomy struggle, distractibility and any stress can be observed. The quantity of feed can also be measured to assess for adequacy.

Presence of oromotor dysfunctions, swallowing difficulties, sensory based feeding problems, i.e., inability to appreciate texture of various food substances, causes poor feeding especially in early infancy. Congenital anomalies like cleft lip and palate, neuromuscular disorders causing hypotonia/hypertonia, organ system symptoms like recurrent or chronic diarrhea, vomiting, breathlessness, cyanosis, jaundice, seizures, etc., should be elicited. Contact with tuberculosis, HIV status, immunization

**Table 4** Etiology of failure to thrive

By age of onset	Likely cause
Prenatal period	Prematurity Intrauterine growth restriction (IUGR) Intrauterine infection (TORCH) Exposure to drugs/substance abuse/teratogens
Neonatal period	Breastfeeding problems Incorrect milk/formula preparation Inadequate number of feedings Poor feeding interactions, neglect Misread signals of satiety/hunger <i>Metabolic disorders:</i> Lethargy, poor feeding, seizures, dehydration, jaundice, respiratory distress, etc. <i>Chromosomal anomalies:</i> Dysmorphic features <i>Structural anomalies:</i> Cleft lip, cleft palate
3–6 months	Underfeeding (poverty, lack of knowledge) Milk protein allergy—cow's milk <i>Celiac disease:</i> On weaning to wheat containing diet Recurrent/chronic diarrhea, blood in stools, oily greasy stools, worms in stools <i>Oromotor dysfunction:</i> Poor swallowing <i>Cardiac diseases:</i> Poor feeding, suck-rest-suck, cyanosis, breathlessness <i>Gastroesophageal reflux disease:</i> Recurrent vomiting
7–12 months	Poor quality and inadequate quantity of complementary foods <i>Systemic illnesses:</i> Heart disease, liver dysfunction, repeated infections due to poor hygiene Feeding problems include difficulty to appreciate texture of various food, autonomy struggle, strict parenting approach, delayed introduction of solid food Oromotor dysfunction
> 12 months	Poor quality and inadequate quantity of complementary foods Coercive feeding, highly distractible child, distractible environment Autism and other behavioral problems Poverty, child neglect/abuse

**Table 3** Severity of failure to thrive (FTT)

Method	Mild FTT	Moderate FTT	Severe FTT
<i>Gomez classification</i> Present weight/median weight for age	75–90%	61–75%	< 60%
<i>Wellcome classification</i> Height/Median height for age Weight/Median weight for height	90–94% 80–89%	85–89% 70–80%	< 85% < 70%
<i>McLaren classification</i> (Present Weight: Height)/ (Median Weight: Height for age)	81–90%	70–80%	< 70%
<i>Classification based on height</i>	90–95%	85–89%	< 85%



history is useful to exclude associated infection as a cause. Family history of short stature, any significant illnesses and parental height need to be elicited to rule out genetic causes of short stature (**Table 5**).

### Physical Examination

Accurate measurement of the anthropometric parameters, weight, height/length, head circumference is essential for diagnosis of FTT. A meticulous plotting of these growth parameters on the reference chart is the cornerstone of accurate and timely diagnosis.

Assessment of weight for age, length for age and weight for length parameters not only helps in differentiating FTT versus constitutional or genetic causes of growth faltering, but these parameters also are used to assess severity of FTT and acute versus chronic malnutrition. In children with FTT, the weight for age is uniformly affected as also the weight velocity. In acute malnutrition weight for age is more affected as compared to chronic nutritional deprivation where length for age is affected to a similar extent as weight. Children with organic cause of FTT present earlier and have more severe weight deficit as compared to nonorganic causes

**Table 5** Clinical evaluation of failure to thrive (FTT)

<i>History</i>	<i>Interpretation</i>
<b>Diet</b>	
• Diet assessment	Quantification of total calorie intake
• Technique of milk/formula preparation	<i>Overdiluted milk:</i> Low calorie content <i>Overconcentrated milk:</i> Unpalatable
• Type of food—fruit juice, soda, aerated drinks, water, inadequate or inappropriate complementary foods	Poor calorie intake
<b>Feeding behavior</b>	
• Observed feeding session	Helps to understand behaviors like easy distractibility, proper supervision, feeding battles, parent child interactions, swallowing dysfunction
• Technique of feeding	Improper technique
• Intermittent snacks	Poor meal time eating, early satiety
<b>Medical history</b>	
• <i>Birth history:</i> Intrauterine growth retardation, prematurity, complications at birth	Catch-up growth may be incomplete in many babies
• <i>History of recurrent illness:</i> Otitis media, diarrhea, pneumonia	Inadequate catch-up growth opportunity in between illnesses
• Contact with tuberculosis, human immunodeficiency virus (HIV), recurrent infections	Tuberculosis, HIV infection, other immune deficiency states
• Stool pattern, worms in stool	Malabsorption syndrome
• Polyuria, polydipsia, FTT despite increased appetite	Renal tubular acidosis, diabetes insipidus, diabetes mellitus, hyperthyroidism
• Vomiting and reflux	Gastroesophageal reflux disease (GERD)
• <i>Past medical history:</i> Chronic anemia, asthma, renal disease, cardiac disease, liver disease	Pointers towards organic causes of FTT
• Injury marks, frequent accidents	Neglect, abuse
<b>Family history</b>	
• Parental height, sibling height	Shorter parental height and higher parity has been shown to have slow weight gain in infancy
• Any illnesses in family	Developmental delay, constitutional delay
• Discord/stressors in family	Child neglect
<b>Clinical examination</b>	<b>Interpretation</b>
<i>Anthropometry:</i> Accurate measure weight, height/length, head circumference and plot on reference growth chart	Severity of FTT
Recurrent diarrhea, anemia, poor growth, poor appetite	Celiac disease
Steatorrhea, chronic respiratory signs, bronchiectasis, salt wasting crisis, increased sweat chloride	Cystic fibrosis
Icterus, hepatomegaly, splenomegaly, pallor bleeding, ascites	Chronic liver disease
Breathlessness, with/without cyanosis, murmur	Congenital heart disease
Recurrent abdominal pain, bloody diarrhea	Milk protein allergy, inflammatory bowel disease (in older children)
Recurrent aspiration pneumonia, asthma mimic with/without vomiting	Gastroesophageal reflux disease
<i>Organ specific signs:</i> Neurological, immunological, renal, etc.	Organ specific illnesses

of FTT. Once it is ascertained that the child has FTT, it is essential to detect any features of dysmorphic/genetic syndrome, signs of any underlying organ system disease or infections and detailed evaluation for features of child abuse.

Signs of vitamin deficiencies and any danger signs should be looked for (**Fig. 1**). Presence of pallor, dry sparse hair, cracked skin, loss of subcutaneous fat, poor musculature, distension abdomen and features of sepsis are suggestive of severe FTT.



**Figure 1** An 8-week-old male child born at term with a birthweight of 1.7 kg, with severe failure to thrive (FTT) due to systemic illness—chronic liver disease, ichthyosis and sepsis. Present weight is 1.7 kg

Signs of organic causes of FTT like organomegaly, lymphadenopathy, anemia, cardiac signs like features of congestive failure, cyanosis, cardiac murmurs, pulmonary problems like respiratory distress, chronic respiratory failure, diarrhea, dehydration, and presence of recurrent unexplained injuries must be observed (**Table 5**).

Observing the parent child interactions in children with psychosocial cause of FTT is essential. Observe for eye to eye contact, response of the parent to the baby's cue of hunger or satiety. Aggression or anger while feeding on the part of parent has often caused rupture frenulum, poor feeding and feeding battles. Disinterest in feeding, anxiety also cause poor nutrient intake and FTT.

In a large number of cases, there may be no clinical features of FTT and hence serial growth monitoring is essential to diagnose these children early.

### Laboratory Evaluation

Routine laboratory testing not guided by history and physical examination has limited utility in evaluation of children with FTT. Hence laboratory investigations are recommended only in presence of clinical clues to get better yield. Complete blood counts, serum creatinine, blood urea nitrogen (BUN), electrolytes, blood sugar and urine analysis would be useful as initial screening tests. Tests for hypoproteinemia, hypoalbuminemia and calcium-phosphorus disturbances along with hepatic and renal function tests as well as stool examination for parasites and fat globules can be done in cases of severe FTT. Specific tests like antigliadin antibodies, tissue transglutaminase IgA for celiac disease, sweat chloride test in suspected cases of cystic fibrosis, venous blood gases for renal tubular disorders, metabolic screen for suspected metabolic disorders, karyotype for chromosomal disorders, etc., are done as and when indicated (**Table 6**).

**Table 6** Laboratory evaluation of failure to thrive

Tests	Interpretation
Complete blood counts	Anemia, infections
Urine analysis	Urinary tract infections
Stool examination for ova cyst, fat globules	Parasitic infestations, fat malabsorption
Total protein and albumin	Hypoproteinemia
Liver function tests: ALT, AST, PT, PTT, aPTT	Chronic liver disease
Tests for tuberculosis and congenital infections	Tuberculosis, congenital infection
Tests for HIV	HIV
Renal function tests: Serum creatinine	Chronic kidney injury
Serum electrolytes, venous blood gases	Renal tubular acidosis
Celiac screen	Celiac disease
Sweat test	Cystic fibrosis
Skeletal survey	Look for evidences of physical abuse; dysmorphic syndromes
Bone age	To differentiate genetic causes from nutritional causes: BA = CA (genetic) BA < CA (nutritional)
Thyroid function tests	Hypothyroidism/hyperthyroidism
Metabolic screen	Inborn errors of metabolism
Allergy testing	Specific food allergy
Karyotype	Chromosomal disease

**Abbreviations:** BA, bone age; CA, chronologic age; ALT, alanine aminotransferase; SGPT, serum glutamic pyruvic transaminase; AST, aspartate aminotransferase; SGOT, serum glutamic oxaloacetic transaminase; PT, prothrombin time; PTT, partial thromboplastin time; aPTT, activated partial thromboplastin time; HIV, human immunodeficiency virus; BA, bone age; CA, chronological age.

### MANAGEMENT

Failure to thrive especially in early infancy has long-term effect on stature and neurocognitive function. Prompt diagnosis and early intervention helps in preventing these irreversible deficits. The goals of treatment include:

- Improving nutritional status through provision of adequate nutrition
- Treating the underlying medical cause of FTT, if present
- Improving caregiver's ability to provide appropriate and adequate diet to the child through education, capability enhancement and psychosocial support
- Preventing a relapse of FTT through close follow-up and monitoring.

The management depends on the severity of FTT. In mild FTT, increase in nutrient intake can be achieved by making appropriate changes in diet content, feeding schedule and/or feeding environment. Continuing to provide home-based food with correction of faulty feeding practices and suitable modifications to improve calorie content are helpful. Feeding environment with minimal distractions helps in achieving better intake of food and less of *food battles*. Thus there is no need for any special diet or drugs in mild FTT. These children should be regularly monitored to document a catch-up in weight.

Moderate FTT needs a multidisciplinary team comprising of a pediatrician, dietician, child psychologist, developmental

specialist, social worker and a nurse practitioner for optimum management. Although these children can be managed in outpatient clinics, frequent follow-up and sometimes home visits may be needed. Diet modified to provide calorie-dense food, treatment of any underlying medical illnesses, improving psychosocial problems, changing feeding environment, feeding routine may help in treatment of these children. Failure to exhibit a catch-up growth is an indication for admission for dietary management under observation and evaluation of an underlying organic cause. Children with severe FTT need to be hospitalized so as to prevent further deterioration of nutritional status and to provide controlled refeeding under direct observation. Indications for hospitalization in a child with FTT include:

- Severe FTT
- Underlying medical problem requiring in-hospital care
- Failure to respond to several months of outpatient management
- Psychosocial circumstances that put the child at risk for harm
- Practicality of distance, transportation, or family psychosocial problems precluding outpatient management.

*For management of severe acute malnutrition in hospital setting please refer to the Section 23 on Nutritional Disorders.*

### Calorie Requirement

In children with FTT improving intake of calorie and other micronutrients and vitamins is important to achieve catch-up growth. High calorie diet should be provided at 150% of recommended daily calorie intake based on the expected weight and not the actual weight. Thus a 1-year-old child with FTT, who is expected to weigh 10 kg, will need 1,100 Cal/day. This can be achieved by gradually increasing food intake or by enrichment of food to increase calorie content.

Increasing food intake helps in catch-up growth in scenarios of insufficient availability of food such as poverty, nonavailability of food, lack of knowledge of adequate and appropriate food and food faddism.

Increasing calorie content of food can be achieved by fortifying food with carbohydrates and/or fat bearing in mind the calorie density so as not to cause an imbalance of ratio of calorie, protein, water and nutrients. Calorie content can be increased by providing concentrated formula milk, or by adding cereals, pureed food or cream, to milk.

Multivitamins as per recommended daily allowance must be added. It has been shown that addition of zinc helps reduce the energy cost of weight gain during catch-up growth.

As consumption of excess fluids decreases the appetite for solid food, intake of fruit juices should be avoided/restricted to 8–12 oz per day. The focus should instead be on addition of fresh fruits and vegetables. At meal times solids should be offered before liquids.

### Feeding Pattern

As far as possible a constant feeding schedule as per the age of the child should be followed. An infant will need to feed 8–12 times per day in the first 4 months as compared to 6–8 feeds per day in later infancy. Children more than 1 year of age should follow the pattern of *rule of 3*, i.e., 3 meals, 3 snacks and 3 choices. Grazing diet should be avoided and snacks should be timed at least 1 hour before meal time.

Feeding environment should be comfortable and relaxed with minimum distractions. Eating with other family members should be encouraged. Forced feeding, strict parenting approach, autonomy struggles lead to food battles and create unpleasantness

and should be avoided. Regular interaction between physician, dietician, nurse practitioner, and psychologist is essential for achieving a good catch-up growth.

### Treatment of Underlying Medical Illness

Organic cause of FTT should be treated with appropriate management. Pancreatic enzyme replacement in fat malabsorption, cystic fibrosis and other conditions with pancreatic insufficiency, gluten free diet in celiac disease, avoidance of allergic substances in food allergy, specific treatment for chronic liver disease, congenital heart disease, renal failure, renal tubular acidosis, and endocrine disturbances should be provided. Immunization as per national schedule should be administered. Any intercurrent illness should be treated promptly.

### Psychosocial Interventions

Interventions to improve parent-child interactions through group activities, empowerment through provision of knowledge, guidance and support are important aspects of management of FTT, both organic and nonorganic.

### Follow-up and Monitoring

Catch-up growth is achieved with appropriate nutritional, medical, behavioral and environmental interventions within 3 days to 2 weeks based on severity of FTT. Usually 6–9 months of catch-up growth is essential to restore weight for height. The restoration of normal height velocity takes longer as compared to weight recovery and hence close monitoring, continued nutritional intervention and ongoing care are essential. At each follow-up visit besides anthropometric assessment, developmental and behavioral monitoring should continue.

Not achieving a catch-up growth despite 2–3 months of adequate nutritional intervention is treatment failure and calls for hospitalization and detailed evaluation of organic causes of FTT.

### OUTCOME AND PROGNOSIS

Failure to thrive is a nutritional syndrome with long-term effects on stature, developmental and cognitive functions. Although the final height is dependent on parental height and genetic potential, the severity of FTT, age at onset of FTT and severity of associated underlying medical illness contribute to the final height outcome. Effect of FTT with onset in first 6 months of life is difficult to overcome and these children remain stunted despite adequate treatment. Various follow-up studies show a good catch-up for weight, though the stature remains affected in nearly 25–60% cases on long-term follow-up.

A systematic review of long-term outcome of children with FTT showed that these children remain shorter, lighter and score less on psychomotor developmental scales than their peers. It is nevertheless a challenge for physicians to identify children with FTT early, make an etiological diagnosis and initiate interventions as required to prevent long-term sequel related to stature, developmental and cognitive outcome.

More recently malnutrition and enteric infection in early infancy have been linked to risk factors for cardiovascular disease and type 2 diabetes mellitus in adulthood. Although the etiology remains unclear, both calorie deficit and infection-related inflammation are contributors to future cardiovascular and metabolic disease besides having effect on stature and neurocognitive development. Given the long-term implications on stature, neurocognitive development and adult diseases, prevention of FTT is an important aspect of child care.

### IN A NUTSHELL

1. Failure to thrive denotes inadequate growth especially in early childhood, due to lack of sufficient *usable* nutrition contributed by biological, environmental and psychosocial factors.
2. Accurate measurement of the anthropometric parameters and their meticulous plotting on the reference chart is the cornerstone of accurate and timely diagnosis.
3. Inadequate calorie intake is the most common cause of FTT. Organic and nonorganic causes of FTT may often coexist in the same child.
4. FTT has long-term implications on stature, neurocognitive development and vulnerability for adult-onset diseases. Hence prevention of FTT and early diagnosis are important aspects of child care.

### MORE ON THIS TOPIC

Cole SZ, Lanham JS. Failure to Thrive: an update. *Am Fam Physician*. 2011;83(7):829-34.

Rudolf MC, Logan S. What is the long-term outcome for children who fail to thrive? A systematic review. *Arch Dis Child*. 2005;90:925-31.

Yoo SD, Hwang EH, Lee YJ, Park JH. Clinical characteristics of failure to thrive in infant and toddler: organic vs. nonorganic. *Pediatr Gastroenterol Hepatol Nutr*. 2013;16:261-8.



## Chapter 19.7

# Overweight and Obesity

Rajesh Khadgawat, Aashima Dabas

Childhood obesity is a major public health problem of the modern world which has shown increasing trends globally in the recent years. The World Health Organization (WHO) defines childhood obesity as one of the most serious public health challenges of the 21st century, due to its rapidly increasing prevalence and tracking seen till adulthood. Out of the projected 1.5 billion overweight people in 2015, it is estimated that children will constitute around 10% and approximately 75% of these will be from developing countries. There has been a parallel rise of conditions like dyslipidemia, hypertension, abnormal glucose tolerance, and reduced health-related quality of life in pediatric age group which is attributed to increased prevalence of obesity in the population. India is fighting a dual problem; on one hand malnutrition is still widely prevalent while on other hand, childhood obesity is becoming frequent in urban locations particularly among children of higher socioeconomic status.

## EPIDEMIOLOGY

The prevalence of overweight/obesity is dramatically higher in the developed countries as compared to the developing world. However, in recent past, it has almost plateaued after introduction of obesity prevention and control programs at community level. On the contrary, obesity still remains a big challenge in developing countries. Cross-sectional studies across India have shown prevalence of overweight in 10–14% and obesity in 3–6% of pediatric population in the last few years. Obesity in Indian preschool age group has not been well studied but available data indicates rising prevalence.

Obesity can occur at any age, but the three most vulnerable periods for its development are prenatal period, age of 5–7 years and adolescence. More than 90% of the fetal fat deposition occurs in the last trimester of pregnancy. During early infancy (4–6 months), fat deposition accounts for 40–65% of total body weight gain. This burst of fat accumulation is followed by a gradual decline to a *lean state* by 5–6 years of age. This is followed by rapid gain in fat as well as muscle mass during adolescence under influence of sex steroids.

## DEFINITION

Obesity is excess accumulation of body fat. The definition of *excess* varies with the parameter used for measuring. Measurement of weight is the earliest parameter used for definition of obesity; weight more than 120% of expected was considered as excess for defining obesity in adults. One of the major drawbacks of using a weight-based criterion is its dependency on height. This led to use of weight corrected for height defined as *body mass index (BMI)*. The gold standard for fat measurement is hydrostatic/underwater weighing. Other parameters like waist circumference (WC), waist-hip ratio (WHR), total body fat, fat mass index have also been used, but BMI remains most widely accepted and used parameter for defining obesity in children.

## Body Mass Index

In relation to age, BMI progressively increases after birth to around 1 year, followed by decrease till the age of 6 years, and then increases through the remainder of the childhood and adolescence. The point of the lowest level of BMI around 6 years after which it starts increasing again is termed as *adiposity rebound*. Adiposity starting earlier than the time expected for obesity rebound is associated with increased risk of subsequent obesity. In children, there is no single cut-off of BMI for definition (as in adults) in view of rapid

changes in BMI during puberty. Age and gender specific BMI charts have been used by many countries for definition of obesity. Based on National Health and Nutrition Examination Survey (NHANES, USA) data, an expert committee recommended age and gender matched BMI greater than 95th centile as cut-off for *obesity* and that between 85th and 95th centiles as *overweight*. UK90 BMI charts are used in UK where obesity is defined as age and gender matched BMI greater than 95th centile. Recently BMI reference data for Indian children have been published (See Chapter 19.3).

The International Obesity Task Force (IOTF) has set age and gender specific cut-offs for defining *overweight* and *obesity* based on BMI data from children in six high and middle income countries. These charts have yielded gender specific cut-offs of BMI at six monthly age intervals. The IOTF data was pooled together from six countries (data collection period 1963–1993) and centile curves were drawn in such a way that they pass through the points of 25 kg/m<sup>2</sup> and 30 kg/m<sup>2</sup> (reflecting WHO recommended definitions of adult overweight and obese) at age 18. Although, the available reference data do not represent the world's population, these cut-offs are widely used all over the world for both clinical, research as well as epidemiological purposes. A major shortcoming of BMI is that it measures excess weight relative to height, and not excess body fat. Therefore, it cannot differentiate between muscular and fatty bodies.

Other methods of body fat estimation are summarized in Table 1.

## CLASSIFICATION

### Primary/Constitutional Obesity

This is by far the most common type of obesity seen in children and responsible for more than 95% cases. Its cause is primarily nutritional and it results from an imbalance between energy intake and energy expenditure. It is not explainable by known genetic or metabolic defects. However, with improved understanding of epigenetics, more cases of primary obesity can be explained by single gene disorders.

### Secondary Obesity

These are uncommon causes of obesity seen in practice.

- **Monogenic** Monogenic obesity is associated with a single gene mutation, insertion or deletion (e.g., a mutation in the leptin/melanocortin pathway, resulting in severe obesity). Certain genes near which variants have been discovered for children with obesity include fat mass and obesity associated gene (*FTO*), melanocortin-4 receptor (*MC4R*) and others such as *ADCY5*, *ETV5*, *KCTD15*, *GNPDA2* and *TMEM18* loci.
- **Polygenic** Polygenic obesity results from a complex interaction of multiple genetic, social, environmental, and behavioral influences, e.g., single nucleotide polymorphisms of the *PSMA6* and *PSMA3* proteosomal genes affecting gene expression.
- **Syndromic** It involves concurrent mental retardation, dysmorphism, and/or organ-specific developmental abnormalities, e.g., Prader-Willi syndrome (PWS), Down syndrome, Albright hereditary osteodystrophy, Bardet-Biedl syndrome, fragile X syndrome, Cohen syndrome and Carpenter syndrome. PWS results from deletion of paternal deoxyribonucleic acid (DNA) in the region of long arm of chromosome 15 (q11–13) and manifests as neonatal hypotonia, delayed milestones, hyperphagia, obesity, short stature, delayed puberty, epilepsy and mild to moderate degree of cognitive impairment. Bardet-Biedl syndrome presents with obesity, hyperphagia, retinitis pigmentosa, polydactyly, hypogonadism and mental subnormality.
- **Endocrine** These include Cushing syndrome, pseudohypoparathyroidism and hypothyroidism and are discussed in separate chapters (Section 44).
- **Hypothalamic** This is an extreme form of obesity resulting from functional or anatomical damage to hypothalamus.

**Table 1** Available methods of body fat/body composition assessment

Method	Instrument	Available cut-offs	Role/feasibility	Comments
Hydrodensitometry (under water weighting)	Complex large equipment setting	No	Based on Archimedes' principle of buoyancy, expensive, used only in research setting	Often considered as "Gold Standard", difficult to carry out in pediatric population
Air displacement plethysmography (ADP)	Relatively smaller but costly equipment	No	Air is used in place of water, used in research setting	Useful for infants also, quick measurement
Body mass index (BMI)	Weighing machine and stadiometer	Yes	Simple, inexpensive, applicable to field studies	Does not differentiate body fat and muscle mass
Waist circumference/ Waist hip ratio (WC:WHR)	Estimate of abdominal fat, measured midway between the lateral lower rib margin and the uppermost lateral border of iliac crest, measured by measuring tape	No	Simple, reproducible, measures subcutaneous fat, applicable to field studies	Lack of valid cut-offs in children, poor correlation to estimation of visceral fat
Skin fold thickness	Old research tool, measured by caliper at different sites (biceps, triceps, subscapular, suprailiac and thigh) and an equation is used for calculation of total body fat mass	No	Low cost instrument, applicable for field studies, widely used for estimation of total body fat	Expertise needed, lack of validity, may underestimate body fat in obese, does not measure visceral fat, poor reproducibility
Ultrasound	Portable ultrasound machine	No	Portable, noninvasive, measures subcutaneous fat	Underestimates body fat in obese, interobserver variability, poor reproducibility, not cost-effective
Bioelectrical impedance analysis	Based on ability of different tissues of the body to give different resistance to flowing current in the body. This resistance is measured for total body water and fat free mass content, from which, total body fat can be calculated. Analyzer: 2/4/8 electrode	No	Portable, simple, convenient and inexpensive method for assessing adiposity	Variability with body hydration, limited availability and validity
Dual energy X-ray absorptiometry (DEXA)	Provides precise body composition analysis and is able to detect small changes in body composition in both, adults and children, DEXA machine	Yes	Often considered as gold standard, scan time is more, difficult for epidemiological studies	Requires standardization, high costs, equipment not widely available

Initially, it was described in patients with hypothalamic tumor but later, was also reported in other diseases (**Table 2**). It results from functional impairment of the hypothalamic regulatory centers especially ventromedial nucleus (VMN), which is a key regulator of appetite and weight in the human body. Markedly increased and uncontrollable urge to eat is one of the important features of this condition along with decreased physical activity. Other disturbances like autonomic imbalance, growth hormone (GH) or gonadotropins or thyroid-stimulating hormone (TSH) deficiency have also been reported. These patients also exhibit hypomobility of joints, insomnia, inappropriate behavior and emotional blunting. Obesity in these children is associated with other endocrine dysfunctions such as hyperleptinemia and hyperinsulinemia. Hyperinsulinemia in hypothalamic obesity results from altered neural regulation of the  $\beta$ -cells of pancreas, unlike peripheral insulin resistance seen in children with simple obesity. There is no single effective treatment in such cases as hyperphagia is difficult to control; both drugs and surgery have shown limited results.

- **Drugs** Certain drugs like antiepileptics, steroids, estrogen can also result in substantial weight gain.

## PATHOPHYSIOLOGY

Unlike earlier belief, the adipocytes are not mere passive energy storage sites. The preadipocytes are capable of functioning as macrophages and producing various inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor alpha (TNF $\alpha$ ), and adiponectin. The adipocytes also produce adipokines which regulate concentrations

of C-reactive protein and interleukin-10 (IL-10). Other inflammatory molecules produced by adipocytes include leptons, lipoprotein lipase, angiotensin, atrial natriuretic peptide, free fatty acids, insulin-like growth factors, etc. These molecules are responsible for insulin resistance and endothelial dysfunction as seen in obesity.

Appetite and satiety control is a complex interplay between leptin (hormone secreted by adipose tissue) and ghrelin (hormone secreted by gastric fundus) with support from other cytokine and hormones. During fasting, low leptin levels increase appetite and decrease energy expenditure by stimulating neuropeptide-Y synthesis and inhibiting sympathetic and other catabolic pathways. Conversely, during feeding and weight gain, increased leptin levels decrease appetite and increase energy expenditure through release of melanocortin and corticotropin-releasing hormone (CRH). The integrated output of these molecules leads to the behavioral and neurohumoral outputs to maintain body weight and adiposity. Both leptin and insulin enter the brain and act as inhibitors of food intake, activate thermogenesis and inhibit the production of proopiomelanocortin (POMC) which has catabolic properties. **Table 3** summarizes the role of hormones and other mediators in pathophysiology of fat regulation.

## Risk Factors Associated with Obesity

The factors influencing obesity start with in utero fetal programming and continue into adulthood with lifestyle/behavioral factors. The various sociodemographic risk factors, associated with obesity in children and adolescence are summarized in **Table 4**.

**Table 2** Causes of hypothalamic obesity in children and adolescents

• <i>Tumors:</i> Primary as well as secondary tumors involving hypothalamus—craniopharyngioma the most common cause
• <i>Inflammatory lesions of hypothalamus:</i> Tuberculosis, sarcoidosis, arachnoiditis, histiocytosis X, viral encephalitis
• <i>Head trauma or neurosurgery</i> in the vicinity of hypothalamus
• <i>Cranial radiotherapy</i>
• <i>Single gene mutations:</i> Leptin, leptin receptor, CART, POMC, prohormone convertase-1, MC4R, BDNF (TrkB), single-minded 1 (SIM-1)
• <i>Genetic syndromes:</i> Prader-Willi syndrome, Bardet-Biedl syndrome, Rapid-onset obesity with hypoventilation, hypothalamic dysfunction, and autonomic dysregulation (ROHHAD) syndrome
• <i>Psychotropic drugs:</i> Antipsychotic and antidepressants drugs

**Table 3** Various cytokines/adipokines and hormones implicated in pathogenesis of obesity

Hormone/ cytokine	Site of production/ secretion	Physiological effects/function
Leptin (satiety hormone)	Adipocytes	Crosses the blood-brain barrier and inhibits energy intake at the level of hypothalamus, thus regulates the amount of fat stored in the body by modulating food intake and energy expenditure
Ghrelin (hunger hormone)	Stomach	Regulates energy balance, appetite and promotes fat deposition by decreasing usage of fat for metabolism
Adiponectin	Adipose tissue	Insulin-sensitizing, anti-inflammatory and antiapoptotic actions, also increases energy expenditure and cause weight loss. Levels are inversely correlated with body fat percentage in adults
Tumor necrosis factor (TNF)	Macrophages and other immune cells, also by adipose tissue	Multifunctional cytokine implicated in inflammation, apoptosis and cell survival as well as induction of insulin resistance Major link between insulin resistance and obesity
Obestatin	Stomach and small intestine	Postulated to influence long-term weight control
Orexins A and B	Hypothalamus	Primarily involved in the stimulation of food intake
Resistin	Macrophages	Induces insulin resistance
Interleukin-6 (IL-6)	Macrophages and other immune cells	Proinflammatory cytokine, link between obesity and insulin resistance
Apelin, Visfatin, Vaspin	Adipose tissue	Not clear role, probably link between obesity and associated complications like insulin resistance and atherosclerosis

Abbreviation: POMC, proopiomelanocortin.

## COMPLICATIONS AND COMORBIDITIES

Obesity in childhood and adolescence is associated two types of risk/complications: (1) those manifesting during childhood and adolescence; (2) those whose risk of occurrence during adulthood

**Table 4** Risk factors/etiology of childhood obesity

Risk factor	Details	Comments
Prenatal factors	Growth retardation (IUGR), maternal pre-pregnancy overweight	Postulation of Barker's hypothesis on fetal origin of adult diseases
Early feeding practices	Lack of breastfeeding, increased formula consumption during early infancy, complementary feeding before 4 months	Breastmilk contains bioactive factors which inhibit adipocyte differentiation. Preterm infants fed on human milk have lower leptin levels in adolescence than formula-fed infants
Dietary	Increased junk food consumption, sweetened beverages, less fiber in diet	
Lifestyle	Increased screen time, lack of physical activities at home and school, shorter and irregular sleep duration	Electronic media exhausts the available play time. It is frequently associated with unhealthy snacking
Demographic	Parental overweight, low socioeconomic status and low parental education	Obesity higher in low socioeconomic class as lower parental education and food scarcity encourages habitual energy intake higher than energy expenditure with issues of healthy and nutritious food procurement
Medications/toxins	Drugs like antipsychotics (olanzapine, risperidone, antiepileptics and glucocorticoids. Toxins like endocrine disrupting chemicals (EDC) and bisphenol-A	Compounds like Bisphenol-A are used in packaging of common food stuffs like disposable plastics, cans and plastic packaging

Abbreviation: IUGR, intrauterine growth retardation.

is increased, these are summarized in **Table 5**. In addition, a constellation of these metabolic risk factors are increasingly being recognized among overweight and obese children known as *metabolic syndrome*. **Table 6** defines metabolic syndrome in children as per the classification by International Diabetic Federation (IDF).

## Long-Term Risk Associated with Childhood Obesity

Obese children and adolescents are more likely to become obese adults, and are therefore at higher risk of chronic noncommunicable diseases including hypertension, cardiovascular disease, dyslipidemia, insulin resistance and type 2 diabetes. The factors associated with persistence of childhood and adolescent obesity into adulthood obesity are severity of obesity, early age of onset of obesity and history of obesity in parents.

## EVALUATION

The main aims in evaluating a child who presents with obesity is to first ascertain the cause of obesity—whether primary or secondary and subsequently, assessment of obesity associated comorbidities and risk factors.

**Table 5** Comorbidities linked with obesity in children and adolescents

<i>System</i>	<i>Comorbidity/disease risk in childhood</i>	<i>Comorbidity/disease risk in adulthood</i>
Metabolic	Insulin resistance, dyslipidemia, impaired glucose tolerance, metabolic syndrome	Metabolic syndrome, type 2 diabetes
Cardiovascular	Hypertension, increased vascular stiffness	Atherosclerosis, left ventricular hypertrophy, diastolic dysfunction
Respiratory	Sleep abnormalities, asthma, obstructive sleep apnea syndrome (OSAS)	(same as during childhood)
Musculoskeletal	Slipped capital femoral epiphysis, tibia vara	Osteopenia
Gastrointestinal	Gastroesophageal reflux disease, nonalcoholic fatty liver	Nonalcoholic fatty liver, cholelithiasis, hernia
Endocrine	Early puberty in girls, hyperandrogenism and polycystic ovarian syndrome in girls	Type 2 diabetes
Psychosocial	Low self-esteem, depression, anxiety, social isolation	(same as during childhood)
Dermatological	Striae distensae, cellulitis, intertrigo, acanthosis nigricans, intertrigo, carbuncles, acrochordon (skin tags)	(same as during childhood)
Miscellaneous	Subclinical inflammation (elevated acute phase reactants), proteinuria, pseudotumor cerebri, meralgia paresthetica	(same as during childhood)

## History

A detailed clinical evaluation is mandatory in all children presenting with overweight/obesity; this may give important information regarding diagnosis and management, especially diagnosis of secondary obesity. Apart from general history taking in all subjects, following points should also be elucidated:

- History of maternal gestational diabetes or any other complication of pregnancy like gestational hypertension, intrauterine growth restriction (IUGR)
- Birthweight

- Weight gain during infancy, toddler and adolescent age groups
- Detailed history of sleep pattern including daytime somnolence
- Family history of obesity, diabetes in grandparents, parents and siblings, history of premature coronary artery disease (CAD)—clinically evident CAD below 55 years in men and below 65 years in women
- History of medications/supplements by the child—especially about use of steroids or psychotropic medications
- History of use of nutritional supplements for weight loss or height gain
- Developmental assessment—age of attainment of milestones, current school performance, any developmental disabilities (more likely to be affected in syndromic or endocrine types of obesity)
- Menstrual history in girls—age of menarche, menstrual irregularities.

## Examination

Apart from routine general and systemic physical examination, following should be recorded in all subjects with overweight and obesity:

- Anthropometric measurement—height, weight, waist and hip circumferences
- Blood pressure
- Signs of insulin resistance—acanthosis nigricans and skin tags
- Signs of hyperandrogenism (girls)—acne, hirsutism and increased hair fall
- Any dysmorphic feature/stigmata which may suggest secondary cause of obesity
- Pubertal status
- Psychiatric evaluation is very important and should be done in all children where any psychological maladjustment or disorder is suspected. It should be done only by professionals who have experience in dealing with psychological problems in children.

## Investigations

It is crucial to differentiate between primary and secondary obesity to plan subsequent work-up and management for the child. Children with primary obesity have normal or slightly accelerated growth and their bone age corresponds to age and height. However, those with secondary obesity generally have stigmata of underlying pathological process in case of genetic/endocrine causes such as dysmorphism, skin manifestations, etc. They are short and have delayed bone age. The distribution of fat is predominantly central in these children. Children with secondary causes may also have developmental delay/intellectual impairment and deviant sexual maturity (retarded/accelerated).

**Table 6** Definition of metabolic syndrome in children as per International Diabetic Federation (IDF)

<i>Age group (years)</i>	<i>Waist circumference (WC)</i>	<i>Serum triglyceride</i>	<i>Serum HDL-cholesterol</i>	<i>Blood pressure</i>	<i>Fasting blood sugar</i>
6–< 10	> 90th centile <sup>#</sup>	Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, type 2 diabetes (T2DM), dyslipidemia, cardiovascular disease, hypertension and/or obesity			
≥ 10–< 16	> 90th centile <sup>#</sup> or adult cut-off if lower	≥ 150 mg/dL	< 40 mg/dL	Systolic > 130 mm Hg or diastolic > 85 mm Hg <sup>#</sup>	≥ 100 mg/dL or known T2DM
≥ 16	WC ≥ 94 cm for men and ≥ 80 cm for women plus any two of the next four factors	≥ 150 mg/dL	< 40 mg/dL for men < 50 mg/dL for women	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension	≥ 100 mg/dL or known T2DM

\*Age specific cut-offs for defining hypertension in Indian children

Abbreviation: HDL, high density lipoprotein

<sup>#</sup>National High Blood Pressure Education Program recommends blood pressure cut-off points of > 90th or > 95th percentile adjusted for height, age, and gender



**Table 7** Blood investigations required in evaluation of obesity

Investigations routinely required in evaluation of obesity	Investigations required only if clinical examinations suggest
<ul style="list-style-type: none"> <li>Complete blood count and blood film</li> <li>Liver and renal function tests including electrolytes</li> <li>Fasting lipid profile</li> <li>Oral glucose tolerance test—with 1.75 g glucose/kg body weight with maximum of 75 g; samples at 0 and 120 minutes</li> </ul>	<ul style="list-style-type: none"> <li>Tests of thyroid functions</li> <li>Tests of cortisol axis—overnight dexamethasone suppression test</li> <li>Tests of gonadal axis—serum LH/FSH/testosterone</li> <li>X-rays hand for bone age assessment</li> <li>Tests of growth hormone axis</li> <li>Serum vitamin D/parathyroid hormone—in subjects with skeletal symptoms</li> <li>Serum insulin/C-peptide—only in research settings</li> <li>Glycosylated hemoglobin (HbA1c)—no proven usefulness in children</li> </ul>

Abbreviations: LH, luteinizing hormone; FSH, follicle-stimulating hormone.

Basic and limited laboratory investigations are advisable in obese and overweight children to assess for associated metabolic abnormalities (**Table 7**). When secondary obesity is suspected, a detailed work-up and opinion of concerned specialist may be required.

## PREVENTION

Prevention of obesity begins with maternal health promotion activities before delivery of the child to prevent fetal growth restriction and ensure smooth antenatal course. Primary prevention of obesity is targeted at all levels, i.e., family, school, health professionals, government, industry and media. The *Global Strategy on Diet, Physical Activity and Health (DPAS)* was developed by the WHO in 2004. The four main objectives were:

1. To encourage the implementation of public health action and preventative intervention to reduce the risk factors resulting from unhealthy diet and physical inactivity.
2. To increase recognition of the implications of unhealthy diet and inadequate physical activity levels and knowledge of preventative measures.
3. To promote policies and action plans at all levels to address diet and physical activity behaviors.
4. To encourage monitoring, evaluation and further research.

The preventive strategies at individual level include changes in diet, lifestyle and physical activity as well as behavior.

## Diet

Health promotion activities should begin in early infancy reinforcing exclusive breastfeeding, timely complementary feeding and healthy feeding practices. As per dietary recommendations by American Academy of Pediatrics (AAP), no fat restriction should be done for infants younger than 2 years. For children older than 2 years, fat should contribute 20–30% of total calories. The fiber content in the diet should be approximately  $\text{age} + 5$  in grams. Feeding modifications suggested are:

- A variety of food products which are nutrient-rich and less energy dense should be included in the diet. The *traffic-light* diet approach should be emphasized—*Green (go)* for foods to be consumed in unlimited quantities like fruits and vegetables; *yellow foods (caution)* which have average nutritional value like grains and lean meat and ‘red foods (stop)’ for less nutrient, high energy density like sweetened and fried foods.
- The childhood feeding patterns should be facilitatory instead of adopting a coercive attitude.

- Proper guidance on age appropriate portions and energy density of foods should be emphasized.
- Skipping breakfast, frequent snacking and eating out should be avoided.

## Lifestyle/Physical Activity

The AAP recommends no television viewing for less than 2-years-old and the advised screen time (inclusive of television, computer and internet) should not exceed more than 1–2 hours per day for older children. Younger children and toddlers should have daily half to one hour of outdoor play. Older children should have moderate to vigorous exercise for 60 minutes daily of which 30 minutes should be during school time. Also, most of daily physical activity should be aerobic; however, vigorous activities which strengthen muscle and bone should also be included at least three times a week. Various studies have demonstrated that both aerobic and resistance type of exercise alone (without weight loss or calorie restriction) resulted in significant improvement in insulin sensitivity, suggesting that exercise alone is an effective therapeutic strategy for reducing insulin resistance in overweight and obese children and adolescence. In addition other activities like dance and sports are other attractive options which may be offered to a child. Sleep should be sufficient and timings should be regular. A preschooler should also have regular bedtime rules.

## Behavior

Parental motivation, commitment and simulation of healthy lifestyle are necessary. Older children should be educated and made responsible for their nutrition and exercise pattern. Facilitatory techniques include no stacking of unhealthy foods in house, setting realistic goals for exercise, positive reinforcement on successful diet change or exercise and timely monitoring.

## MANAGEMENT

The clinician should focus on child and develop a family-oriented approach with active involvement of parents. A multidisciplinary approach with a team including a pediatrician, dietician, psychologist and physical instructor is ideal. A need for a continuous life-long support is now more widely recognized due to the increasing knowledge of inherited susceptibility for developing obesity.

## Nonpharmacologic

The goals should be realistic, age-oriented and severe energy deprivation is avoided. Thus instead of a *set point*, a *settling point* for bodyweight is recommended. The weight is maintained fairly constant for long periods of time; and responsible behaviors for controlling energy intake and energy expenditure are developed influenced by environmental and cognitive stimuli. An overview of the dietary interventions is tabulated in **Table 8**.

Dietary management should be advised by qualified nutritionist or dietician in consultation with treating physician and parents. The ideal role of parents during weight-reducing period is supervision (of both physical activity and diet restriction) and inspiration for strict follow-up of advised measures.

The physical activity prescribed should be safe, developmentally appropriate, interesting and practical. It should involve the other family members too, to keep it sustainable and to improve compliance.

## Pharmacologic

Antiobesity drugs which are approved for use in adults are still being evaluated in children for their long-term safety and effect on growth. There have been instances where drugs which were approved earlier but withdrawn later due to potential side effects and safety issues (e.g., fenfluramine, sibutramine and rimonabant).

**Table 8** Dietary therapy for childhood overweight and obesity

Parameter	Age group	Weight monitoring	Recommendation
Overweight	Irrespective	Only monitoring, no targets set	Balanced diet (Traffic signal approach). Vitamin and minerals and average 1.5 liter water intake
Obese	Toddlers	Loss 0.5 kg/month	Carbohydrate as 45–65% of total calories, protein 10–20% and fat as 30–40% (< 8% as saturated)
	4–11 years	Loss 0.5 kg/month	Carbohydrate should constitute 45–65% of total calories, protein 10–30% in older children, and fat as 30–35% (< 8% as saturated)
	> 11 years	Loss 1.0 kg/week	Carbohydrate should constitute 45–65% of total calories, protein 10–30% in older children, and fat as 30–35% (< 8% as saturated)

The meta-analysis of available data for improvement in BMI with the use of these drugs in pediatric population is not more than 0.5–0.7 kg/m<sup>2</sup>, which is less than that reported by behavioral intervention trials.

The Expert Committee on Prevention and Pediatric Obesity (Endocrine Society Clinical Practice Guidelines) recommends the use of drugs for childhood obesity on individualized assessment after an adequate multidisciplinary conservative trial (generally for 6 months) has failed. Pharmacotherapy has been prescribed in children above 16 years of age who suffer from obesity-related complications. The only drug which has been approved by US Food and Drug Administration (FDA) is orlistat, and that too for use in 12–16 years old adolescents with obesity. No antiobesity drug is safe in younger than 12 years age.

### Surgical

The bariatric surgical procedures have shown good success with long-term safety in adults. These procedures can be malabsorptive, restrictive, or a combination of both. The two commonly used procedures are laparoscopic adjustable gastric banding (LAGB) and Roux-en-Y gastric bypass (RYGB). LAGB is a restrictive procedure where an adjustable plastic band is placed over stomach to divide it into two portions, proximal small pouch and distal large segment, thereby limiting amount of food to be ingested. RYGB is a combination procedure which restricts food intake as well as decreases nutrient absorption. Another procedure which is becoming popular nowadays is sleeve gastrectomy, which involves creating a tubular stomach through resection of the greater curve of the stomach. A J shaped tubular stomach is left with very limited capacity. This restrictive procedure also reduces appetite markedly. The use of surgical procedures in pediatric population is limited from case reports to very small case series only. The major concerns about these procedures in pediatric age group are ethical issues of consent from an adolescent for a nonreversible surgical procedure, absence of data on long-term safety and the effect of these procedures on growth, and development and fertility in case of girls. They may be offered to adolescents who have completed puberty (at least Tanner stage 4 or 5) with failed attempts to reduce weight by conservative methods with or without a trial of pharmacotherapy for at least 6 months and have:

- BMI more than 50 kg/m<sup>2</sup> in the absence of any comorbidity
- BMI more than 40 kg/m<sup>2</sup> and comorbidities like type 2 diabetes, obstructive sleep apnea or pseudotumor cerebri.

Although advancements in surgical techniques have made these surgeries simple with minimal complications, they should be carried out by only by experienced surgeons along with a trained team of supportive staff. A critical issue to be considered before opting for surgery is the child's and the family's motivation to adhere to advised nutritional and lifestyle related guidelines after surgery and commitment for long-term follow-up.

To summarize, obesity is an emerging chronic disease which has gained impetus since last decade or so. Childhood obesity should be treated as a serious medical illness as it has deleterious

long-term effects till adulthood. It needs to be recognized early and timely action should be instituted to prevent development of associated complications. Healthy diet and healthy lifestyle are the keys to prevent obesity and should be instituted from early childhood to be most beneficial.

### IN A NUTSHELL

1. Obesity can be either primary (constitutional) or secondary.
2. BMI is the most practical and widely used method for defining obesity in children and adolescents.
3. Age and gender based IOTF cut-off points should be used for diagnosis of obesity.
4. Asians are prone to central obesity than whites, and thus have higher risk for cardiovascular disease at lower levels of adiposity.
5. Dyslipidemia is common in overweight and obese children. Hypertriglyceridemia and low high density lipoprotein (HDL)-cholesterol levels are the most common derangement.
6. Metabolic syndrome in children (as defined by IDF) is based on raised waist circumference with any two of the following: hypertriglyceridemia, hypertension, fasting hyperglycemia or low HDL-cholesterol.
7. Evaluation of obesity includes careful history and examination to exclude secondary causes of obesity. Hormonal work-up should not be done unless clinically indicated.
8. The mainstay of therapy is conservative management which includes dietary, physical and behavioral modifications. Drugs have very limited role to play since none except orlistat are approved for use in this age group.

### MORE ON THIS TOPIC

- Arslan N, Erdur B, Aydin A. Hormones and cytokines in childhood obesity. *Indian Pediatr.* 2010;47:829-39 August GP, Caprio S, Fennoy I, et al. Prevention and treatment of pediatric obesity: an endocrine society clinical practice guideline based on expert opinion. *J Clin Endocrinol Metab.* 2008;93:4576-99.
- Barlow SE. Expert Committee recommendations regarding the prevention, assessment and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics.* 2007;120:S164-92.
- Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ.* 2000;320:1240-3.
- Khadgawat R, Marwaha RK, Tandon N, et al. Percentage body fat in apparently healthy school children from Northern India. *Indian Pediatr.* 2013;50:859-66.
- Marwaha RK, Khadgawat R, Tandon N, et al. Reference intervals of serum lipid profile in healthy Indian school children and adolescents. *Clin Chemistry.* 2011;44:760-6.
- Sherafat-Kazemzadeh R, Yanovski SZ, Yanovski JA. Pharmacotherapy for childhood obesity: present and future prospects. *Int J Obes.* 2013;37:1-15.
- Zimmet P, Alberti G, Kaufman F. International Diabetes Federation Task Force on Epidemiology and Prevention of Diabetes. The metabolic syndrome in children and adolescents. *Lancet.* 2007;369:2059-61.

## Chapter 19.8

# Abnormalities of Stature

Senthil Senniappan, Leena Patel

## SHORT STATURE

### Definition

The definition of short stature requires interpreting the height of an individual in comparison to age and gender matched peers as well as the genetic potential based on parent's heights. The simplest way to do this in clinical practice is by plotting the child's and parent's heights on growth charts derived from local reference standards. Thus, an arbitrary definition of short stature is a height less than 2 standard deviations (SD) below the mean for age and gender at a single point, irrespective of a child's growth rate and/or ethnic origin. However, this definition is not absolute.

Short stature at a particular age does not necessarily imply that the individual has always been short nor does it predict short stature in the future and as an adult. Thus the following must be taken into consideration when determining whether an individual has short stature: previous stature, gender, stage of pubertal development, parents' heights, ethnic background and the growth performance of the reference population. A child can be considered to be short if height is below  $-2$  SD, there is a significant discrepancy between the child's height centile and mid-parental height centile, and the child's height trajectory has crossed two lower centile lines. Although a normal statured individual may have a negative psychological perception of being short, this is not within the remit of this chapter.

Normal growth through childhood, adolescence and until full pubertal maturation is well characterized. Therefore any deviation from this pattern in an individual is a sensitive indicator of active pathology until proven otherwise. Deviation downwards with declining centile positions means that the individual is shorter compared to their previous height. This is described as growth failure or faltering growth and reflects suboptimal height velocity (Fig. 1). It can occur in an individual who was previously of normal, short or tall stature, and requires careful evaluation.

### Epidemiology

Since height in any population follows a normal distribution, only 2.3% of healthy children are expected to have height measurement 2 SD below the mean for the population. Therefore, the further below this cut-off that an individual's height is, the greater is the likelihood that there is a pathological explanation for the short stature.

### Etiology

For the Indian subcontinent, the conditions associated with short stature and commonly encountered by general pediatricians include:

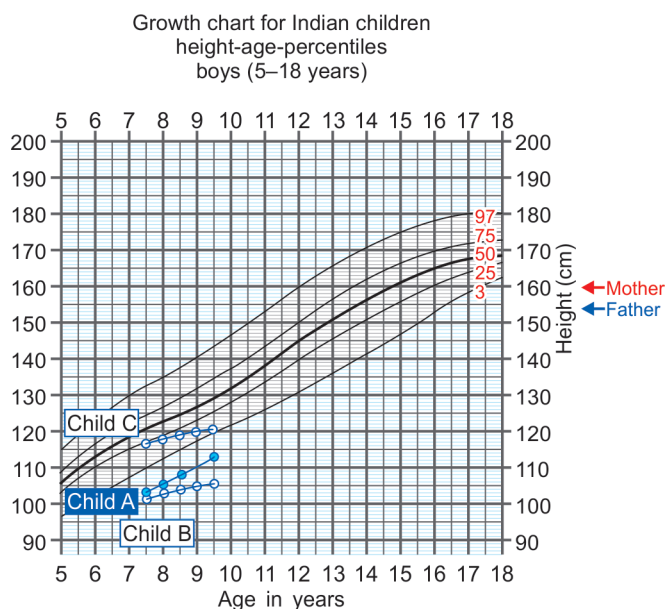
- Chronic undernutrition with deficiencies of energy, macronutrients (calcium) and micronutrients (vitamin D, iron)
- Chronic infections and infestations such as recurrent malaria, tuberculosis, human immunodeficiency virus (HIV), giardiasis, and intestinal worm infestations
- Chronic systemic conditions such as chronic renal failure, significant congenital defects (acyanotic defects associated with heart failure or cyanotic defects) and chronic hemolytic anemia.

In contrast, patients presenting to tertiary specialists are more likely to have normal variant short stature (constitutional delay in growth and puberty and familial short stature), endocrine causes (primary hypothyroidism and growth hormone deficiency) and syndromes such as Turner syndrome. Celiac disease and inflammatory bowel disease are increasingly being identified within the differential diagnosis owing to increased awareness and availability of diagnostic facilities.

### Pathogenesis/Pathophysiology

Growth impairment is a consequence of a pathology affecting any of the basic requirements for normal growth viz.: (1) hormones, (2) nutrition, (3) cell structure and function, (4) physical health and (5) psychosocial health (Table 1).

After a period of impaired growth, there is potential for catch-up growth if the underlying growth inhibiting condition is treated or modified. Catch-up is seen as accelerated linear growth and normalization of height towards the child's original trajectory. The extent of catch-up and whether normal adult height will be attained is influenced by the nature and severity of the underlying



**Figure 1** Growth chart to illustrate different patterns of linear growth. Mother's height is 146 cm and is plotted at 160 cm on a boy's chart ( $146 + 14$  cm). Father's height is 155 cm. Thus the mid-parental height (MPH) is 157.5 cm and the target range is 147.5–167.5 cm ( $MPH \pm 10$  cm)

Child A has familial short stature: He is short but his initial height is within parental target range. Follow-up measurements show that the height trajectory remains below but parallel to the 3rd centile and this suggests normal height velocity. The family can be reassured that this is familial normal variant short stature and no investigations or intervention are required.

Child B also has familial short stature. However follow-up measurements show the height trajectory deviating further away from the 3rd centile, characteristic of growth faltering. The latter suggests underlying pathology and needs to be investigated. The child also requires more frequent growth monitoring.

Child C is relatively tall for these parents but his initial height is still within parental target. Although his subsequent measurements remain within the parental target range as well as within the normal range for the population, there is a decline in the height trajectory similar to Child B. This child also has growth faltering and requires investigations for underlying pathology.



**Table 1** Basic requirements for normal growth and corresponding causes of growth impairment

Basic requirements for normal growth	Causes of growth impairment
Normal endocrine function The key hormones which regulate growth are growth hormone (GH) and sex steroids. Other hormones required for normal growth are thyroid, insulin, leptin, vitamin D and glucocorticoids	Defects in hormone secretion and action
Adequate nutrition	Undernutrition
Normal cells, cartilage and bones	Defects which impair structure and function
Physical health	Physical illness
Psychosocial health	Psychosocial deprivation

disease, age at onset and at diagnosis, pubertal timing, treatments and their success.

## Differential Diagnoses

### Normal Variant Short Stature

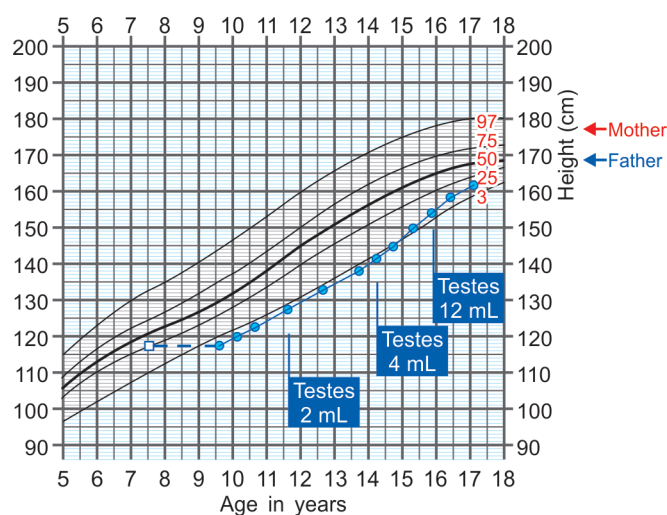
In a child with good general health and nutritional status, the most common causes of short stature are familial short stature (FSS) (**Fig. 1**), constitutional delay in growth and puberty (CDGP) (**Fig. 2**) or a combination of these two diagnoses. Birthweight, birth length, height velocity and body proportions are normal in both these conditions. Family stature, family history and normal height velocity helps to clinically differentiate these from growth hormone deficiency (GHD). Individuals with FSS have no delay in bone age, normal pubertal timing and will be short adults in keeping with a familial tendency. Those with CDGP may have a history of delayed puberty in parents. They have delayed bone age and delayed onset of puberty. Although they appear relatively short during childhood compared to parental target, their adult height will be on a higher centile position as compared to their childhood height centile and within their parental target (**Fig. 2**). Sometimes FSS and CDGP may coexist in a child. These children present at a younger age with concerns about short stature and will attain short adult height owing to the familial tendency.

### Chronic Undernutrition

Undernutrition is an important cause of short stature in resource-limited settings. It can also be associated with delayed puberty which further exaggerates the short stature. Undernutrition leads to low weight for height as well as low weight for age and gender. Although the most common deficiency is in energy, lack of other macronutrients (calcium) and micronutrients (vitamin D, iron and zinc) also needs to be considered. The cause of these deficiencies includes inadequate intake (poverty and feeding difficulties), unmet increased requirements (chronic inflammation) or excessive losses (malabsorption).

Adaptive mechanisms in chronic undernutrition are aimed to conserve energy and provide alternative sources of energy for body functions that are critical for survival. In such a state, substrate is diverted away from processes that are not a priority, such as growth, pubertal development and reproduction. Growth suppression is associated with relative GH resistance as indicated by normal or high spontaneous and stimulated serum GH in relation to low insulin-like growth factor 1 (IGF-1) and low IGF binding protein-3 (IGFBP-3) levels. Both IGF-1 and IGFBP-3 levels correlate with measures of nutritional status. Delayed puberty in

Growth chart for Indian children  
height-age-percentiles  
boys (5–18 years)



**Figure 2:** Growth chart to illustrate the pattern of growth in constitutional delay. At age 9.5 years, this boy is short for his parents (height below parental target range) and also for the population. His bone age is 7.5 years and thus delayed by 2 years compared to the calendar age. His subsequent growth measurements until age 14.2 years suggest normal height velocity for a prepubertal boy. Thereafter he has a pubertal growth spurt and his height at age 17 years is within the parental target as well as the normal range for the population. Note more frequent growth monitoring during the teenage years when the young person is prone to be psychologically affected about their physical appearance. That adult height attained will be on a higher centile compared to that in childhood can provide reassurance  
Source: Agarwal DK, Agarwal KN, Upadhyay SK, et al. Physical and sexual growth pattern of affluent Indian children from 5 years to 18 years of age. Indian Pediatr. 1992;29:1203-82; Reproduced with permission.

adolescents with chronic undernutrition and energy deficiency is associated with functional gonadotropin deficiency, possibly from an apparently dormant hypothalamic gonadotropin-releasing hormone pulse generator.

Leptin is a hormone produced from fat cells and reflects energy stores. It is a critical hormone that provides signals to the hypothalamus about the nutritional state, and in turn regulates appetite and body weight. It also has other influences on the hypothalamus that affects a number of pituitary hormones, notably GH, gonadotropins and adrenocorticotrophic hormone (ACTH). In undernourished children, circulating leptin levels are low and correlate with low insulin, high GH but low IGF-1 concentrations, low gonadotropins and high cortisol levels. This endocrine milieu facilitates the adaptation from carbohydrate to fat-based metabolism by augmenting fatty acid mobilization, proteolysis and gluconeogenesis. These adaptive endocrine effects from chronic undernutrition are partly reversed by nutritional recovery but sustained weight gain is required for linear growth to improve.

### Chronic Systemic Disease

Growth impairment is a well-recognized feature of any unremitting or relapsing chronic systemic condition (**Fig. 1**). Delayed puberty due to functional gonadotropin deficiency in such conditions can further exaggerate the impairment in height in adolescents. Short stature can be the presenting feature in conditions such



as celiac disease, chronic inflammatory bowel disease, chronic infections like HIV and renal tubular acidosis. The severity and duration of growth impairment will depend on the nature, course, complications, management and response to treatment of the underlying disease. Catch-up in growth and attainment of normal height can be expected for conditions that can be successfully managed (e.g., gluten free diet in celiac disease). However, growth outcome remains guarded for other conditions that are refractory, associated with major complications, not easily treatable (e.g., chronic renal failure), not responsive to treatment or where treatment itself has adverse effects on growth (e.g., corticosteroids). The pathophysiology of growth impairment in chronic systemic disease is multifactorial. Chronic undernutrition, inflammation and prolonged corticosteroid treatment disrupt the functional integrity of the GH-IGF-1 axis and give rise to a state of relative GH resistance.

Proinflammatory cytokines are implicated in playing an important role in increased energy expenditure, fat mobilization, proteolysis, negative nitrogen balance, gluconeogenesis, anorexia and weight loss seen in chronic inflammation. However, reduced growth in chronic inflammation occurs even when nutrition is adequately supplemented and highlights a modulatory effect of the cytokines on the integrity of the GH-IGF-1 axis and direct local effect on the epiphyseal growth plate. Levels of proinflammatory cytokines, interleukin-6 (IL-6), tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) and IL-1 $\beta$ , are high in a number of chronic inflammatory conditions (juvenile chronic arthritis, inflammatory bowel disease, cystic fibrosis), correlate with the severity of the underlying condition and are associated with GH resistance (normal or high GH but low levels of IGF-1 and IGFBP-3).

The immunosuppressive and anti-inflammatory properties of corticosteroids are of benefit in the treatment of specific chronic diseases. However, long-term treatment carries the risk of growth impairment. The adverse effects of corticosteroids on linear growth are mediated through complex processes and include disruption of the GH-IGF axis, direct effects on the epiphyseal growth plate,

inhibitory effects on gonadotropin secretion and suppression of endogenous adrenal corticosteroid production.

### *Intrauterine and Early Postnatal Growth Retardation*

Intrauterine growth retardation (IUGR), being born small for gestational age (SGA) as well as wasting and stunting in early childhood are common problems in India. Among the numerous contributing factors, maternal ill health (especially from communicable diseases), poor nutrition and adverse lifestyles (such as smoking) during pregnancy and lactation remain most significant. While most infants with a history of IUGR show catch-up growth in first 2–4 years, approximately 10% infants do not catch-up and thus remain short.

IUGR with poor postnatal growth and short stature is also a feature of specific syndromes such as Russell-Silver and 3-M, both clinically and genetically heterogeneous (**Table 2**).

### *Endocrine Disorders*

**Hypothyroidism** Short stature due to growth failure is among the characteristic features of hypothyroidism in children, irrespective of the underlying cause. Although hypothyroidism is most commonly primary due to pathology in the thyroid gland, it can also be secondary due to pituitary thyroid-stimulating hormone (TSH) deficiency or tertiary due to a hypothalamic defect in thyrotropin-releasing hormone (TRH) secretion.

Primary hypothyroidism can be congenital or acquired. The causes of primary acquired hypothyroidism include autoimmune thyroiditis (Hashimoto) and iodine deficiency. Children with these conditions may have goiter.

In countries where neonatal screening has been implemented, primary congenital hypothyroidism is diagnosed in the first few weeks of life from raised blood TSH levels. This means that thyroxine (T4) replacement can be started in the neonatal period. Provided these children are appropriately managed and compliance with thyroxine replacement is good, they are unlikely to develop short stature. In countries such as India where there are no national

**Table 2** Characteristic features of genetic short-stature syndromes associated with a child being born small for gestational age

Characteristics	Russell-Silver syndrome	3-M syndrome
Estimated incidence	1 in 3,000–100,000 and male predominance	Rare autosomal recessive primordial growth disorder
Growth characteristics	IUGR, SGA and poor postnatal growth; short and lean with poor weight gain; relative macrocephaly; limb length asymmetry; hemihypertrophy	IUGR, SGA and poor postnatal growth; short and lean; relative macrocephaly
Pubertal development and adult height	Onset of puberty normal or early short adult height (average F: 140 cm; M: 150 cm)	Normal age of onset of puberty; short adult height
Facial features	Prominent forehead, small triangular face, bluish sclera, downturned corners of the mouth, small jaw and narrow chin	Frontal bossing, small triangular face with midfacial hypoplasia, full eyebrows, fleshy nose tip, anteverted nares, long philtrum, full fleshy lips, pointed chin, short broad neck
Other features	Feeding difficulties from birth, clinodactyly, café-au-lait patches	Short chest with sternal deformity, fleshy prominent heels, slender bones, relatively tall vertebral bodies, dysplastic hips, joint hypermobility
Genetics	Defects on chromosomes 7 and 11 in 50% cases; hypomethylation of <i>H19</i> differentially methylated region at the 11p15 locus in 40–50% cases; 10% have maternal uniparental disomy of chromosome 7	Defects in three separate genes have been identified in cases with 3-M syndrome: <i>CUL7</i> mutations in about 70%; <i>OBSL1</i> mutations in 25%; <i>CCDC8</i> mutations 5%
GH-IGF status	Normal GH levels to stimulation tests but abnormalities in 24-hour spontaneous GH secretion; low IGF-1 and IGFBP-3 levels indicate abnormal GH secretion and relative GH insensitivity	Normal GH levels to stimulation tests; relatively low IGF-I levels indicate relative GH insensitivity
Management	Potential for attaining normal adult height with GH treatment in some patients	No significant improvement in height with growth hormone treatment

Abbreviations: IUGR, Intrauterine growth retardation; SGA, small for gestational age.

screening programs, children with congenital hypothyroidism may present with short stature after the first few years of life.

In addition to short stature, children with hypothyroidism may appear relatively overweight. Clues to the diagnosis include delay in achieving developmental milestones, drowsiness, lethargy, apathy, poor concentration and slow academic progress. Although constipation is a feature of hypothyroidism, it is also a common problem in otherwise healthy children. Other important history and examination findings are coarse facial features, hoarse voice, rough dry skin, cold intolerance, mottled skin, bradycardia, slow relaxation of deep tendon reflexes and delayed bone age.

Thyroid function with both TSH and free T<sub>4</sub> (or total thyroxine) level is the most important investigation and will help confirm the clinical suspicion of hypothyroidism and whether it is primary or secondary. Although establishing the underlying cause of hypothyroidism requires additional investigations, these are not critical if resources are limited and should not detract from starting T<sub>4</sub> replacement.

**Growth hormone deficiency (GHD)** It can be isolated or associated with other pituitary hormone deficiencies. Growth failure leading to a decline in a child's height centile and consequently short stature is the most salient feature in children with GHD (**Fig. 1**). This is especially important to recognize because it may be the only overt finding that helps distinguish isolated idiopathic GHD from FSS or CDGP.

In preschool age children, the most common cause of GHD is a congenital or genetic defect in hypothalamic pituitary development or function, such as septo-optic dysplasia. Acquired causes need to be considered in older children and adolescents. However, no definite cause is identified in many cases.

In addition to the distinct growth pattern, history and examination can provide clues suggestive of GHD and the underlying etiology (**Table 3**).

**Growth hormone insensitivity** GH insensitivity is defined as high GH levels to stimulation tests and low IGF-1 levels. Acquired GH insensitivity occurs in chronic undernutrition, systemic disease and inflammation, as described earlier. Congenital GH insensitivity can be due to defects in the GH receptor, GH signaling, IGF-1 gene or its receptor. Children with these defects are exceptionally short and have clinical features similar to GHD. Head size is normal in GH receptor and signaling defects but small in children with defects in the IGF-1 gene or its receptor.

**Cushing syndrome** Corticosteroids are used long-term to manage a wide range of conditions such as intractable asthma, nephrotic syndrome, juvenile chronic arthritis and inflammatory bowel disease. Growth impairment and short stature are well recognized side effects of prolonged treatment with systemic corticosteroids

and also reported with potent inhaled corticosteroids. Excess endogenous corticosteroid secretion from primary adrenal pathology or secondary to increased pituitary ACTH secretion (Cushing disease) is rare in children.

### Genetic Syndromes

The major genetic syndromes characterized by short stature are Down syndrome, Turner syndrome, Noonan syndrome, Aarskog syndrome and Prader-Willi syndrome. The salient distinguishing features are presented in **Table 4**.

**Down syndrome** In addition to the chromosomal defect, the factors contributing to short stature are hypothalamic dysregulation of growth hormone secretion, coexisting systemic problems, especially symptomatic heart disease, autoimmune problems such as hypothyroidism and celiac disease, and an attenuated pubertal growth spurt.

**Turner syndrome** Two copies of the *SHOX* gene are required for normal growth in height and the chromosomal defect with a single copy of the *SHOX* gene explains the short stature in this syndrome. Defects in both copies of the *SHOX* gene are associated with severe short stature and found in Léri-Weill dyschondrosteosis.

Presentation of Turner syndrome can be antenatal (nuchal fold on ultrasound examination), at birth (lymphedema, coarctation of the aorta), school age (short stature which becomes more obvious after age 3–4 years) or adolescence (delayed or arrested puberty, primary hypothyroidism). Clinical features in girls with Turner syndrome vary considerably but the single consistent feature in all is short stature and reduced adult height (136–147 cm). The syndrome should therefore be considered in any girl presenting with short stature. Treatment with growth hormone can improve final height. However, in resource limited settings the priority is to identify and manage life limiting abnormalities such as coarctation of the aorta. In addition, primary ovarian failure necessitates estrogen replacement to enable pubertal maturation and optimize bone health.

### Skeletal Dysplasia (Osteochondrodysplasias)

Skeletal dysplasias are a heterogeneous group of disorders that affect cartilage and bone, and can present with disproportionate short stature. The most widely recognized among these are the two autosomal dominant conditions achondroplasia and hypochondroplasia due to mutations in *FGFR3*. Hypochondroplasia is less striking than achondroplasia, and the disproportion may only be evident when sitting height and subischial leg length are plotted on charts. Other features notable in achondroplasia such as large head and lumbar lordosis may also be subtle. A skeletal survey helps in establishing the diagnosis.

**Table 3** Clues from the history and examination that suggest growth hormone deficiency (GHD) and the underlying etiology

Characteristics	Features suggestive of GHD	Clues to underlying etiology
Symptoms	Declining height centile, short stature, tiredness	Morning headache, persistent vomiting, visual impairment, squint, nystagmus
Birth and neonatal history	Hypoglycemia, prolonged jaundice	Breech or traumatic delivery
Childhood events		Head injury, intracranial infection, cranial irradiation
Family history		Consanguinity, exceptional short stature
Examination	High pitched voice, cherubic face with crowding of mid facial structures, normal head circumference and frontal bossing, chubbiness with more subcutaneous fat compared to muscle bulk, anterior abdominal adiposity with dimpling of fat, small phallus and nonpalpable testes (where gonadotropin deficiency is coexistent), delayed bone age, delayed dentition, delayed puberty	Visual field defect, features to suggest other pituitary hormone deficiencies such as midline abnormalities: cleft lip/palate, single central incisor, optic nerve hypoplasia

**Table 4** Salient distinguishing features of syndromic causes of short stature

	<i>Down syndrome</i>	<i>Turner syndrome</i>	<i>Noonan syndrome</i>	<i>Aarskog syndrome</i>	<i>Prader–Willi syndrome</i>
Growth characteristics	Normal birth size, decline in height centiles evident from age 6 months–3 years, tendency to obesity, relatively short limbs, mean adult height 168 cm in males and 142 cm in females	Birth size normal, decline in height centiles evident by age 3–5 years, relatively short limbs, mean adult height 140 cm	Birth size normal, short stature evident in childhood, adult height can vary from normal to short stature	Birth size normal, short stature evident by age 1–3 years, adult height normal	Birth size normal, feeding difficulties and poor weight gain in infancy, obsessive food seeking behavior, insatiable appetite and excessive weight gain evident from age 2–3 years, adult height can vary from normal to short stature (mean 162 cm in males, 150 cm in females)
Pubertal development	Relatively early, attenuated pubertal growth spurt	Majority will not start puberty spontaneously, no pubertal growth spurt	Delayed in males, attenuated pubertal growth spurt	Delayed, good catch-up in height during puberty	Delayed
Facial features	Flat face, eyes slant upwards and outwards, epicanthic folds, depressed nasal bridge, small nose, small mouth and large tongue	Down-slanting eyes, low set ears, high arch palate, neck webbing, low posterior hairline	Eyes wide spaced, ptosis, low set ears, broad nasal tip, grooved philtrum, high arch palate, small jaw, short webbed neck, low posterior hairline	Round flat face, broad forehead with widow's peak, eyes wide spaced, short broad upturned nose, anteverted nostrils, long philtrum, thin short upper lip, large broad upper incisors in permanent dentition, maxillary hypoplasia	Almond shaped eyes, fair hair
Other features	Hypotonia, broad hands and short fingers, single transverse palmar crease, sandal gap between 1st and 2nd toes	Cubitus valgus, hyperconvex hypoplastic nails, multiple naevi, broad chest and wide spaced nipples	Undescended testes, sternum deformities, café-au-lait spots	Short broad hands and feet, broad thumbs and big toes, hyperextension at proximal and flexion at distal interphalangeal joints (swan neck appearance), interdigital webbing, ventral scrotal folds encircling penis (shawl scrotum), undescended testes	Learning difficulties, floppiness from birth, increased fat mass compared to lean mass, small hands and feet, undescended testes and underdeveloped genitalia, scoliosis
Associated problems	Mild to moderate learning difficulties, congenital heart defects, gastrointestinal defects, thyroid dysfunction, myopia, hearing impairment	Specific learning difficulty, primary ovarian failure, left sided heart defects, renal abnormalities, ear infections and hearing impairment, autoimmune hypothyroidism	Mild learning difficulties, right sided heart defects (pulmonary stenosis), hypertrophic cardiomyopathy, bleeding tendency	Mild to moderate learning difficulties, hyperactivity and attention deficit	Mild to moderate learning difficulties, high pain threshold and self-mutilating behavior, type 2 diabetes

### Approach to Diagnosis

When assessing a child with short stature or concerns about growth, serial measurements of the child's height/length, weight and head circumference as well as measured (preferably) or reported heights of natural parents should be obtained and plotted on population specific growth charts (**Figs 1 and 2**). This helps to differentiate true short stature and growth failure from perceived short stature. Such a record is also vital for monitoring health status, disease activity, adverse clinical events and response to treatment.

The age of the child when concerns about growth in height were first aroused and pubertal status during the adolescent years gives some clues to the etiology (**Table 5**). A family history along with heights of parents and other family members helps differentiate whether the problem is familial. Consanguinity raises the possibility of an inherited condition.

The most prominent presenting complaint or clinical feature provides a helpful clinical classification of short stature (**Table 6**). This also aids in gathering hypotheses generated information from a focused history and examination. In addition to potential causes, the impact of short stature on the individual's physical and psychological wellbeing, their concerns and expectations, should

be elicited. These will need to be taken into consideration when deciding on further management.

Maternal nutrition, health (e.g., rubella, malaria), lifestyle (e.g., alcohol, smoking) and treatment can affect fetal growth and birth size. These should be explored in children with a history of poor growth in utero and those born small for gestational age. Salient features to elicit in the postnatal history include prolonged jaundice (congenital hypothyroidism, congenital hypopituitarism), neonatal hypoglycemia (congenital hypopituitarism), floppiness and feeding difficulties (Prader–Willi syndrome), puffy hands and feet (Turner syndrome).

A detailed medical history should provide clues for chronic energy deficiency (inadequate dietary intake or malabsorption) and chronic systemic illness, recurrent infections (malaria, respiratory tract infections, urinary tract infections and gastroenteritis). Short stature can be due to the medical problem as well as adverse effects of treatments, such as prolonged systemic corticosteroids and frequent blood transfusions (for chronic hemolytic anemia).

Concerns about neurodevelopment in global or specific aspects of hearing and language, vision (e.g., septo-optic dysplasia), motor, cognitive (e.g., Prader–Willi syndrome) and

social development raise the possibility of syndromes. In addition to specific findings of the most likely diagnoses suspected from the elicited history, general examination should include:

- Nutritional status and muscle bulk
- Skin for nevi (Turner syndrome) and café-au-lait spots (Fanconi anemia, Russell-Silver syndrome, Noonan syndrome), pigmented macules (neurofibromatosis type 1).

**Table 5** Clues to causes of short stature according to the age of onset

Age when short stature first noted	Causes of short stature
Birth to 2 years	<ul style="list-style-type: none"> <li>• Familial short stature</li> <li>• Chronic undernutrition owing to lack of food (poverty), inadequate dietary intake (e.g., feeding difficulties), malabsorption (e.g., chronic diarrhea, giardiasis, celiac disease), unmet high metabolic requirements (e.g., chronic lung disease)</li> <li>• Rickets</li> <li>• Skeletal dysplasia</li> </ul>
2–5 years	<ul style="list-style-type: none"> <li>• Untreated congenital hypothyroidism</li> <li>• Growth hormone deficiency, e.g., isolated, congenital hypopituitarism</li> <li>• Turner syndrome</li> <li>• Chronic renal failure and other chronic systemic diseases</li> </ul>
5–9 years	<ul style="list-style-type: none"> <li>• Constitutional delay in growth</li> <li>• Chronic systemic conditions, e.g., poorly controlled asthma, acquired heart disease (e.g., complication of rheumatic fever)</li> </ul>
9 years and older	<ul style="list-style-type: none"> <li>• Familial short stature</li> <li>• Constitutional delay</li> <li>• Chronic systemic conditions</li> <li>• Acquired primary hypothyroidism</li> <li>• Acquired growth hormone deficiency, e.g., tumor, trauma, surgery, radiotherapy</li> </ul>

- Head size (relatively large in Russell-Silver syndrome)
- Face and neck (characteristic features in Turner syndrome, Noonan syndrome, fetal alcohol syndrome)
- Hands and limbs (radial abnormalities in Fanconi anemia, dinner fork deformity of forearm in Léri-Weill dyschondrosteosis)
- Body symmetry and proportions (short limbs and arms shorter than forearms in achondroplasia and hypochondroplasia, leg length discrepancy in Russell-Silver syndrome)
- Signs of chronic systemic illness.

## Investigations

Specific investigations should be considered when clues point to pathological causes. In the absence of such clues along with normal weight gain a pathological cause is unlikely and investigations are not required. This is further supported by normal height velocity (evaluated from reassessment at 3–6 monthly intervals) during follow-up and a normal bone age. In all cases with low growth velocity and/or delayed bone age, screening investigations should be done since some disorders may present with growth failure as their only manifestation (**Fig. 1**). These include a hemogram, erythrocyte sedimentation rate (ESR), liver and kidney function tests, venous blood gas analysis, thyroid function tests and serology for celiac disease. A karyotype should be done in all girls with unexplained short stature to check for Turner syndrome should be done. A delayed bone age heralds good potential for future growth and can be reassuring for subjects with CDGP (**Fig. 2**).

## Management

In addition to the specific management of the underlying pathology, management of a child with short stature entails addressing physical and psychological concerns (**Fig. 3**). The two growth promoting treatments that are available, namely recombinant human growth hormone and recombinant IGF-1, have specific indications (**Table 7**). However, these treatments are

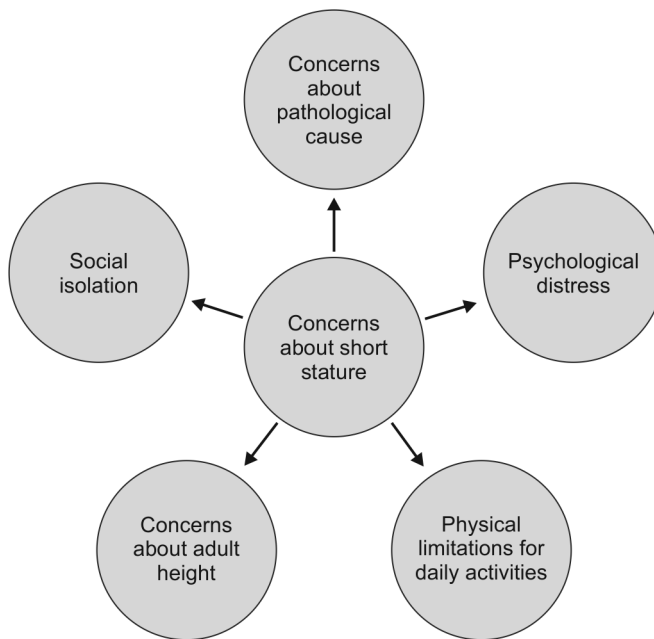
**Table 6** Classification for causes of short stature categorized by the most prominent presenting complaint or clinical feature

Most prominent clinical feature	Other distinguishing features	Causes of short stature
Otherwise healthy child, height velocity normal for stage of puberty and no growth failure	Family history of short stature, no bone age delay	Familial short stature
	Family history of delayed puberty, bone age delayed	Constitutional delay in growth and puberty
Born small for gestational age	Head size normal or relatively large	Russell-Silver syndrome, 3-M syndrome
	Small head	Congenital infections such as rubella; fetal alcohol spectrum disorder; Fanconi anemia
Chronic systemic disease	Overt features of underlying problem	Undernutrition, chronic infection; chronic gastrointestinal disease; symptomatic congenital or acquired heart disease; chronic renal failure
	Occult or asymptomatic problem	Celiac disease; renal tubular defects
Endocrine disorder	Features of underlying problem	Hypothyroidism; growth hormone deficiency; primary IGF-1 deficiency
	Adverse effect of treatment	Excess corticosteroids
Dysmorphic features	Girls	Turner syndrome; SHOX deficiency (Léri-Weill dyschondrosteosis or Langer mesomelia)
	Girls or boys	Down syndrome; Noonan syndrome; Prader-Willi syndrome
	Boys	Aarskog syndrome
Disproportion between trunk (sitting height) and limbs (subischial leg length)	Short limbs	<i>Skeletal dysplasias</i> : Hypochondroplasia, achondroplasia
	Short trunk	Mucopolysaccharidosis type 4 (Morquio syndrome), type 2 (Hunter syndrome); osteogenesis imperfecta
Long-term medication	Features of the condition being treated	Corticosteroids; stimulants such as methylphenidate



**Table 7** Evidence-based indications for recombinant human growth hormone and recombinant insulin-like growth factor 1 (IGF-1)

Indications for recombinant human growth hormone treatment	Indications for recombinant IGF-1 treatment
Growth hormone deficiency Turner syndrome SHOX haploinsufficiency Exceptional short stature in a child born small for gestational age Chronic renal failure Prader-Willi syndrome	Primary IGF-1 deficiency

**Figure 3** The different facets of concerns about short stature

costly and ethical considerations alongside potential benefits and risks must be discussed with families.

## TALL STATURE

Tall stature is considered when height is greater than 2 SD above the population mean for age and sex (using growth charts based on local reference standards) or where there is a significant discrepancy between the mid-parental centile and child's height. A detailed assessment of tall stature by the endocrinologist is essential to predict final adult height, exclude any underlying disorder and provide treatment if needed.

### Etiology and Epidemiology

The causes of tall stature are listed in **Table 8**. Familial tall stature (or constitutional tall stature) is the most common cause of tall stature in children and adolescents.

### Clinical Approach

#### History

A detailed history of the child's growth including birthweight and length and the pattern of early growth should be obtained. Birthweight and length are usually above 2 SD in children with primary growth disorders, such as Sotos, Beckwith-Wiedemann and Marfan syndromes. They continue to show accelerated growth velocity in infancy and early childhood. Conversely,

**Table 8** Causes of tall stature

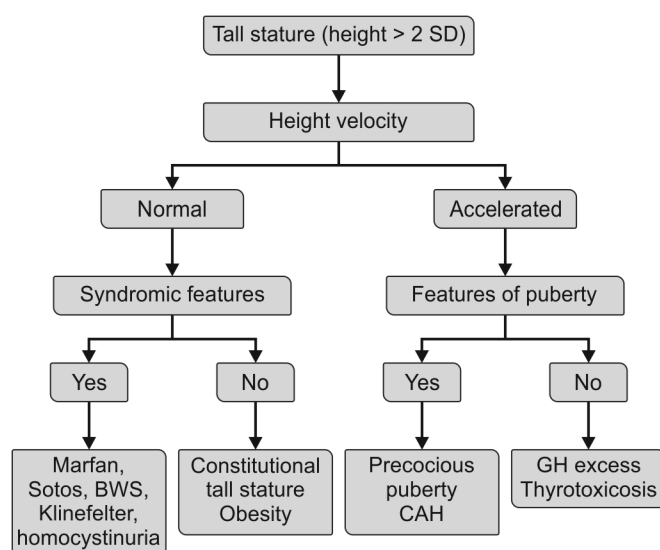
Primary	Sex chromosome abnormalities	Klinefelter syndrome (47,XXY) and variants
	Overgrowth syndromes	Sotos syndrome; Weaver syndrome; Beckwith-Wiedemann syndrome
	Genetic syndromes with tall stature	Marfan syndrome; Multiple endocrine neoplasia 2B (MEN 2B)
Secondary	Endocrine causes	Growth hormone (GH) excess; thyrotoxicosis; precocious puberty Adrenal tumor; hypogonadism; androgen insensitivity; defects of estrogen production; isolated ACTH insensitivity; congenital adrenal hyperplasia
	Metabolic causes	Homocystinuria
Constitutional	Familial tall stature	
Others	Exogenous ('Simple') obesity	

children with constitutional tall stature are within the normal range for birthweight and length and demonstrate accelerated growth velocity in early childhood. Neonatal hypoglycemia can be a feature of Beckwith-Wiedemann syndrome. An underlying endocrine disorder is suspected when the growth initially follows a lower centile and then crosses up the growth chart centiles. A history of excessive weight gain, eating habits and pubertal history should be taken in all cases. Simple obesity can lead to tall stature and advanced bone age. Children with hyperthyroidism may be noted to cross down weight centiles. Symptoms of hyperthyroidism include palpitations, muscle weakness, diarrhea, weight loss, heat intolerance. A history of ophthalmic problems, including lens subluxation, retinal detachment and glaucoma can suggest Marfan syndrome or homocystinuria. Visual impairment may be noted in a growth hormone secreting tumor. Developmental delay and learning difficulties can be features of children with homocystinuria, Sotos and Klinefelter syndromes.

#### Physical Examination

Physical examination must include auxology, examination for features of syndromic and systemic causes and pubertal staging. Obtaining the height of each biological parent, sibling and other family members is necessary. It is essential to calculate mid-parental height and target centile range for final adult height. A significant discrepancy between the child's height and mid-parental centile points towards a growth disorder than constitutional tall stature. Sitting height and arm span should be measured. Marfan and Klinefelter syndromes are associated with disproportionate tall stature. Arm span is greater than height in Marfan and Sotos syndromes. Head circumference is greater than 2 SD in most patients with Sotos syndrome. Precocious puberty is associated with an early pubertal growth spurt, but results in a shorter than expected final height due to the premature closure of the epiphyses. Tremor, tachycardia, diarrhea, hair loss, exophthalmos and goiter are signs of thyrotoxicosis. GH-secreting pituitary adenoma can present with bitemporal hemianopia. Sotos syndrome is characterized by dysmorphic features like prominent forehead, hypertelorism, large ears and high arched palate. Macroglossia and earlobe creases are features of Beckwith-Wiedemann syndrome.

A diagnostic approach to the assessment of tall stature is shown in **Figure 4**.



**Figure 4** Diagnostic approach to the evaluation of tall stature

Abbreviations: SD, standard deviation; GH, growth hormone; CAH, congenital adrenal hyperplasia; BWS, Beckwith–Wiedemann syndrome.

## Differential Diagnosis

### Constitutional (Familial) Tall Stature

The features of constitutional tall stature include tall stature in one or both parents, predicted adult height within mid-parental target range and normal height velocity. The birth length is usually normal and the tall stature usually becomes apparent from 3 years to 4 years of age. It results in increased final height within the range defined by parental size. Tall stature may not arouse undue concern in a family with tall individuals. It is also perceived as socially advantageous and more acceptable than short stature especially in males. Thus females with tall stature are more likely to seek medical help than males. Physical examination is normal and there is a normal age of onset of puberty. The legs are often relatively long in comparison to sitting height. Assessment of bone age (which is likely to be advanced) and calculation of final height prediction may be helpful. The management will predominantly involve reassurance.

### Obesity

Exogenous (*simple*) obesity is a becoming a global epidemic. It can be associated with tall stature and advanced bone age, although the final height does not appear to be increased. Excess calorie intake is available for growth and may produce relatively tall stature (at upper end of predicted target range). Striae and a high cheek color may mimic mild Cushing syndrome. However, unlike Cushing and other endocrine causes of obesity, where affected children are characteristically short, exogenous obesity is associated with tall stature and with elevated levels of serum insulin concentrations. Insulin acting at the IGF-1 receptor in the skin produces acanthosis nigricans. Treatment is aimed at weight reduction (with calorie restriction and increased physical activity).

### Klinefelter Syndrome

It is caused by an extra sex chromosome (47,XXY) due to nondisjunction during meiosis. The incidence is around 1 in 1,500 males. The clinical features include tall stature, eunuchoid body proportions (increased arm span to height ratio), hypogonadism with small testes (secondary to tubular hyalinization), pubertal failure or arrest, gynecomastia, behavioral problems and learning

**Table 9** Clinical features of Marfan syndrome

System	Clinical features
Skeletal	Long arms (arm span > 5 cm than the height), long legs compared to the back (reduced US/LS ratio), arachnodactyly, joint laxity (wrist and thumb sign) Scoliosis and chest deformities (pectus excavatum or carinatum), high arched palate and flat feet
Eyes	Myopia, upward dislocation or poor fixation of the lens, flat cornea and hypoplastic iris
Cardiovascular	Mitral and aortic valve incompetence, peripheral pulmonary stenosis Aortic root dilatation and dissection
Chest	Spontaneous pneumothorax
Skin	Hernia, striae

Abbreviations: US, upper segment; LS, lower segment.

difficulties. The legs are relatively long compared to the back, especially with late diagnosis or after failure of puberty.

The other sex chromosomal variants associated with tall stature include 47,XYY, 47,XXX, 48,XXXY, 48,XXYY and 49,XXXXY.

### Marfan Syndrome

Marfan syndrome is an autosomal dominant condition of the connective tissue caused by mutations in the fibrillin gene FBN1 located on chromosome 15q21. The incidence is 1 in 5,000–10,000. It is characterized by disproportionate tall stature and the clinical features involve a number of systems as detailed in **Table 9**. The features can vary from mild to severe and the cardiac defects are the most serious complications of Marfan syndrome.

### Homocystinuria

Homocystinuria is an autosomal recessive disorder of the metabolism of the amino acid methionine which results in an abnormal accumulation of homocysteine and its metabolites in the blood and urine. It is associated with disproportionate tall stature but usually presents with marked learning difficulties, ectopia lentis (downward dislocation of the lens) and severe myopia with later thromboembolic and cardiovascular complications.

### Sotos Syndrome (Cerebral Gigantism)

Sotos syndrome is an autosomal dominant condition caused by mutations in the *NSD1* gene. It is characterized by excessive prenatal and postnatal growth, increased birthweight, tall forehead, large head circumference, a high arched palate, down slanting palpebral fissures, flushed cheeks, large chin, large hands and feet, scoliosis and developmental delay of variable severity. Individuals are tall during childhood but attain normal adult height owing to an advanced bone age.

### Beckwith–Wiedemann Syndrome

Beckwith–Wiedemann syndrome is an autosomal dominant condition caused by dysregulated expression of imprinted genes in the region 11p15.5. The pancreas is hyperplastic and can lead to neonatal hypoglycemia secondary to hyperinsulinism. It is an overgrowth disorder characterized by macrosomia, macroglossia, hemihypertrophy, transverse ear crease, organomegaly and omphalocele. It can be associated with tumors like Wilms tumor, hepatoblastoma and germ cell tumors.

### Growth Hormone Excess

Excessive GH production prior to fusion of the epiphyses leads to pituitary gigantism which is exceptionally rare. It can be due

to a GH-producing adenoma in the pituitary or GHRH excess from hypothalamic tumors. Pituitary hyperplasia with excess GH secretion may be seen as part of McCune-Albright syndrome and Carney complex (a rare disorder characterized by myxomas, lentigenes, endocrine and nonendocrine tumors). Although the most common pituitary tumors in multiple endocrine neoplasia (MEN) type 1 are prolactinomas, GH secreting adenomas may also occur. Familial acromegaly and familial isolated pituitary adenomas are rare conditions of GH excess due to dominantly inherited mutations in aryl hydrocarbon interacting protein. A proportionate, worsening tall stature with a rapid height velocity is a feature of all these conditions. GH excess causes prominent soft tissues, prognathism, frontal bossing, large hands and feet and signs and symptoms resulting from optic chiasm compression caused by the pituitary tumor. In the absence of treatment, adult heights up to 247 cm in the female and 274 cm in the male may be found. Concentrations of GH and IGF-1 are high and the GH does not suppress in response to a glucose load.

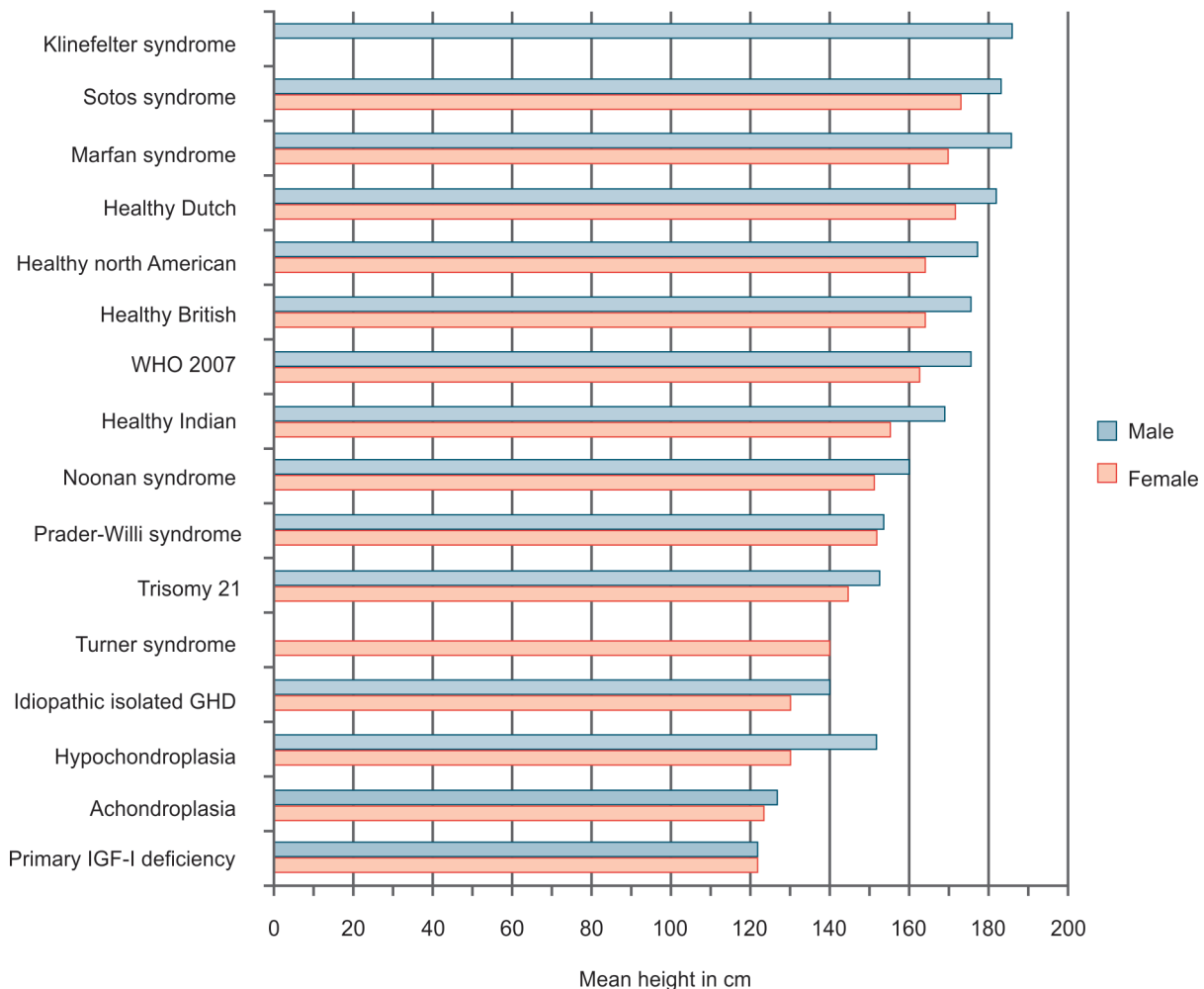
### Other Endocrine Abnormalities

Precocious puberty (both central and peripheral) can be characterized by tall stature, although the final height is compromised if untreated. Thyrotoxicosis can lead to rapid growth and advanced bone age. Aromatase deficiency resulting from mutation of the *CYP19* gene prevents the conversion of testosterone to estrogen in the male and hence there is lack of

epiphyseal fusion. These males continue growing into adulthood and have osteoporosis and delayed bone age.

### Investigations

The history and examination will guide further investigations. Most children may not require extensive investigations apart from regular growth and pubertal monitoring at intervals of 6 months. Constitutional tall stature and primary growth disorders generally demonstrate normal growth velocities, whereas secondary growth disorders will be characterized by accelerated growth velocity. Estimation of bone age will help to estimate skeletal maturation and calculate predicted height. Advanced bone age may be seen in constitutional tall stature, obesity, precocious puberty, thyrotoxicosis and Sotos syndrome. Delayed bone age can be noted in hypogonadism. Further investigations, like measurement of T4 and TSH, IGF-1, GH suppression test, magnetic resonance imaging (MRI) pituitary, 9 am cortisol, prolactin urinary and total plasma homocysteine levels may become necessary based on the initial evaluation. Investigations of precocious puberty and congenital adrenal hyperplasia (CAH) should be guided by the initial assessment. In the presence of behavioral or learning difficulties a karyotype should be performed. If there is a suggestion of MEN2B from the family history or examination (presence of mucosal neuromas in a child with a marfanoid habitus), it is essential to measure calcitonin concentration and to confirm the diagnosis by analysis of the ret-proto-oncogene.



**Figure 5** Adult height of males and females with a range of conditions that significantly affect stature. These are illustrated in comparison to normal stature of western populations and healthy Indians

## Management

The management of constitutional tall stature will include reassurance to address the parental anxieties and providing an estimate of final adult height (**Fig. 5**). Medical intervention is generally not necessary. It can be considered for children in whom the tall stature or predicted adult height is expected to have significant psychosocial consequences. Tall children can feel different from their peers and are likely to be teased about their height. Some experts recommend height reduction with medical treatment that requires use of high doses of exogenous sex steroids. Although treatment is most effective when initiated at both lower chronological and bone age, it is not recommended before the normal age of puberty. In adolescent girls ethinyl estradiol orally combined with cyclic progesterone can reduce final height by around 7 cm. Similar results have been found in boys with high dose intramuscular testosterone. Side effects of estrogen include weight gain, acne headaches, dysmenorrhea, and venous thromboembolic events. Side effects of testosterone include behavior problems, weight gain, gynecomastia and acne. Surgical epiphysiodesis (surgical ablation of growth plate) has occasionally been undertaken in rare cases.

The pitfalls in the management of tall stature include failure to examine the patients carefully for dysmorphic features suggestive of Marfan syndrome. This diagnosis may have serious consequences as these patients need life-long cardiovascular surveillance. Failure to appreciate that tall stature and delayed puberty are an unusual combination can lead to delayed diagnosis of Klinefelter syndrome.

## MORE ON THIS TOPIC

### Short Stature

Bhadada SK, Bhansali A, Ravikumar P, et al. Changing scenario in aetiological profile of short stature in India-growing importance of celiac disease: a study from tertiary care centre. *Indian J Pediatr.* 2011;78:41-4.

Bhadada SK, Agrawal NK, Singh SK, Agrawal JK. Etiological profile of short stature. *Indian J Pediatr.* 2003;70:545-7.

Dutta D, Biswas K, Arora R, et al. Profile and height outcomes of children with short stature in north India: an experience from a tertiary care centre. *Indian J Pediatr.* 2014;81:205-6.

Young MF, Martorell R. The public health challenge of early growth failure in India. *Eur J Clin Nutr.* 2013;67:496-500.

## IN A NUTSHELL

1. Accurate auxology, calculation of height velocity, evaluation with pubertal status, comparison with parents' heights (using local growth reference standards) thorough clinical consultation are essential for the assessment of short and tall stature and other growth disorders.
2. Familial and constitutional short/tall statures are the most common causes of deviations in stature and are characterized by normal height velocity.
3. Follow-up evaluation is crucial in identifying decline or acceleration in height velocity. This along with other clues such as body disproportions, dysmorphic features and systemic problems suggest underlying pathology and warrant further investigations.
4. Expert advice from a pediatric endocrinologist should be sought before embarking on specific growth promoting or suppressing treatments.

## Tall Stature

de Waal WJ, Greyn-Fokker MH, Stijnen T, et al. Accuracy of final height prediction and effect of growth-reductive therapy in 362 constitutionally tall children. *J Clin Endocrinol Metab.* 1996;81:1206-16.

Hindmarsh PC, Pringle PJ, Di Silvio L, Brook CG. A preliminary report on the role of somatostatin analogues in the management of children with tall stature. *Clin Endocrinol.* 1990;32:83-91.

Sotos JF. Overgrowth. Section V. Syndromes and other disorders associated with overgrowth. *Clin Pediatr.* 1997;36:89-103.

Venn A, Hosmer T, Hosmer D, et al. Oestrogen treatment for tall stature in girls: estimating the effect on height and the error in height prediction. *Clin Endocrinol.* 2008;68:926-9.



# Section 20

## DEVELOPMENT AND DEVELOPMENTAL DELAY

**Section Editors** Anand Pandit, Sudha Chaudhari

### Chapter 20.1

## Introduction to Development, Laws of Development, and Factors Affecting Development

Satnam Kaur

### INTRODUCTION TO DEVELOPMENT

Development, or more precisely *neurodevelopment*, refers to a process of functional maturation and acquisition of new skills related to maturation of neural structures. It refers to the qualitative changes occurring in a progressive, orderly and coherent manner that enable the child to function on a higher level. Progressive denotes that changes are unidirectional (forward). Orderly and coherent signify that attainment of a particular skill builds on achievement of earlier skills and skills are not skipped. It is different from *growth* that connotes quantitative changes of increase in size and structure and refers to measurable quantities such as weight and height.

### Process of Development

Development is a continuous process that starts in utero and continues postnatally and birth is just a transitional event between the two. As early as 8–9 weeks of gestation, isolated muscular contractions in response to local stimulus may be seen. By 13–14 weeks, graceful flowing movements may be produced by stimulation of all areas except back and vertex and mother may feel fetal movements. Breathing and swallowing movements appear at about the same time. Grasp reflex appears at about 17 weeks and is well developed by 27 weeks. Response to sound and eye-opening appear at about 26 weeks. During the third trimester, the fetus responds to external stimuli by elevation of heart rate, and movements and reactivity varies depending on behavior state as is seen in a neonate. Habituation (repeated stimulation causing progressively decreased responsiveness) can be demonstrated in late pregnancy. This orderly development continues into infancy and childhood with mastery over increasingly complex tasks and transforms a totally dependent baby into a fully independent person. However, it is continuously influenced by intrinsic and extrinsic factors as discussed subsequently. Thus, development occurring in infancy and childhood is truly remarkable. During this period, the child learns to move about and explore the environment (motor development), builds up knowledge (cognition), learns to communicate (language) and develops a sense of self, learns to control his emotions and to adapt to his social environment (personal-social).

Development is a qualitative process and is not something that can be measured using a weighing scale or ruler. Nonetheless, it can be observed, assessed and followed over time. Developmental

milestones provide a systematic approach to study the neuro-developmental sequences and to observe the progress of a child over time. Milestones have been organized into four domains—motor (gross motor and fine motor), cognitive/adaptive, language, and personal-social—for the ease of assessment. However, they are all interrelated and delay in one domain may impair development in another domain. For example, a neuromuscular disorder will not only affect motor development but also affect cognitive development by interfering with ability to explore the environment.

### Theories of Development

Several theories about child development have been proposed and have influenced our understanding of child development. Each theory provides some insights into how children grow and develop. Some of the key theories that have helped shape our understanding of development are described here.

#### *Maturational Theory by Arnold Gesell*

As per this theory, development occurs in an orderly and predictable sequence that is genetically determined and related to neurological maturation. Gesell provided a time-table of milestones and usual age range for acquiring them. He did not give much importance to environmental influences on development. The real usefulness of this theory is the importance given to neuromaturation and predictable sequence of child development.

#### *Psychoanalytic Theories by Freud and Erikson*

These theories emphasized the importance of early childhood experiences in modeling personality and social development.

As per Sigmund Freud, behavior is controlled by unconscious urges and the three parts of personality are id, ego and superego. Id reflects basic instincts and is the dominant force during infancy. Ego develops during late infancy and toddler years and is the aware self. Superego or the conscious appears over preschool years. He hypothesized that successful development and integration of these components during early childhood determines adult personality. He stated that each stage has sexual meaning focused on a particular body part. The focus shifts from oral stage (sucking, feeding and biting in infancy) to anal stage (mastery of bowel function in toddler years) to oedipal/phallic stage (interest in genitals and possessiveness toward opposite gender parent). He asserted that successful resolution of sexual conflict of each stage leads to a new level of social and emotional development.

Erik Erikson further built upon Freud's work. He identified eight separate stages of development across lifespan and hypothesized that in each stage the child faces a crisis that must be resolved before moving onto the next stage. The outcome of each stage is determined by the social and cultural environment and caregiving strategies. The stages he described for children include trust versus mistrust (0–18 months), autonomy versus shame and doubt (18 months to 3 years), initiative versus guilt (3–6 years), industry versus inferiority (6–11 years), and identity versus role confusion (adolescent).

### Behavioral and Social Learning Theories (By Ivan Pavlov, JB Watson, BF Skinner, Albert Bandura)

The main premise of these theories is that if behaviors are rewarded, they will repeat. But if behaviors are ignored/punished, they will decrease. These theories give little importance to the child's own emotions/motivations. However, these theories provide an important foundation for some of the interventions used for problematic behaviors like temper tantrums and applied behavior analysis technique used for teaching complex behaviors in children with autism spectrum disorders.

### Cognitive Theories

Jean Piaget postulated that children's thinking passed through four *stages of development* and changed qualitatively in each of these stages. He believed that children were active learners and emphasized the importance of maturation and provision of a stimulating environment for children to explore. Piaget's different stages are as follows:

1. *Sensory-motor stage (0–2 years)* In this stage, children use their motor skills and senses to explore and develop their cognitive abilities. They need to master the concept of object permanence (objects continue to exist even when not in sight), causality, spatial relationships and use of instruments (e.g., using rake to reach for object) before moving onto next stage.
2. *Preoperational stage (2–6 years)* In this stage, children's thinking is egocentric (belief that world revolves around them). They need to understand the sense of animism (objects do not actually have life), egocentrism (he is not the center of the world), idiosyncratic associations and transductive reasoning (things are not necessarily related if they are occurring at the same time).
3. *Concrete operational thinking (6–12 years)* During this stage, children start thinking logically. However, they need concrete materials to help them reach correct conclusions and have trouble imagining hypothetical situations. They need to master the concept of numbers, mass, volume and objective causality.
4. *Formal operational thinking (12 years onward)* In this stage children develop abstract thinking, ability to solve problems in the head and to deal with complex issues.

Lev Vygotsky also proposed that the thinking of children develops in stages, but he emphasized the importance of social and cultural influences on learning. He did not see children as solitary discoverers of knowledge, but believed that the child's cognitive ability was enriched and deepened when they were *scaffolded* by adults. He proposed the term *zone of proximal development* to describe extension of a child's skills with adult help.

Lawrence Kohlberg built on Piagetian framework to describe children's moral problem-solving. He proposed six stages of moral development moving from egocentric behavior in preschool years to conventional morality of adults.

### Importance of Developmental Assessment

Developmental assessment is an integral component of comprehensive child evaluation. A thorough understanding of normal and typical sequence of development allows the clinician to ascertain the child's true developmental status.

- Knowledge of normal development and acceptable variations along with accurate interpretation of clinical examination findings is essential to recognize early patterns that are pathological and may indicate developmental disability. This is especially important for follow-up of *high-risk* babies and children with conditions that may cause brain damage, e.g., babies with perinatal asphyxia, meningitis and metabolic disorders.

- Early recognition of developmental disabilities allows early referral for *early intervention* services and enables the child to attain maximal developmental potential as brain plasticity permits reorganization of neural networks and there are critical *windows of opportunity* for learning different types of skills.
- Normal findings on developmental assessment can be reassuring to parents especially if there is a previous child with developmental disability in the family or before adoption.
- Assessment of behavioral problems also needs knowledge of normal development as behavior can be interpreted in context of a child's level of developmental functioning. For example, temper tantrums normally appear toward end of first year and peak between 2 years and 4 years of age and do not signify behavioral problem.
- Early identification of giftedness can be made on developmental assessment. Gifted children have significantly advanced skills in one domain or other and require optimum environment and educational placement for attaining their full potential.

Thus, developmental pediatrics is concerned not only with children with developmental disabilities but contributes to care of children who are developing normally and those who are at risk for developmental disorders because of medical conditions and adverse environment.

### LAWS OF DEVELOPMENT

Having discussed briefly some general concepts of development and theories of development, we can identify some general principles/laws that govern development.

1. Development is a continuous process from conception to maturity and is related to maturation and myelination of nervous system.
2. Infant development occurs in an orderly and predictable sequence that is intrinsically determined, i.e., development pattern is similar for all, e.g., a baby cannot learn to walk before acquiring ability to sit and stand independently.
3. Attainment of new skills builds on achievement of earlier skills, i.e., skills are not skipped and if so happens, the advanced skills may represent deviant development pattern, e.g., three-four-word sentence in a child who does not follow commands and has limited vocabulary, may represent echolalia and suggest autism. Similarly, early hand preference before 18 months of age is abnormal and indicates paresis of the other upper limb.
4. Development proceeds in cephalocaudal direction, i.e., from head to toe. A child has to learn to hold his head before acquiring truncal and limb control and arm movements come under cortical control before leg movements.
5. Development follows proximodistal principle, i.e., from the center of the body outward. Accuracy in reaching, grasping, transferring and manipulation (proximal development) are achieved before infant can isolate and use the index finger to explore the object (distal development).
6. Though development follows a predictable sequence, it proceeds at different rates influenced continuously by intrinsic and extrinsic factors that produce individual variations and make each child's development unique, e.g., all children learn to sit and crawl before standing, but the age at which they do so is different.
7. Development in one field may not necessarily parallel development in other fields, termed *developmental dissociation*. In other words, development in one field may be more rapid than in another or there may be retardation in one particular field. Thus, normal development in one field does not automatically imply normal development in another field. For example, a child with hearing impairment will have delay in language but not in motor domains.

8. Development proceeds from general to specific. Responses to stimuli change from generalized reflexes involving the whole body as seen in the fetus and newborn to discreet voluntary actions that are under cortical control, e.g., a young infant responds to a stimulus by vocalizing, kicking and arm movements, whereas an older infant will just go for the object and grasp it or may say the specific word and smile.
9. Cognitive development proceeds from simple to complex tasks, e.g., a child learns to coo and babble before saying meaningful words.
10. Certain primitive reflexes have to be lost before achieving voluntary functions. For example, grasp reflex has to be lost before the infant can learn to reach for objects and grasp them. Similarly, asymmetrical tonic neck reflex has to go before the infant can roll from supine to prone, bring the hands to midline or reach for objects.  
Persistence of primitive reflexes beyond the age at which they should disappear predicts abnormal development.

## FACTORS AFFECTING DEVELOPMENT

Child development is a product of both biological inheritance (the inborn genetic endowment from biological parents' nature) and environmental factors (nurture). Which one is more important for development is a topic of debate. However, both are critical for healthy brain development. There is an active interplay between innate potential of the child (genetic and temperament) and the environment (both intrinsic and extrinsic—nutrition, infections, exposure to chemicals and toxins, trauma, social and cultural, etc.). This makes development of each child unique.

The concept of brain plasticity helps to understand the importance of environmental influences on development. Plasticity refers to the ability of brain to reorganize neural pathways based on environmental stimulation. At birth, a child's brain contains billions of neurons. After birth, synapses develop rapidly with each neuron developing an average 15,000 synapses by 3 years of age. Neuronal pruning causes preservation of synapses in frequently used pathways and atrophy of less used ones. Thus, environment, both positive and negative, has a direct effect on the brain.

The transactional model of development proposes that infants, caregivers and their environment determine the child's developmental and behavioral outcome. It holds that the child and the caregiving environment tend to alter each other mutually, i.e., biological factors affect child-rearing environment and in turn are affected by it. In the following section, we discuss various biological and environmental factors affecting child development.

### Intrinsic (Biological) Factors

#### *Temperament*

Temperament has a major influence on all aspects of development. It refers to style of child's behavioral and emotional response to a variety of situations. It is mainly determined by genetic factors but can be modified by environmental forces. Temperament of a child is apparent during early infancy and shows considerable stability over time. Temperament influences development as it determines the child's adaptation to the environment, his activity level, attention, distractibility, quality of mood and intensity of reaction. Conflict, stress and behavioral difficulties may arise when the child's temperament does not match with caregiver's expectations.

#### *Brain Dysfunction*

Normal development requires anatomically and functionally normal central nervous system (CNS) and pathways. A child with CNS malformation (e.g., neural tube defects, lissencephaly) is unlikely to have normal development. Abnormal development

may result not only from intrauterine/perinatal insults (e.g., intrauterine infections, perinatal asphyxia, exposure to drugs/teratogens, radiation), events occurring later in life during period of brain growth (e.g., meningitis, encephalitis, intracranial hemorrhage) may affect development.

### *Genetic and Chromosomal Abnormalities*

Both chromosomal and multiple/single gene disorders can affect development to varying extent. Down's syndrome causes varying degrees of intellectual disability apart from causing other multisystem involvement. Fragile X syndrome is a single gene disorder causing developmental disabilities. Many other developmental disorders are being recognized to be caused by polygenetic inheritance.

### *Defects of Vision and Hearing*

Defects in special senses of vision and hearing have profound effect on development, especially if impairment is severe. A child with visual impairment would not be able to explore the environment, affecting his cognitive development. A child with hearing impairment would not develop spoken language unless his impairment is corrected.

### *Gestational Age*

The incidence of developmental disabilities like cerebral palsy, especially spastic diplegia, sensorineural deafness, visual defects, mental subnormality, learning disorders is more in preterm infants. Postmature infants are also at high risk because of high incidence of fetal distress and hypoxia.

### *Chronic Illnesses*

Impact of chronic illnesses, like congenital heart disease, chronic kidney disease, is dependent on multiple complex factors. Need for repeated hospitalization, impact of illness on physical activity and nutritional status and altered focus of parent's attention affect development.

### *Nutrition*

Adequate nutrition including adequate proteins, vitamins and essential minerals has a profound positive effect on child development. Exclusive breastfeeding for first 4–6 months of life has been associated with better intelligence (IQ) and cognition in infants. Inadequate nutrition before birth and in first years of life can interfere with brain development and can lead to intellectual disability and learning disabilities. Children with failure to thrive and severe malnutrition function at a lower cognitive level. Iodine deficiency and iron deficiency anemia are long known to be associated with cognitive development. Recent evidences show that mild iron deficiency without anemia can also interfere with cognitive development.

### *Environmental Exposure to Toxins*

Exposure to environmental toxins, e.g., lead, mercury, arsenic can have long-lasting effect on growth and development. Children with lead toxicity have lower cognition and higher rate of behavior problems

### *Stress*

Early stress can affect brain function, learning and memory adversely and permanently. Children exposed to extreme stress in early years of life illness/death of family member, parental separation, disasters, household move are at greater risk of developing a variety of cognitive, behavioral and emotional problems later in life.

## Extrinsic (Environmental) Factors

### Parental Health Status

Parental health status, especially mental health, has a clear impact on child development. Children of depressed mothers have substantial delay in cognitive and language development.

### Parenting Style

Time and attention given to the child by parents play a major role in infant and toddler development. Warm, supportive, caring, encouraging and enriched stimulating environment encourages development. Children continue to practice skills if they are rewarded and their behavior is reinforced. Positive emotionality, sensitivity and responsiveness toward child and avoidance of harsh physical punishment facilitate social-emotional development. Parenting styles differ with respect to degree of nurturance and discipline. Parenting styles can be classified as *authoritarian* (high demands and low nurturance); *permissive* (low demands and high nurturance); or *authoritative* (firm but democratic style combined with high nurturance). Authoritative approach is most desirable and associated with optimum outcomes, where parents provide warmth and support to their children and allow children to have input in the decision-making process, although parents have the final say. Parenting style should be consistent, clear and fair across caregivers and across situations. Disorders of attachment may result from inconsistent caregiving.

### Family Environment

Families have a profound effect on a child's development, especially cognitive and language development. Interaction between the child and family and quality of interaction plays a major role in development. Abusive and aggressive household environment has long-term consequences on development and mental health. Young children exposed to violence show increased risk of behavioral problems, aggressiveness and reduced level of prosocial behavior.

### Sociocultural Environment

Culture refers to a society's total way of life including customs, traditions, beliefs, values and language which is passed on from parents to children. Cultural patterns influence composition of household, how members interact with each other and child-rearing practices, thus affecting development.

## Socioeconomic Status

Socioeconomic status (SES) combines several factors including income, education and occupation of parents. Factors associated with SES that affect development include amount of time spent by parents with children, parents' emotional status, nutrition, neighborhood environment, access to education and other opportunities. Young children of educated parents have higher level of cognition.

## MORE ON THIS TOPIC

- Colson ER, Dworkin PH. Toddler Development. *Pediatr Rev.* 1997;18:255.  
 Carey WB, Crocker AC, Elias ER, et al. Developmental-behavioral Pediatrics. USA: Saunders; 2009.  
 Johnson CP, Blasco PA. Infant growth and development. *Pediatr Rev.* 1997; 18:224.  
 Johnston MV. Plasticity in the developing brain: implications for rehabilitation. *Dev Disabil Res Rev.* 2009;15:94-101.  
 Walker SP, Wachs TD, Grantham-McGregor S, et al. Inequality in early childhood: risk and protective factors for early child development. *Lancet.* 2011;378:1325-38.  
 Walker SP, Wachs TD, Gardner JM, et al. Child development: risk factors for adverse outcomes in developing countries. *Lancet.* 2007;369:145-57.

## IN A NUTSHELL

1. *Neurodevelopment* is a process of functional maturation related to maturation of the nervous system.
2. Developmental assessment should be a part of every comprehensive child evaluation.
3. Developmental milestones are organized into four domains for ease of assessment. However, they are all interrelated.
4. Development proceeds in a sequential, orderly and coherent pattern following certain laws that can be observed.
5. Attainment of one skill builds on attainment of earlier skills and skills are not skipped.
6. Development is a product of functional maturation of nervous system and learning. It is affected by various intrinsic (biological) and extrinsic (environmental) influences.
7. Developmental pediatrics is concerned not only with children with developmental disabilities but also contributes to the care of children who are developing normally and those who are at risk for developmental disorders because of medical conditions and adverse environment.



## Chapter 20.2

# Normal Development

Ujjwal Nene

Child development refers to the biological, psychological and emotional changes that occur in humans in the period between birth and the end of adolescence, as the individual progresses from dependency to increasing autonomy. It is a continuous process with a predictable sequence and yet it has a unique course for every child. Other processes such as social, moral and language development occur simultaneously in the course of development.

### THE FIRST YEAR

The newborn starts to learn through interacting with his environment and acquires competencies in all domains of development. Therefore, adequate interaction with caregivers and nutritional care play a crucial role in providing a *learning* experience to the infant. Normal development of the brain structure and effective functioning during infancy is normally an outcome of a healthy environment. Most of the child's understanding of his surroundings during this stage occurs through motor responses to the different sensations he receives. These early sensory-motor experiences influence the child's perceptual, cognitive and intellectual abilities. The parent-child relationship and quality of interactions form a foundation for further normal development.

### Motor Development

The first year of life is the stepping stone for achieving two major types of skills—gross motor and fine motor. Gross motor skills require the use of large muscles to achieve sitting, crawling and walking, jumping, kicking and running. These skills are normally achieved in the first two-and-a-half years to 3 years of age. Fine motor skills involve the use of small muscles in the hands and fingers in tasks such as picking up small objects, and later for feeding, writing, dressing, etc. Fine motor skills need practice and opportunities and continue to develop till the late ages. **Table 1** illustrates motor milestones achieved in the first year and the upper limits to achieve the same.

### Cognitive Development

According to Piaget, birth to 30 months is a period of sensory motor development. The child explores his environment and acquires various competencies using different senses in his waking state and is able to perceive objects and events as coherent.

A 2-month-old infant can differentiate between colors and patterns. Human facial expressions, such as *smile*, are successfully recognized at around the same age. Infants can match different properties in their surroundings, such as curvature, sequential, patterns and native versus nonnative rhythmic language patterns. They seek stimuli actively, integrating all the sensory inputs in the central nervous system and begin to use their innate reflexes. For example, grasping and sucking of objects are practiced as a way to stimulate and satisfy themselves. In this early stage of cognitive development, infants repeat and modify their actions that are focused on their own bodies to seek pleasure and satisfaction. For example, a baby may accidentally bring its finger close to its mouth and start sucking on it. On finding this behavior pleasurable, it will repeat this behavior over and over again. At around 2 months, the child starts smiling voluntarily with stable eye contact which significantly elevates the quality of the parent-child relationship and their bond of affection. A 3-month-old infant shows interest in people, plays with toys, kicks, bounces, reaches for his toes, watches his fingers move, and is attracted to very bright stimuli. A 4-month-old baby's close vision is well-established along with increased eye contact with parents and others. Its eye-hand coordination begins to develop, i.e., the child starts attempting to reach bright objects. Infants explore their own bodies, their surroundings and the people around. Their emerging sense of self helps them distinguish themselves from their mothers. They also start to tell their mothers apart from others and show preference to them as a source of satisfaction, affection and trust.

A 6-month-old infant shows more interest in manipulating, inspecting and exploring objects using all possible senses. Mouthing objects becomes the most prominent way of exploration. Transfer of object from one hand to another, visual inspection in sitting position, free hand and neck movements, voluntary grasp and release allow the child to experience the multisensory input of their surroundings. A safe and secure environment enables the child to master different behaviors.

**Table 1** Gross motor and fine motor milestones achieved during the first year

Milestones	Age	Gains/advantages	Upper limits to achieve the milestone
Neck hold and head control while in sitting posture	11 weeks	Allows visual observation, can follow moving objects more freely	21½ weeks
Pulls to sit with good head balance	13½ weeks	Adequate muscle tone allows child to proceed ahead	24 weeks
Rolls from back to stomach	18½ weeks	More body control and flexibility, motivation for locomotion	28 weeks
Sits alone with good coordination	23 weeks	Allows inspection visually, manipulation using both hands	30 weeks
Stands up on holding on to furniture	32 weeks	Coordinated movements of visual perception and locomotion	40 weeks
Walks independently	52 weeks	More self-control, exploration of surroundings, choice of proximity	61 weeks
<b>Fine motor development</b>			
Retains ring or rattle	14 weeks	Free play with objects	22 weeks
Reaches for toy	14½ weeks	Visuomotor coordination	22 weeks
Loses palmar grasp	20 weeks	Voluntary control on release	29 weeks
Transfers object hand-to-hand	21½ weeks	Exploration of movements and objects—visual and tactile	29½ weeks
Pat-a-cake, midline skill	35 weeks	Social play, grannies games	43 weeks
Turns pages of book	43 weeks	Increased visual observation for small details, autonomy for choice of stimulus	48 weeks

Acquisition of the concept of *object permanence* is a major milestone in cognitive development. The term was introduced by Jean Piaget to describe a child's ability to know that objects continue to exist even though they can no longer be seen or heard. A newborn focuses on objects in front of it only as a reflex activity. During 1–4 months, babies look at the spot for a long time from where an object disappears but do not visually or manually search for it. During 4–8 months, they search for partially hidden objects whereas by the age of 12 months, they search for completely hidden objects, i.e., toy hidden under a napkin. By 18 months, the child can find the object that he has seen being hidden but has difficulty if the object is displaced more than once. A 1-year-old likes to play *peek-a-boo* as an active play with caretakers. Children between 18 months and 24 months know that their parents exist even when not present, but cannot guess where they are and thus protest when separated.

### Language Development

Language development is the progressive growth in the ability to use language, from simple sound production to subsequent word fluency. Language development entails the maturation of a set of connected psychological processes including perception, cognition and memory as well as the biological maturation of the brain and those nervous system pathways that control the voluntary movements of the tongue and oral muscles. During the first 2 months, a child's language development can be observed by its ability to vocalize, recognition of its mother's voice, interest in and responses and smiles given to human talk. The first stage of language development is known as the prelinguistic, babbling or cooing stage, typically lasting from 3 months to 9 months of age when babies begin to make vowel sounds and by 5 months, they start producing consonant sounds too. By the end of 1 year, the child reaches the second stage—one-word or *holophrase* stage—the child tries to communicate its needs and wants effectively using a single word that stands for a sentence, i.e., water, mummy, etc.

### Emotional Development

An infant feels safe and secure only if trusted caretakers are consistently satisfying its emerging needs. This positive experience can develop a secure bond between parent and child which finally results in attachment. Erikson's first stage of psychosocial development, basic trust versus mistrust, completely depends on reciprocal attachment and maternal bonding. Parenting style and the child's temperament are two major factors that can significantly affect its emotional status. The infant's discomfort due to hunger that results in crying is alleviated by the parent who offers it food. This relief from distress is instrumental in developing an increased attachment and bond between the parent and child. The baby's emotions may be divided into two groups—pleasant or positive and unpleasant or negative. At birth, display of emotions is only through crying and screaming. During the sixth month, the baby can match emotions to others. During the ninth month, it starts showing negative emotions. At around 1 year, crying becomes a response to show dislike. Demand for autonomy emerges at this age that is manifested by throwing tantrums.

### Social Development

The first *social* relationship and feeling of attachment that most infants develop is with a parent and in most cultures that parent is the mother. A child's smile at seeing the mother's face is the beginning of social development. At around 3 months, the child regards his mirror image and at the fifth month, he enjoys playing with it. During the initial 6 months, the child shows interest in touching and looking at other infants and cries in response to the others crying. Through 6–12 months, the infant tries to influence

other infants by looking, touching, vocalizing, laughing or waving. Interactions with them are generally friendly, but they may hit or push one another.

**Table 2** provides the normal cognitive, language, emotional and social developmental milestones achieved during the first year and their approximate upper age limits.

### Implications of Delay in First Year

Delay in motor development can have major effects on the child's mental and social development. If the child fails to attain the expected milestones even after reaching the outer limit age, the pediatrician and parents should begin the required investigations and provide the child with adequate stimulation with the help of professionals, i.e., occupational therapists.

Babies kept in the neonatal intensive care unit (NICU) for a longer duration may face problems in their cognitive, social and emotional development due to deprivation or restricted mother-child interactions as well as the various NICU procedures. In such cases, the pediatrician should guide the parents regarding proactive preventive actions for dealing with the delay. Intervention in terms of multisensory stimulation, cognitive stimulation may be provided using the multidisciplinary approach. Infants left alone for a long duration, overexposure to television and mobiles are at risk of delayed social, emotional and language development. The child who does not respond to its own name should be observed carefully since it can be an early sign of autistic spectrum disorder.

## THE SECOND YEAR

Some of the important characteristics of the second year are an emerging sense of self, increased independence due to motor development and acquisition of primary communication skills. The child learns to organize its behavior through symbolic thinking and newly acquired skills in different areas.

### Motor Development

Most of the children start walking independently by the end of first year and latest by 15 months. A toddler's body proportion, i.e., its big head, short legs and big torso, makes its walk broad-based and unsteady with poor balance, with bent knees and arms flexed at the elbow. After few weeks of learning, the child's walk becomes noticeably refined. At 13–14 months, the child can walk backward and sideways. By the end of 15 months, it can climb up and down the steps with help and by the end of 22–23 months, independent climbing is achieved. Coordinated actions of running, watching and holding an object with adequate balance become easy.

### Cognitive Development

In this stage of tertiary circular reactions, the child becomes highly curious about its surroundings. This leads to experimentation with various external objects and trial and error is used vastly to understand the different properties of these objects. For example, children drop objects deliberately as they are fascinated to see what happens. Such exploration is an early form of problem-solving. By 18 months, the concept of *object permanence* is ingrained and this helps them understand their surroundings better and develop an imagination. The cognitive changes at 18 months are strongly associated with important changes in the emotional and language domains. Parallel development of fine motor movements, improved dexterity and development in language and communication help enhance the child's cognitive abilities which become evident in the child's behavior. For example, a 2-year-old child can match circles on a board game, can draw shapes such as lines on paper that stand for real objects such as a curved line for a flower, etc. Make believe play activities (symbolic play), mainly with their own bodies, become prominent at this stage, e.g., bathing or feeding the doll.

**Table 2** Normal cognitive, language, emotional and social development during the first year and their \*upper limits (in parentheses)

Age in months	Cognitive development	Language development	Emotional development	Social development
1 month	Momentary regard of object Visually follows moving objects Searches with eyes for sound	Expresses distress by crying	Cries Becomes quiet in response to auditory or tactile stimuli	Shows interest in human talk
2 months	Recognizes mother visually (13 weeks) Differentiates between familiar and unfamiliar stimuli Reaches for dangling ring/object, carries to mouth (17 weeks)	Babbles Coos Vocalizes two syllables (13 weeks)	Shows distress, excitements and pleasure	Smiles when mother touches, talks Gives social smile to face-to-face talk—other than mother (13 weeks)
3 months	Follows vanishing object/persons (17½ weeks) Turns head to sound of bell/rattle (19 weeks) Manipulates/starts simple play with toys (19 weeks) Stares at own hands (20 weeks)	Responds to talk using sounds	Can match facial emotions such as pleasure and distress with adults	Becomes more friendly with caregivers
4 Months	Engages in explorative play with paper or sound-making objects (20½ weeks)	Increased vocalization	Continues expressing emotions from simple to complex in progressive manner	Discriminates between caregivers and strangers (26 weeks)
5 months	Reaches for cube, objects (22½ weeks) Sustains inspection of red ring (24½ weeks) Eye cooperation in reaching and picking up object (20½ weeks) Lifts a cup by handle (20½ weeks) Persists in reaching objects (24½ weeks) Shows high interest in banging as a play (24½ weeks) Transfers object hand-to-hand (28½ weeks)	Shows discomfort or comfort through vocalizing, smiling (23 weeks) Shows interest in sound production (24½ weeks)	Exhibits primitive resistant behavior Turns head to show dislikes	Smiles to mirror image of self (24½ weeks)
6 months	Uncovers hidden toy (36 weeks) Manipulates objects—shows interest in details (28½ weeks) Pulls string adaptively and secures toy (32 weeks)	Vocalization of different syllables (32½ weeks) Listens selectively to familiar words, recognizes names of close family members and familiar objects (36 weeks)	Expresses anxiety, discomfort in strangers company Can respond to and express range of emotions, i.e., excitement, anger, fear, joy, interest Smiles and laughs when the mother does so	Shows more attachment to familiar adults
7 months	Uses thumb opposition for objects hold (30 weeks) Actively manipulates objects with eye-hand coordination (30 weeks)	Babbles in a complex manner mixed with few syllables (35 weeks)	Responds to vocal tone, shows resistance. Displays fear, anger, defiance, affection and shyness	Shows interest in interacting with caregivers and in simple play (32 weeks)
8 months	Looks at pictures in books (40 weeks) Looks for disappeared contents of box (44 weeks)	Says <i>da-da</i> , <i>ba-ba</i> or equivalent (36 weeks)		
9 months	Plays pat-a-cake, achieves midline skill (40 weeks)	Recognizes native language (36¾ weeks)	Shows anxiety and distress when separated from parents	Enjoys games with series of actions with adults
10 months	Holds crayons adaptively, attempts scribbling (45 weeks)	Starts using expressive gestures (45 weeks) Inhibits on verbal command <i>no</i> (45 weeks)	Frowns when annoyed and shows a fear of strangers	Imitates simple actions like combing, patting, etc.
11 months	Turns pages of books (45 weeks) Unwraps cover and secures object hidden in front of child (45 weeks)	Follow simple commands such as put, give (52 weeks) Imitates words (57 weeks)	Expresses likes and dislikes using sounds, gestures and facial expressions	Enjoys interacting with other children and adults Enjoys imitative play, imitates simple actions
1 year		Uses particular words for needs and demands	Throwing tantrums for demands Becomes distressed when others are distressed	

\*Upper limits are derived from *Developmental Assessment Scales of Indian Infants* developed by Dr Pramila Phatak (1998) that gives most precise estimation about development.

## Emotional Development

Family environment plays an important role in the child's emotional world. A stressful atmosphere at home makes the child feel vulnerable, insecure and anxious. Irritability, anger, problems related to feeding and sleep can be manifestations of internal anxiety and fear. Temper tantrums are often results of conflicts between parental control and the infant's need for autonomy and mastery over its actions. Fear responses are usually associated with the fear of loud noises or falling. Fear, rage and love are the basis for many other emotional responses. A one-and-a-half-year-old child can show shame, shyness and can express dislike through restlessness and tantrums. The child develops a preference for soft objects, i.e., stuffed toys, blankets for soothing, etc. At around 21 months, the child attempts to control those emotions that are not approved by its parents and tries to gauge its parent's feelings in order to behave accordingly.

## Language Development

In this domain, receptive language is achieved first, followed by expressive language, during the second year of life. 1-year-old children use *one-word expressions* but their understanding of language far exceeds their capacity to express themselves. An average 15-month-old child can show body parts, objects like shoes, watches, fans, etc. The rapid increase in vocabulary is typically found at about 18 months, when a child learns about 50 words. A dramatic change in the child's linguistic development occurs typically when it realizes that words (labels) stand for things. As a result, by 2 years of age, the average child knows about 900 words. A 2-year-old can follow two-step commands such as *sit-down here and drink water*. Increased use of language gives them a sense of control over their surroundings. **Table 3** provides a list of achievements to be checked by the pediatricians.

## PRESCHOOL PERIOD: 2–5 YEARS

The most drastic change in a preschooler's personal life is the separation from parents. At this age, the child acquires a good amount of control in the areas of language and communication. He is exposed to a larger world where he learns to behave as per the rules of society and school and tries to fulfill the different expectations of people and situations. The child learns to spend time away from parents, begins to enjoy the company of his age mates and becomes aware of his ability to utilize his resources as and when they are needed. Major check points at 3, 4, and 5 years of age are listed in **Table 4**.

## Motor Development

Normally, most of the 2 years and 4 months old children can raise themselves to the standing position from supine without turning to a side. They can build a tower of 8 cubes, hold a pencil in fingers with the opposable thumb, jump with both feet, and walk on tip-toe when asked and fold paper after demonstration. As they approach 3 years, they learn to walk with good coordination and a mature gait and can even run. Various motor actions are acquired successfully, such as kicking, catching, throwing, dancing, climbing on structures, etc. At 3 years, they can dress and undress themselves with a little help in buttoning. Bedwetting is normal up to the age of four in girls and five in boys. Handedness is normally established by the third year, though hand dominance is often observed at around 2 years itself.

## Cognitive Development

The period between 2 years and 7 years was labeled as preoperational stage by Piaget, which is characterized by perception-dominated thinking, egocentrism, and magical thinking. Inanimate objects are given life, e.g., a doll talks to the

**Table 3** Developmental check-points at 18th and 24th months

18 months	24 months
Walks independently	Climbs up and down the stairs with hand held
Throws a small ball	Builds tower of three cubes
Responds to word or command with appropriate actions	Combines two words like <i>go-out</i> , <i>me-ice cream</i>
Understands inhibiting verbal commands	Understands and follows simple verbal instructions

Data are derived from Developmental Assessment Scales of Indian Infants which offers the most precise estimates of developmental level.

**Table 4** Developmental check-points at 3rd, 4th and 5th years

3-year milestones	4-year milestones	5-year milestones
Runs forward well	Copies a cross	Swings, hops, somersaults
Turns single page of book	Walks down stairs like adult without support	Says name and address
Makes a circle, vertical and horizontal line	Uses plural	Defines objects of daily use verbally
Strings beads	Cooperates with other children	Draws a square
Gives full name, names common pictures and things	Gives opposites of simple adjectives	Counts ten or more objects
Identifies pictures by their descriptions	Matches shapes, animals, colors	Likes to sing and dance
Understands basic color concept of black and white		

Data are derived from Stanford-Binet test, and other scales that offer the most precise estimates of developmental level.

child, plants feel pain when flowers are plucked. They find it difficult to understand the cause and effect relationship as true logical thinking develops at a later stage. Now there is a beginning of abstraction, e.g., a wedding is a representation of meeting relatives or eating sweets.

Normally, a 30-month-old baby can point to seven pictures, name objects and pictures, understand the concept of 1, which is the beginning of arithmetical thought. Similarly, awareness about the human body often develops by 30 months. A 3-year-old child can differentiate between big and small, more and less, understanding of body parts and their functions. A 5-year-old can define objects verbally by their uses, draw a square, and understand similarities and differences on a concrete level.

## Language Development

Children's language development is very rapid during 2–5 years. At 2 years, they can make short, multiword sentences that have a subject and predicate in a more mature manner. For example, a child might say *ice cream is nice* or *want more candy*. 3-year-olds have sufficient vocabulary to meet immediate needs of life. At 5 years of age, a child can communicate complex thoughts with appropriate descriptions. At four, they can use past tense and at five, they can also use future tense. As they grow, they continue to learn new words every day. By the time they enter the school at the age of five, children typically have a vocabulary of 10,000 words or more.

Acquisition of language is significantly dependent on environmental factors such socioeconomic background.



The amount and quality of interactions and communication with children directly influence their language development. Language development is also closely associated with cognitive and emotional development. Children with delayed speech tend to throw tantrums as they are unable to articulate their feelings using expressive language. Delay in language acquisition may also be a sign of mental subnormality. In school, language plays a crucial role in learning. First the child understands language only after which he starts using it for self-expression. This is followed by recognition and reading of letters and words and finally the acquisition of writing skills. The foundation for reading and writing is laid in the preschool stage which is a prerequisite for future academic progress.

### Emotional Development

Emotional experiences are strongly linked to learning. Different children express different emotions in different manners, intensities and frequencies. For example, the frequency with which children smile and laugh seems to vary with the nature of the environment in which they are raised. Appreciation or a positive response to a baby's smile from parents will increase the frequency of the smile. Learning experiences can also elicit and reinforce other emotions like fear, anxiety, etc.

Typically, at the end of 30 months, children start showing shame and embarrassment and at around 3 years, they show guilt and pride too. From age 4 years to 6 years, they are able to conjure only one emotion at a time. They start controlling unapproved emotional expressions and adhere to the socially acceptable ones.

Children in the preschool stage normally experience attraction, passiveness, attachment and affection toward the parent of the opposite sex and jealousy and resentment for the other. Normally, curiosity about genitals and adult sexual organs is demonstrated. At times, masturbation is also seen in young children.

### Social Development

Children begin to adopt behaviors that are approved by their parents in social surroundings. Their imaginative and social play increases throughout this period. In the due course of socialization, the child starts learning the expected standards of behavior, attitudes and skills that are considered appropriate in society. *Play* is instrumental in the child's social, moral and emotional development since it involves physical activity, learning and interacting with peers, understanding and practicing adult roles. Social and moral developmental achievements can be seen in **Table 5**.

### Moral Development

Parental values, surrounding culture and environment influence the child's moral development immensely. Adults expect children to learn these rules and experience satisfaction when conforming to them and emotional discomfort or guilt when violating them. A

child begins learning *wrong* and *right* from the age of two and his learning is reinforced by parental approval. Internalized standards, the *voice of conscience* or the super-ego, restrain the child from doing wrong even when he is alone. The rules are internalized to avoid punishment (physical consequences) and to attain parental love, approval and security.

### Concerns in Preschoolers

Decrease in food intake during this period can cause parental anxiety. The pediatrician can deal with it by providing charts and proper counseling about adequate nutrition for the child. Very active children or slightly hyperactive children are more prone to physical hurt and accidents; hence, parents should be counseled regarding safety precautions. Impulsive children, who are at a higher risk, should be evaluated in detail.

Working parents should be counseled regarding spending quality time with their children. Parents should interact with them using different skills and types of play activities. Telling stories, reading out books, looking at pictures in books, and ample opportunities for the child to express and observing verbal and nonverbal behaviors of parents facilitate language development. Regular communication also helps them gain emotional control and understand social and moral expectations.

Children need guidance to understand what is expected from them. Excessive control can lead to low initiative and lack of confidence, whereas too much flexibility may create anxiety and insecurity due to confusion and lack of control. Corporal punishment and harsh handling that lead to insecurity and anxiety should strictly be avoided. Parental interference in the development of the child's *handedness* should be prevented by counseling. Some toys and books kept before the child can reduce its anxiety during clinical examinations.

Children differ in temperaments, emotional characteristics and the types of responses they give to various stimuli. These inborn temperaments have a great impact on the pattern and quality of the parent-child relationship. Parents may need guidance to understand their child's temperament and best suitable handling. A child with delayed speech who does not like to play with peers, gives poor eye contact and is more engrossed in solo play, must be evaluated in detail to rule out features of autism.

## MID AND LATE CHILDHOOD

### Physical Development

This stage is characterized by major increases in height, weight and build. Genetic makeup, as well as nutrition and exercise, may affect a child's growth. At this age, children usually have steady and strong motor skills. In this age group, i.e., 6–11 years, a steady increase in muscle strength, stamina, body coordination and eye-hand coordination is seen. They can perform many complex activities involving different motor skills, such as playing musical instruments, playing skillful games, like badminton, dancing, bicycling, shooting, etc. Usually they have high endurance and satisfactory balance which can be seen in their sport activities. Good fine motor control is reflected in activities, such as writing neatly, drawing and dressing up appropriately. Body image begins to develop at around 6 years of age and continues in later stages too. Towards the end of this phase, they begin to develop secondary sexual characteristics.

### Cognitive Development

Late childhood is distinctly different in cognitive functions from the preschool age. This period is considered a concrete operational stage by Piaget. Children start operating logically in which they combine different mental functions in a flexible manner to solve

**Table 5** Social and moral development in 3rd, 4th and 5th years

Age	Social development	Moral development
3 years	Begins to engage in complex and dramatic play	Has little concern for and awareness of rules
4 years	Engages in fantasy play to overcome specific fears	Starts learning about rules, starts controlling undesired behavior
5 years	More open and willing for coordinated friendship to achieve successful play Can dress and undress oneself Engages in role plays	Develops great respect for rules set by significant adults for gaining their approval

problems. Logical thinking enables the child to organize objects into hierarchies and categories. They acquire different fundamental skills such as reading, writing, rules of language and basic arithmetic to achieve academic goals. They start understanding the meaning of abstract words like sympathy, surprise, etc. They prepare themselves for more difficult and complex mental functions. The interplay of their emotional worlds and cognitive functions has a great impact on their school performance. A child's cognitive performance can be assessed using standardized assessment tools and by deriving an intelligence quotient (IQ).

### Social Development

In this phase of development, the child enters a formal school set up and faces many challenges. Stable parent-child relationship is the basis of healthy social relationships in later life. The school allows the child to move away from parents successfully and takes the child toward self-reliance and independence. In families, the siblings play the roles of competitors, role models and supporters, whereas in schools, these roles are played by peers. The child also develops social relationships outside of school, which exposes him to different facets of sociocultural life. Internalization of gender-specific roles and an understanding of gender-appropriate behavior take place in this stage. Their understanding of social roles and acceptable and desired behavior develops. Along with outdoor, strategy and word games, they show a preference for same sex playmates. The family environment and quality of relationships with close family members, especially parents, play an important role in social and emotional adjustment.

### Emotional Development

Acceptance by parents, peers and authority figures like teachers help in laying the foundation for the child's emotional well-being. Positive experiences in their world can help them build positive self-concepts, sense of security and feelings of adequacy. Social skills, such as appreciating others, being able to initiate interactions effectively and being able to communicate well play a vital role in social acceptance. Fear of death, ghosts and inanimate objects are commonly experienced in this stage. Curiosity about birth, death and sexual matters are common topics of conversations among peers. Masturbation, exploring their own sexual organs as well as of others is common. Unconditional affection from parents helps them feel secure about their own importance in their parents' lives. Tender emotions such as sympathy, compassion, humor are experienced by them. They start gaining control over the display of emotions, such as jealousy, anger, fear and disgust.

### Moral Development

Approval and disapproval of parents and other authority figures become vital at this stage. Internalization of set cultural and familial rules, approved standards in the given cultural setup and the emergence of a belief system occurs in these years. According to Piaget, children in elementary school begin to develop moral concepts, such as justice, fairness and reciprocity in interpersonal relationships.

### Concern

Children in this age group are highly aware of and sensitive about their physical attributes. Hence, regular physical activity should be recommended. Any disability, deformity or handicap can make significant impression on their self-concept and cause emotional disturbance. This needs to be addressed carefully through professional intervention.

Parents should be made aware that children of this age are vulnerable to sexual abuse. The pediatrician must talk to the parents regarding this so that necessary precautions can be taken. If a child is excessively anxious regarding being separated from his parents, does not mix with his peers and is poor in scholastic progress, he must be evaluated in detail to rule out emotional and cognitive difficulties. Parents may have concerns regarding their child's school-related problems, such as poor academic performance, difficulty in reading, writing, mathematics, behavioral issues, such as lying, aggressiveness, etc. which they may share with the pediatrician. In such cases, further evaluation must be recommended. Gifted children may also need help and guidance in order to keep them challenged adequately.

Parental support, affection, acceptance and guidance are strongly needed for normal emotional, social and moral development. Children of single or separated parents may face emotional and social issues. The pediatrician must assess all areas of the child's functioning and take the required steps to improve the quality of the child's life.

### IN A NUTSHELL

1. Child development refers to the biological, psychological and emotional changes that occur in humans in the period between birth and end of adolescence, as the individual progresses from dependency to increasing autonomy.
2. Development is described in terms of motor, cognitive, language, emotional and social domains in infancy, toddlers, preschool children and school age children.
3. The chapter provides the normal age of attaining various developmental milestones and their upper limits.

### MORE ON THIS TOPIC

- Bruno FJ. The Family Encyclopedia of Child Psychology and Development. USA: John Wiley & Sons; 1992.
- Crow LD, Crow A. Child Development and Adjustment. New York: The Macmillan Company; 1963.
- Hetherington EM, Parke RD. Child Psychology: A Contemporary Viewpoint. USA: McGraw-Hill College; 1999.
- Illingworth RS. The Normal Child. USA: Churchill Livingstone; 1990.
- Morgan CT, King RA, Weisz JR. Introduction to Psychology. New Delhi: Tata McGraw-Hill Publishing Company Limited; 1986.
- Sadock BJ, Sadock VA. Synopsis of Psychiatry. New Delhi: Wolters Kluwer (India) Pvt. Ltd; 2007.

## Chapter 20.3

# Approach to Diagnosis of Developmental Delay: Developmental Screening and Surveillance

Sudha Chaudhari

Developmental delay is a term used for a condition in which the child is not developing and/or achieving age-appropriate skills. It refers to a childhood physical or mental impairment or a combination of both, that results in substantial functional limitations in major life activities.

Early identification of developmental disorders is critical to the well-being of children and their families. It is an integral responsibility of the pediatrician who is following up that child. Delayed or disordered development can be caused by specific medical conditions and may indicate an increased risk of other medical complications; it may also lead to further behavior disorders or associated developmental disorders.

Child development is a dynamic process and is often hard to measure. The various streams of development, including gross motor, fine motor, language cognitive and adaptive behavior are interrelated and complex within themselves. Children develop skills variably and show a new skill inconsistently when mastering it. A single test at one point in time only gives a snapshot of the dynamic process, making periodic screening necessary to detect emerging disabilities as a child grows.

A survey by the American Academy of Pediatrics showed that few pediatricians use effective means to screen their patients. It is absolutely mandatory that every *high-risk* infant be screened for developmental delay. In fact, the American Academy of Pediatric recommends that a development screening should be done for every well child at 9, 18 and 30 months visit.

Early identification is important because of the potential for improvement of outcome through educational and rehabilitative services for children with or at risk for developmental delay. In the first months of life, abnormal development is indicated by a poor suck, floppy or spastic tone and a lack of visual or auditory response to environmental stimuli. Later, in the first year, motor delay in sitting or crawling and in the second and third years, language and behavioral abnormalities point out to a problem in development.

## DEVELOPMENTAL ASSESSMENT

Early identification has a three-pronged approach—a birth and developmental history, a physical and neurologic examination and developmental screening. Birth history and other adverse prenatal and perinatal events, maternal illness, substance abuse, consanguinity and sociocultural background are important. The presence of multiple risk factors increases the chance of developmental disability.

**Developmental history** A history of delayed or uneven acquisition of milestones in any sphere of development including cognition, fine or gross motor skills, speech and language, adaptive skills and psychosocial skills should alert the pediatrician to the need for further evaluation.

**Physical examination** The general physical and neurologic examination is an integral part of the evaluation of the child.

Dysmorphism, growth abnormalities, major and minor congenital anomalies, skin or eye findings and organomegaly may give a clue. Neuromotor delays may be the presenting feature of several genetic disorders.

**Neurologic examination** A classical neurologic examination may not be enough in children with developmental delay. Some special examination methods like the one described by Amiel-Tison will yield information that is more useful for rehabilitation.

## Hearing and Vision Screening

Hearing and vision screenings should be a routine in the examination of a child. Visual tracking can be checked with a red ball and hearing can be assessed by using a bell. The cause of hearing loss may be related to the etiology of developmental disability (congenital cytomegalovirus infection, microcephaly). Children at high risk for hearing impairment include premature infants, children with cerebral palsy and children with some genetic syndromes.

## Developmental Screening

Studies have demonstrated that pediatricians are unreliable in determining the presence of developmental delay from clinical judgment alone. Hence a standardized screening test must be used. The most effective method for development screening by a busy pediatrician is a combination of a historical review of milestones (in comparison with established norms), observation of development skills using a standardized screening tool and the neurologic examination.

## ALGORITHM FOR DETECTING DEVELOPMENTAL DELAY

(Based on the Recommendations of American Academy of Pediatrics)

### Pediatric Patient at Well-Baby Clinic Visit

Every child attending the well-baby clinic must have a developmental examination (**Flow chart 1**). Many children may have risk factors at birth which may lead to delayed development. Some children may show delayed development in early childhood. If these are not detected and treated early on, the children may end up with social and emotional problems and school failures. Some specific medical conditions may have delayed development, for which there may be medical treatment. Early intervention may help in a wide range of developmental disorders.

## Surveillance

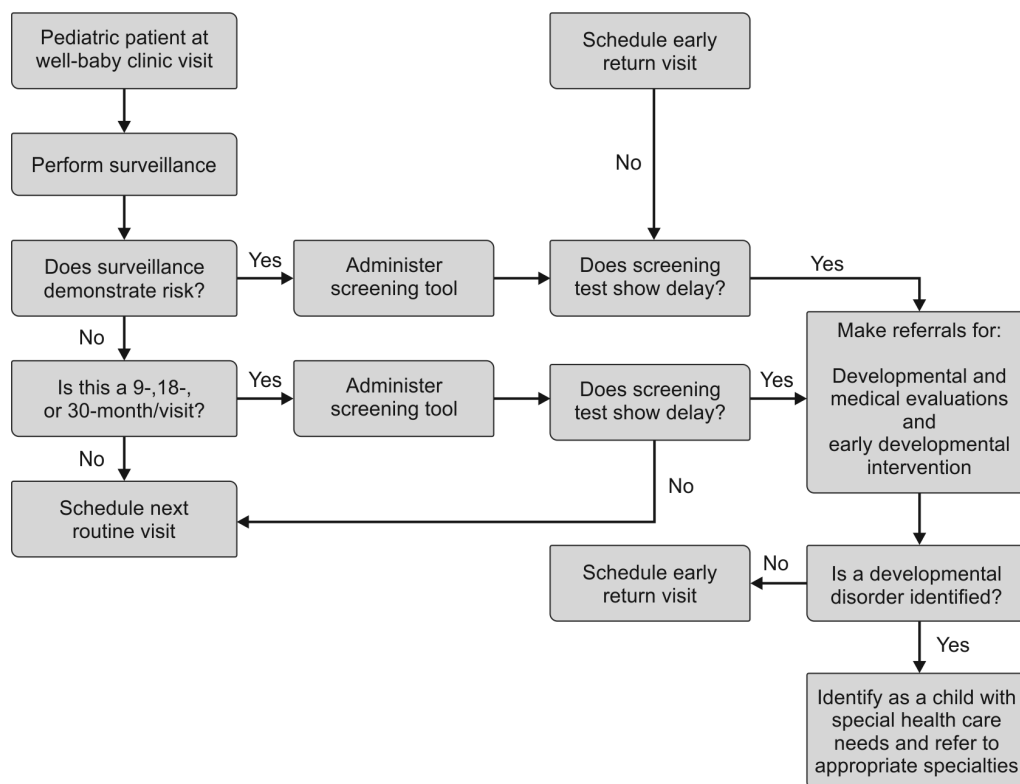
Pediatricians can identify children who may have developmental problems by continuous surveillance and vigilance. Surveillance will result in appropriate referrals, patient education and promotion of healthy development. There are five components of developmental surveillance.

### Parents' Concerns

Educated parents have sharp observational skills. The pediatrician must give serious attention to parental concerns about their child's development. Asking specific questions about the child's behavior may give a clue regarding the child's development because development and developmental delays are often manifested by the child's behavior. Sometimes a child may have a major delay and the parents show no concern, probably because of lack of knowledge about developmental milestones.

### Developmental History

Developmental history taking should be a routine part of the well-baby visit. Age-specific questions such as voluntary reach for a

**Flow chart 1** Developmental surveillance and screening algorithm during a well-baby clinic visit

Adapted from: Council on Children with Disabilities, Section on Developmental Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children with Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics*. 2006;118:405-20.

toy, independent sitting, crawling can be asked to ensure that the child is acquiring skills at the right age. Equal attention should be given to deviations in development, whereby children develop skills out of sequence in conditions, such as cerebral palsy and autism. Normal motor skills and delayed language development may be seen in children with autistic spectrum disorder or mental retardation. Children with spastic diplegia have normal language skills with motor delay. Regression of motor skills suggests some serious neurologic problem.

### Observation of the Child

A careful physical and developmental examination must be done at every well-baby clinic visit.

### Presence of Risk and Protective Factors

Assessment of risk factors is an important aspect of surveillance. The risks may be biological, genetic, social or environmental. The presence of more than one risk factor may increase the chances of developmental delay. Children with known risk factors may require more frequent developmental surveillance or may be directly referred for developmental assessment. A loving, educated, supportive family, where the child grows up in a warm, conductive environment is an important asset in a child's life. Environment plays a major role in a child's development.

### Documentation

Milestones should be documented properly at each visit.

### Demonstration of Risk

If the parents express concern about the child's development, the child should be referred directly for a development test. Similarly, if the pediatrician feels during surveillance that the child is at risk for developmental delay, a screening test may be required. If the screening test is normal, the parents may be reassured, but surveillance should be continued.

### Periodic Development Screening

Development may be proceeding normally and there may be no known risk factors, but it is worthwhile to do a periodic developmental screening test. The American Academy of Pediatrics recommends screening at 9, 12 and 18 months.

- *Nine months of age:* Many motor skills are evolving at this age. Hearing and vision can be reliably tested at 9 months. Important aspects of communication and language skills such as vocalization, gestures are obvious at this age. Since language, motor and cognitive skills develop rapidly at this age, parents should be asked if they have concerns in these areas of development.
- *Eighteen months of age:* Language and communication delays are very obvious at this age. Hence early intervention and speech therapy may be started. Mild motor delays which were not picked up at 9 months, may become apparent at 18 months and intervention can be started.
- *Thirty months of age:* Motor, language and cognitive delays are easily identified at this age using screening tests and intervention can be started immediately.



When pediatricians use only their clinical impression to diagnose developmental delay instead of using a screening test, their impressions are not accurate many a times. Hence, screening tests must be used to improve the precision in diagnosis of developmental delay.

### Screening Test

It is a brief standardized test which helps in identifying children at risk of a developmental disorder. Screening tools like ages and stages questionnaire can be completed by moderately educated parents and the answers can be scored even by a non-physician. However, the final interpretation must be done by the pediatrician. The screening test does not give a diagnosis but merely identifies areas in which the child is lagging behind. Screening tests should be given periodically. If we wait for the child to miss a major milestone like walking or talking, it may be too late and we will be depriving the child of the benefits of early intervention.

### Screening Test Results

If the screening test results are normal, this can be told to the parents and relieve them of their anxiety. If the results are not normal, the child should be referred immediately for more elaborate developmental tests and medical evaluation.

### Developmental Evaluation

Diagnostic developmental evaluation should be done when the screening test is not normal. This evaluation aims at making a specific diagnosis of the development disorder, for counseling the parents regarding prognosis and referring the child immediately for proper therapeutic intervention. These children may have other associated developmental and behavioral problems and these will also have to be treated. An interdisciplinary team consisting of a psychologist, occupational therapist and audiologist will be needed.

### Medical Evaluation

A medical evaluation consisting of biological, environmental and other risk factors for delayed development must be done in an attempt to establish an etiology. Screening of vision and hearing, review of neonatal metabolic screen, growth, family and social history may give a clue to the etiology.

A detailed medical evaluation and additional tests like brain imaging, electroencephalogram, metabolic screen and genetic screen may be required. The parents find it easier to accept the child's disability once the etiology is explained to them. This also helps in treatment, planning, genetic counseling for recurrence and prognosis. It is reported that an underlying etiology will be identified in approximately one quarter of cases of delayed development, with higher rates (> 50%) in children with global delays and motor delays, and lower rates (< 5%) in children with isolated language disorder.

This evaluation can be done by a trained and skilled pediatrician, a developmental pediatrician, pediatric neurologist and, if required, a pediatric geneticist. When a child is identified as having developmental delay, early intervention is mandatory.

### Developmental Disorder

The child can be referred for appropriate therapy if a developmental disorder is identified.

### Referral to Rehabilitation Services

When a child is identified to have developmental delay, the child should be referred to a center which has specialized services. The pediatrician should be aware of the centers in the local area where

psychologists, occupational therapists, audiologists and other such facilities are available for testing and therapy. Unfortunately, there are very few such centers in India.

### THE HIGH-RISK INFANT

The *high-risk* infant is one who is at risk for having a developmental disability. The number of high-risk infants is increasing day by day since we are saving many extremely low birthweight babies, with all the new technological advances. The risk factors may be biological or environmental, or there may be an overlap of both. Some risk factors carry a much higher risk of developmental delay than others. The biologic risk factors are: (i) prematurity; (ii) low birthweight; (iii) intrauterine growth retardation; (iv) hypoxic ischemic encephalopathy; (v) congenital brain abnormalities on imaging; (vi) biochemical abnormalities (hypoglycemia, hyperbilirubinemia; (vii) sepsis/meningitis; (viii) congenital infections; (ix) respiratory distress needing ventilation; (x) seizures; (xi) intracranial hemorrhage; and (xii) maternal substance abuse.

It is absolutely mandatory that a *high-risk* infant be followed up very closely. Besides monitoring the growth and nutrition, a developmental examination at least in every 3 month this is recommended. It is important to use the corrected age while assessing preterm infants. Parents of *high-risk* infants sometimes tend to overrate skills of their children. Hence, the pediatrician should do a good developmental examination, especially of the motor skills.

Pediatricians can elicit key clinical information about a child's motor development from the parents by asking them broad open-ended questions (**Table 1**).

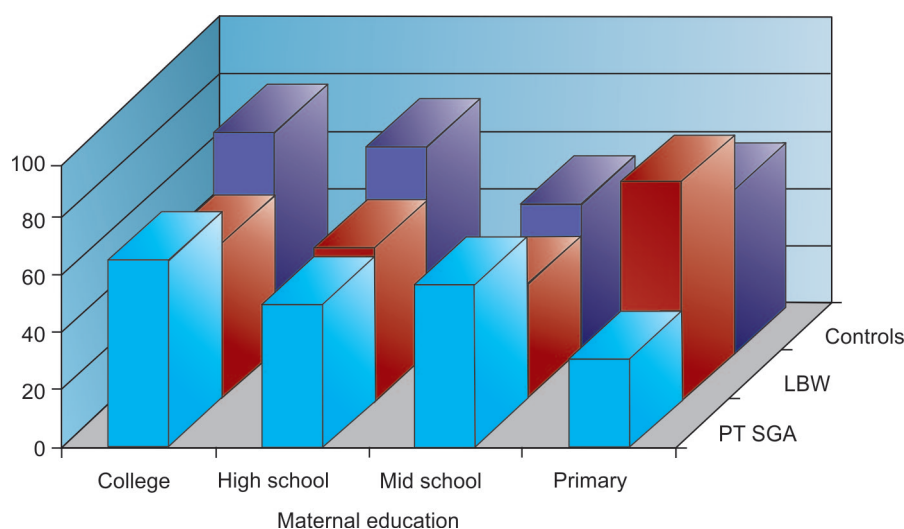
Children with increased tone may attain motor milestones early, asymmetrically or *out of order* like standing before sitting or development of handedness before 18 months. Children born with developmental defects present with developmental delay. Children who show regression of milestones should be investigated for neurodegenerative disorders.

The environmental risk factors are low socioeconomic status, poor maternal education and a single parent. In the *Pune low birthweight study—Birth to Adulthood*, babies who were preterm and small-for-gestational-age (SGA) with double biologic risk factors of prematurity and intrauterine growth restriction, had the lowest intelligence quotient (IQ). But preterm SGA children in the higher socioeconomic group and with college educated mothers had higher IQs at 18 years compared to those from the lower socioeconomic group and mothers with only primary school education (**Fig. 1**).

**Table 1** Key elements of the motor history

Key elements of motor history	Example
Delayed acquisition of skill	Is there anything your child is <i>not</i> doing that you think he or she should be able to do?
Involuntary movements or coordination impairments	Is there anything your child is doing that you are concerned about?
Regression of skill	Is there anything your child used to be able to do that he or she can no longer do?
Strength, coordination and endurance issues	Is there anything other children of your child's age can do that is difficult for your child?

Source: Adapted from Noritz GH, Murphy NA and Neuromotor Screening Panel. Pediatrics. 2013;131:e2016.



**Figure 1** Maternal education and IQ (Standard Progressive Matrices) at 18 years  
 Abbreviations: IQ, intelligence quotient; SGA, small-for-gestational-age; LBW, low birthweight; PT, preterm.

## EARLY INTERVENTION

It implies a system of programs that work with an infant and his or her family to prevent or minimize adverse outcomes in the child. Although a number of studies have demonstrated beneficial effects of early intervention programs, there is no convincing data to suggest that it prevents disability. Nevertheless, many feel that early intervention strategies do help in minimizing secondary complications and generally support the parents through a difficult time of uncertainty and coming to terms with their child's disability. Intervention is most important when it occurs at the time that a developmental skill should be emerging.

We recommend that a neurodevelopmental examination be done at corrected age (chronologic age + weeks of prematurity) of 3, 6, 9, 12 and 18 months and a development quotient (DQ) be done at 18 months to see the motor and especially the mental development.

The development of preterm infants is quite different and has more variability compared to full term infants. It is important to understand the deviations in the development of preterm infant lest you make a rash diagnosis of cerebral palsy. It is reported that 60% of preterm babies have tone abnormalities. However, the brain has tremendous plasticity, and by 9 months, many of these tone abnormalities disappear and tone normalizes by 1 year. These are termed as *transient tone abnormalities*. Chaudhari et al. have reported that 41% very low birthweight infants had transient tone abnormalities, but their cognitive outcome at 5 years was normal. This is why one should never make a diagnosis of cerebral palsy at the first examination, but several sequential examinations should be done over a period time.

One of the best tests for diagnosis of tone abnormalities is the neurological assessment described by Amiel-Tison. Evaluation of tone is the fundamental part of this assessment. The waxing and waning pattern of neuromotor development from 28 weeks to the end of first year should be clearly understood. For example, from 28 weeks to 40 weeks of gestation, the acquisition of muscle tone and motor function spreads from the lower extremities to the head (caudocephalic). After full term, the process is reversed, so that relaxation and motor control proceed downward for the next 12–18 months (cephalocaudal; **Fig. 2**).

Examination of skull and ocular signs must be looked for. Neurosensory development is assessed by noting visual pursuit with a red ball and hearing with a bell. History of convulsions,

sleeping pattern, quality of cry and sucking and swallowing behavior should be noted.

The evaluation of tone is based on the study of (1) spontaneous posture; (2) passive tone; and (3) active tone. Spontaneous posture is studied by inspecting the child while he or she lies undisturbed (**Fig. 3**). Axillary suspension of the child should be done before assessing the tone. A hypotonic infant will slip through the hands, a spastic infant may spontaneously scissor (**Fig. 4**).

Passive tone is evaluated by applying certain maneuvers to an extremity. The resistance of the extremity to these maneuvers is measured as an angle. The angles are the same as those used in the Dubowitz gestational age score, like the adductor angle, popliteal angle, scarf sign, square window, etc. These angles have been standardized by us on normal Maharashtrian infants and are quite similar to those described for Caucasian French infants.

Active tone is studied with the infant moving spontaneously in response to a given stimulus like pull to sit or pull to stand.

Brisk tendon reflexes and clonus are noted. While eliciting ankle clonus, one must look for Achilles tendon tightness because this will make the child do *toe-walking*. (**Fig. 5**)

The persistence of primitive reflexes like asymmetrical tonic neck reflex (**Fig. 3**) is especially looked for. Fisting and cortical thumb are also noted. The appearance of postural reactions like lateral propping and parachute at the right age is also noted. All this information put together makes it a complete neurological examination.

The main drawback of this method is that it does not take mental development into consideration and hence does not replace developmental tests. It is a good screening test to identify infants who need occupational therapy and to decide which infants need to be referred for the more elaborate developmental tests. Chaudhari et al. reported that if the 3 months assessment by Amiel-Tison was normal, the predictive value for a normal 12 months motor development was 93.6%.

## INVESTIGATIONS

Investigations aim at establishing a possible etiology underlying the child's specific developmental delay. The etiology may or may not be apparent at the end of the clinical examination. Determining the underlying etiology is important for many reasons. It imparts an understanding of the pathogenesis to the family, answering their *need to know why*. In genetic conditions, it has implications regarding recurrence risk. It also allows for

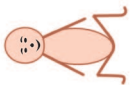
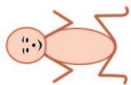
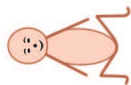







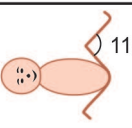
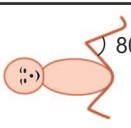
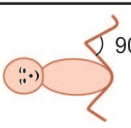
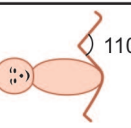
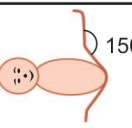
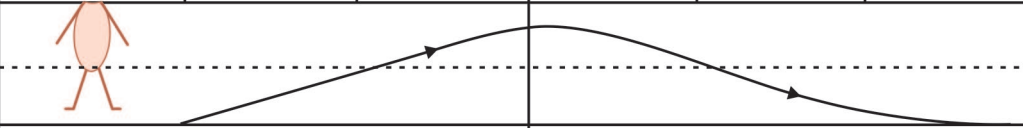
Posture					
Scarf sign					
Popliteal angle					
					
Increasing muscle tone in a caudocaudocephalic wave			Decreasing muscle tone in a cephalocaudal wave		

Figure 2 Evolution of passive tone



Figure 3 Spontaneous posture—persistence of asymmetric tonic neck reflex and scissoring



Figure 4 Scissoring on axillary suspension

more accurate prognostication. Karyotyping may be ordered when there are dysmorphic features. Neuroimaging (Figs 6 and 7) is likely to identify an etiology when it is suspected clinically—microcephaly, tone abnormalities, history of birth asphyxia. Electroencephalography may be done when the child has seizures. Investigations for inborn errors of metabolism should be ordered judiciously. Every child need not have an array of expensive tests and investigations.

## DEVELOPMENTAL TESTS

A summary is provided in Table 2. Individual tests are discussed below in brief.

### Ages and Stages Screening Questionnaire

The ages and stages screening questionnaire (ASQ) is a parent-completed child development screening test with 19 questionnaires

ranging from 4 months to 60 months that are identical in format and organized into five-item domains (communication, gross motor, fine motor, problem-solving and personal-social). Questions can be answered by parents with 7th grade education. For those with low literacy level, it can be administered as an interview. Parents indicate *yes*, *sometimes* or *not yet*. The ASQ needs 15 minutes to complete and 2–3 minutes to score. It has moderate to high sensitivity and specificity. Juneja et al. have used a Hindi translation of the test with good results.

### Trivandrum Development Screening Test

This test can be used in the first 2 years of life. Seventeen test items including motor and mental items were chosen. The range for each test item was taken from the Indian adaptation of Bayley Scales of Infant Development (Baroda Norms) Test. The main shortcoming of this test is that the Denver Developmental Screening Test (DDST) was used as the gold standard, which in itself is a screening test.





**Figure 5** Spastic infant *toe-walking*

### Denver Developmental Screening Test

This test is a screening test of cognitive and behavioral problems in the age group of 0–6 years. Tasks are grouped into four categories (fine motor skills, gross motor skills, social contact and language). In this test, a subject's performance against the regular age distribution is noted. This test is widely used all over the world. But it has been criticized for being unreliable in predicting less severe or specific problems in children, resulting in underreferrals. The test depicts in graphic form the ages at which 25%, 50%, 75% and 90% of children performed from birth to 6 years. It enables the examiner to visualize at any age how a child's development compares with that of other children.

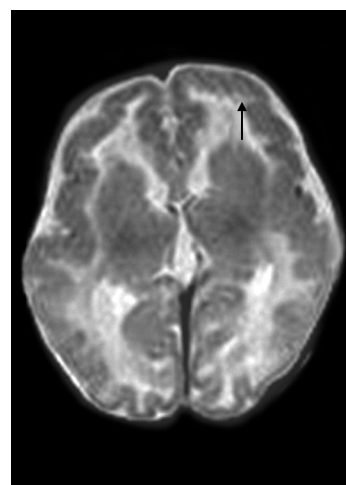
### Developmental Assessment Scale for Indian Infants

The Bayley scale was standardized by Phatak for Indian infants. This test consists of 163 mental items and 67 motor items. Both the scales express the child's performance by the number of items passed by the child. A DQ more than and equal to 85 is considered as normal. The test must be administered by a trained psychologist, it needs a special kit and must be ideally performed in a soundproof room. This test is considered as the gold standard for assessing development.

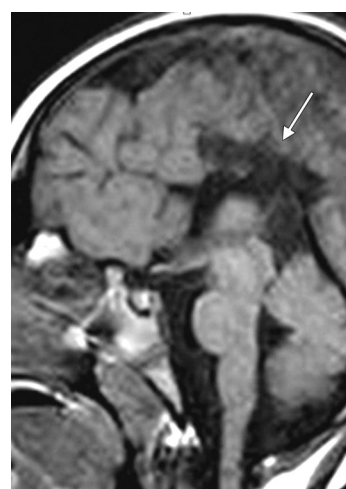
### Bayley III

A new and much longer version of the Bayley scales, it covers the age group of 16 days to 42 months. It covers 5 domains—language, cognitive, fine and gross motor and socioemotional. It takes 30 minutes administration time for children below 13 months and 50 minutes for children 13 months and above. This test has been criticized because it yields higher than expected scores which may lead to underreferrals.

Early identification of children with developmental delays or disabilities can lead to early intervention and treatment and lessen its impact on the child. Developmental surveillance is an important way of detecting developmental delays. The pediatrician should be skilled in the use of screening techniques, carefully listen to parental concerns, and create links with available resources in the community.



**Figure 6** Migrational defect—Polymicrogyria in a term neonate. Thick gyri in bilateral frontal regions with paucity of sulcal spaces



**Figure 7** Corpus callosal agenesis

### IN A NUTSHELL

1. Early identification of developmental delay has a three-pronged approach: a birth and developmental history; physical and neurologic examination; developmental screening.
2. According to the American Academy of Pediatrics, every child attending the well-baby clinic should have a developmental examination at 9, 18 and 30 months.
3. The pediatrician should give serious attention to parental concerns about their child's development.
4. The pediatrician should familiarize himself with a simple screening test.
5. When a child is identified to have developmental delay, early intervention is mandatory.
6. The child with developmental delay must be referred to a center which has specialized services with multidisciplinary team.
7. The *high-risk* infant should be monitored very closely for developmental delay.



**Table 2** Summary of developmental tests

Test	Age	Assessment	Development index	Usefulness	Limitation
1. Ages and Stages Questionnaire Screening Test (ASQ)	4–60 months	Parent completed questionnaire. 19 age-specific questions. Gross motor, fine motor communication, problem-solving, personal, social (pass, fail)	Quantitative sensitivity, specificity moderate to high	Can be used as a screening test in a well-baby clinic	Depends on intelligence and observations of the parents
2. Trivandrum Development Screening Chart (TDSC)	0–2 years	17 items from the Bayley scales are used, motor and mental items	Sensitivity, specificity moderate	Can be used as a screening test in a well-baby clinic	DDST used as a gold standard, which in itself is a screening test
3. Denver Development Screening Test (DDST)	0–6 years	Motor behavior. Adaptive behavior, personal and social behavior, language development, risk category (normal, questionable, abnormal)	Quantitative, low to moderate sensitivity, specificity	For use in a busy clinic	Misses mild delay, resulting in underreferrals
4. Developmental Assessment Scale for Indian Infants (DASII), Adaptation of Bayley II Scales of Infant Development	0–30 months	Mental (163 items) Motor (67 items) Considered to be gold standard	MeQ $\geq$ 85 normal MoQ $\geq$ 85 normal 70–84 delayed development < 70 retardation	Confirmatory test after screening tests have identified delay	Needs a trained psychologist and a soundproof room and a special kit
5. Bayley III Much longer test Takes 30 minutes for children < 13 months and 50 minutes $\geq$ 13 months	16 days to 42 months	Covers cognitive, language, fine and gross motor and socioemotional development	Higher scores compared to Bayley II	Needs further validation before use in Indian children	Gives much higher scores hence may lead to under referral

Abbreviations: MeQ, mental quotient; MoQ, motor quotient.

## MORE ON THIS TOPIC

- Als H, Gilkerson L, Duffy H, et al. A three-center randomized, controlled trial of individualized developmental care for very low birthweight preterm infants: medical, neurodevelopmental, parenting and caregiving effects. *J Dev Behav Pediatr.* 2002;24:399-408.
- Amiel-Tison C, Grenier A. *Neurologic assessment during the first year of life.* New York: Oxford University Press; 1986.
- Bernbaum J, Hoffman-Williamson J. *Primary care of the preterm infant.* Philadelphia: Mosby Yearbook; 1991. pp. 240-9.
- Chaudhari S, Bhalerao M, Chitale A, et al. Transient tone abnormalities in "high risk" infants and cognitive outcome at five years. *Indian Pediatr.* 2010;47:931-5.

- Chaudhari S, Deo B. Neurodevelopmental assessment in the first year with emphasis on evolution of tone. *Indian Pediatr.* 2006;43:527-34.
- Chaudhari S, Otiv M, Khairnar B, et al. Pune low birth study—birth to adulthood—cognitive development. *Indian Pediatr.* 2013;50:853-7.
- Juneja M, Mohanty M, Jain R, Ramji S. Ages and stages questionnaire as a screening tool for developmental delay in Indian children. *Indian Pediatr.* 2012;49:457-61.
- Sand N, Siverstein M, Glascoe FP, et al. Pediatricians' reported practices regarding developmental screening: do guidelines work? Do they help? *Pediatrics.* 2005;116:174-9.
- Shevell MI, Majnemer A, Rosenbaum P, Abrahamowicz M. Etiologic determination of childhood developmental delay. *Brain Dev.* 2001;23:228-35.

## Chapter 20.4

# Global Developmental Delay

Madhuri Kulkarni, Mona P Gajre

Neurodevelopmental disabilities are chronic clinically distinct disorders that share disturbances in developmental process in different developmental domains compared with established norms. The various developmental domains are motor (gross, fine), speech and language, cognition, personal-social and activities of daily living. These domains are not mutually independent and often development in one domain is a prerequisite for the development in other domains. The developmental disabilities are diagnosed over time rather than at a single point of clinical interview.

### DEFINITION

Global Developmental Delay (GDD) is a symptom complex with heterogeneous etiology. It is a developmental disability having essential feature of predominant disturbance in acquisition of skills in two or more domains of cognitive, motor, language or social development. These disturbances significantly impact on developmental progress of an individual.

The terms GDD and intellectual disability are part of the same spectrum. These are now preferred over the previously used *mental retardation*. American Association of Mental Retardation in 2000 defined mental retardation as *a disability characterized by significant limitation both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, practical and adaptive skills*. Assessment of level of intellectual functioning needs measuring intelligence which is problematic in a child younger than 5 years. In older children, intelligence quotient (IQ) testing is more reliable and valid. The infants and young children are rapidly progressing concurrently through various developmental domains. Therefore, for the young child, the term *global developmental delay* is used to describe a disturbance across variety of developmental domains.

The American Academy of Neurology defines GDD as a significant delay in two or more of the following developmental domains, e.g., gross/fine motor, cognitive, speech/language, personal/social and activities of daily living.

According to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the diagnosis of GDD is reserved for individuals under 5 years of age when the child fails to meet expected developmental milestones in several areas of intellectual functioning. It applies to children who are unable to undergo systematic assessment of intellectual functioning, or are too young to participate in standardized testing.

Many children meriting the diagnosis of GDD in the preschool years, when assessed later at school age, continue to meet diagnostic criteria for GDD. Many older children diagnosed with intellectual disability were initially diagnosed on retrospective review with GDD. Thus, these entities share common features and both represent learning continuum. However, a diagnosis of GDD does not necessarily imply intellectual disability in future. A variety of disorders, such as cerebral palsy, congenital muscle disorders, autism spectrum disorder and environmental deprivation might, in fact, be associated with normal cognitive potentials.

### PREVALENCE

Developmental disabilities are reported to be a common problem in child health clinics affecting 5–10% of preschool age children in

North America. A national sample of 9,854 children of 2–3 years age studied in Israel showed a disability rate of 8.9%. In a house to house survey of 3,560 children, 0–6 years of age at Delhi, disability rate was 6.8%. Prevalence of developmental delay, deformity or disability was found to be 2.5% in children below 5 years of age in a rural Kerala study. The common disabilities observed in the same study were speech and language problems 29.8%, vision and hearing problems 22.2%, cerebral palsy 12.2% and mental retardation and related disorders 8%.

### ETIOLOGY

The etiological factors causing GDD are classified as prenatal, perinatal, postnatal and undetermined causes (**Table 1**). The largest category in most studies is prenatal including genetic and acquired. Causes such as low birthweight and prematurity are considered to be risk factors for GDD. In India, birth asphyxia leading to hypoxic-ischemic encephalopathy, and perinatal infections are commonly observed causes. The postnatal causes include infections, trauma, stroke and exposure to toxins.

Several studies have reported wide variation in the etiologic yield for children who have GDD. These variations reflect differences in sample population characteristics, the method of classification, and diagnosis of neurodevelopmental disability in addition to availability of genetic and imaging technology. The Finnish classification of etiology is based on the timing and type of injury to the central nervous system (CNS). Six broad groups described in this classification are (i) genetic causes (e.g., single gene defect, chromosomal abnormalities, and recognizable syndromes); (ii) CNS malformation; (iii) external prenatal factors; (iv) perinatally acquired disorders; (v) postnatally acquired disorders; and (vi) unclassified causes.

Approximately, one-third of etiological diagnoses can be made by history and examination alone. Laboratory testing is used to confirm a diagnosis suspected on the basis of history and examination in another one-third. In the remaining third, etiologic diagnosis is made on the basis of laboratory testing alone. Significant progress has been recently achieved in identifying underlying etiology, using a variety of laboratory tests including neuroimaging and genetic and metabolic investigations. Searching for and determining a specific underlying etiology has important implications with reference to ongoing management-related issues like recurrence risk, accurate prognostication, mechanism of medical follow-up and specific therapeutic interventions. GDD was observed in 44 of 80 (55%) children under 5 years of age referred to ambulatory pediatric neurology

**Table 1** Causes of global developmental delay

Period	Causes
Prenatal	Genetic—chromosomal defects, single gene defect, nonsyndromic gene defect, metabolic disorder Acquired—maternal infections, nutritional deficiencies, fetal alcohol syndrome, maternal substance abuse
Perinatal	Birth asphyxia leading to hypoxic-ischemic encephalopathy Infections Stroke Metabolic disturbances
Postnatal	Infections leading to meningoenitis Trauma Stroke Severe malnutrition Psychosocial deprivation

and developmental pediatric clinics. Etiologies determined in these children included cerebral dysgenesis, *hypoxic ischemic encephalopathy*, toxin exposure, chromosomal abnormalities, psychosocial neglect, neuromuscular disorder, genetic syndromes and other causes.

In a study carried out in Northern India, 66 (54.1%) out of 122 children with developmental disabilities could be assigned a definite etiology and 38 (31.1%) a probable etiology. Amongst 66 children with definite etiology, 17 were prenatal, 38 perinatal/neonatal, and 11 postnatal in origin.

## EVALUATION

The main objective of evaluation of a child with GDD is to confirm the delay and plan the intervention. More than one visit may be required for complete evaluation. The principle elements include:

- Confirming and classifying the neurodevelopmental delay
- Establishing possible etiology through interview, observation, examination and selective laboratory testing
- Identifying the needed rehabilitation and intervention programs
- Counseling of family regarding implications of the disorder and the possible outcomes
- Exploring role of pharmacotherapy for comorbidities (seizure disorders, attention deficit, sleep disturbances, spasticity and behavioral concerns).

## Interview

Assessment of a child with interview of the parents involves recording the history, observing the child and performing detailed physical and developmental examination. The verbal children should also be included in the interview process.

A three-generational comprehensive family history, with possible consanguinity, previous fetal, neonatal deaths, maternal pregnancy details are to be inquired as they may provide invaluable data. A special emphasis on maternal age, adverse antenatal events such as per vaginal bleeding, gestational diabetes, number of antenatal visits, weight gain, medication history, use of tobacco, alcohol should be inquired. The intrapartum history of duration of labor, mode of presentation and resuscitative measures requirements should be noted. History of adverse events during labor or delivery such as meconium staining, premature rupture of membranes, need for cesarean section is also important. Objective measures of neonatal well-being such as birthweight, appearance, pulse, grimace, activity, respiration (APGAR) scores, gestational age, postneonatal stay, feeding pattern, occurrence of neurologic symptoms, abnormal urine order, breathing problems are also noted. These provide important clues to the origin of a child's developmental condition to a prenatal or perinatal event. Subsequently the child's detailed medical history of medical admissions, treatment history, chronic ongoing medical condition needs to be documented. The effect of psychosocial deprivation on the child's development is huge; in this context, parental neglect, abuse, caregiver emotional status have to be determined.

After this important background information, the developmental history can be properly placed into an individual, familial and social context. The precise developmental domain and the age of the child when parental concerns were noted are extremely valuable to proceed further in evaluation. Developmental history with regard to achievement of skills in the motor, language, social/play domains has to be recorded. In this context, pictorial evidence, home videos records are valuable tools. Linking the emergence of a milestone to an important event in the child or parents life (e.g., first birthday party) is often useful. Although not encouraged, sometimes comparing the index child developmental trajectory

with their siblings is often handy especially to know the pace of skill acquisition over time; specifically any loss of developmental skills or functions should be recorded. Current performance in each domain is ascertained in addition to key activities of daily living, such as toileting, dressing, feeding and self-hygiene in the older child.

Possible coexisting conditions, like autistic features, such as poor eye contact, repetitive behaviors, inappropriate social and communication interactions should be asked. Additionally presence of disruptive behaviors, food and sleep hygiene, should be inquired.

The neurodevelopment assessment is to be done by observation of the child and also the family during the interview process. It is facilitated with provision of a child-friendly environment with age appropriate playthings. Observing the child's interaction with them in a nonthreatening manner, with the presence of a caregiver can give invaluable insights into the developmental level of various domains. Additionally, it is of utmost importance to interact with the child to assess his cognitive and language skills, such as identifying pictures, body parts, colors, shapes, story-telling capabilities. Vocabulary can be assessed by child's spontaneous speech, response to direct questions can also provide a clue to semantic and syntactical capabilities. Comprehension is assessed by understanding of multistep complex commands. Cognitive skills can be assessed by the child's grasp of specific concepts, use of objects. Gross motor skills are assessed by direct observation, gait analysis, ball playing activities, whereas fine motor skills are tapped into through the use of blocks, by specific pen and paper tasks such as copying shapes, figure drawing, precision for activities of daily living.

## Physical Examination

It is critical to ascertain the corrected gestational age for preterm babies for appropriate diagnosis of delay till 2 years of age. Physical examination is essential for the diagnostic workup of the child with GDD. Physical development for maturity includes height, weight and head circumference measurements. The height and weight are plotted on the age- and gender-appropriate percentile. Microcephaly suggests poor brain growth, low set ears suggest fetal pattern of posterior ear rotation, a high-arched palate is indicative of oral motor dysfunction. Presence of microcephaly (less than third percentile) mandates obtaining and plotting the parent's head size; checking previous records for the evolution of the head size over time is critical. Dermatologic assessment for *café-au-lait* spots suggestive of various neurocutaneous syndromes is essential. Examination of the spine should be undertaken for any defects or overlying cutaneous abnormalities that suggest a spinal dysraphism.

Neurologic examination is crucial and clues to diagnosis may be provided by abnormalities of tone, power, deep tendon reflexes, cranial nerves examination and coordination. Presence of extrapyramidal movement abnormalities especially dyskinesias such as tremor, dystonia, chorea or athetosis should be documented. The gait of the child is noted in detail, tests of manual dexterity such as grasping objects, throwing and kicking a ball, jumping or hopping on one foot is also noted. Presence of soft neurological signs like dysdiadochinesia, sequential hopping, left and right orientation issues, balance issues suggest neurological immaturity.

## Developmental Assessment

Neurodevelopmental assessment includes the 180 degrees flip test for posture, tone, coordination in different maneuvers such as supine, pull to sit, axillary and ventral suspension and in prone

position. Elicitation of primitive reflexes, such as oral reflexes, Moro reflex, grasp reflex, asymmetric tonic neck reflex, parachute reflex, are useful in assessing the developmental age. Persistence of primitive reflexes is a possible sign of several conditions including cerebral palsy, autism, and speech dysfunction. Importantly, their persistence interferes with development of postural control, mobility and achievement of motor milestones. Role of Amiel-Tison test to assess active, passive muscle tone in various maneuvers is highly informative. It essentially classifies the babies into normal or persistent abnormal tone patterns.

The *red-flag* signs for delays in certain domains are listed in **Table 2**.

A key part in the second follow-up visit of a developmentally delayed child is to exclude the possibility of a progressive encephalopathy or neurodegenerative process. **Table 3** lists the various screening and confirmatory tools available in India which can be easily used for evaluation of children with GDD. The commonly used tools have been already discussed in the previous chapter.

### Laboratory Investigations

The heterogeneity of GDD with a wide-ranging etiology invokes the possibility of extensive laboratory investigations and the choice of tests is often challenging. There is no *one size shoe fits all* algorithms for evaluation of GDD and investigations need to be individualized for a rational approach.

The laboratory investigations should be planned as per the specific clinical diagnosis suspected, based on history and clinical examination. Thus, in children with a history of adverse perinatal events or in those with abnormal neurological findings, seizures or microcephaly, neuroimaging should be undertaken. A high-resolution MRI is preferable to a CT scan. Cytogenetic studies are indicated in children with dysmorphism. If a specific syndrome is suspected, such as Prader Willi or Angelman syndrome, a targeted fluorescent in situ hybridization probe should be done, for a Fragile X syndrome, FMR triplet repeat testing should be done. On suspicion of Rett syndrome, MECP2 gene analysis studies can be done. Additionally, chromosomal microarray may be indicated in some case.

At present, unselected metabolic screening in all cases of GDD is not justified as it has poor yields. In presence of clinical clues such as: (1) a prior family history of an affected child; (2) consanguinity; (3) developmental regression; (4) episodic decompensation; (5) dysmorphism; (6) ophthalmologic or retinal abnormalities; (7) nonscreened newborn; and (8) neuroimaging findings of basal ganglia involvement in the absence of asphyxia or unexplained white matter changes also necessitate a metabolic testing. Metabolic testing involves blood gases, serum lactate, serum ammonia, liver function tests, serum amino acids, urine organic acids, serum carnitine and very long-chain fatty acids levels. The association of multisensory impairments mandates visual and hearing assessments. Hearing screening requires auditory evoked response testing or formal audiometry. A visual evoked potential study can be done in retinal abnormalities. Electromyography or nerve conduction studies are indicated if a possibility of a neuromuscular disorder exists. Electroencephalogram is done in situations of a suspicion of paroxysmal events such as seizures.

*Hypothyroidism* is a common cause of GDD in goiter-endemic areas and early screening with thyroid hormones levels, such as T3, T4, TSH, has been recommended. Serological testing for Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, Herpes (TORCH) and human immunodeficiency virus infection is essential in infants with maternal history of such infections, in low birthweight infants, and

**Table 2** Red flag signs for developmental delay

Developmental domain	Clinical features
Gross motor delay	<ul style="list-style-type: none"> <li>• Tone abnormalities: Hypotonia, hypertonia, dystonia</li> <li>• Asymmetry/dysmorphology</li> <li>• Persistence of primitive reflexes</li> <li>• Abnormal deep tendon reflexes, clonus</li> <li>• Hand preference in less than 18 months</li> <li>• Abnormal gait</li> </ul>
Fine motor delay	<ul style="list-style-type: none"> <li>• Immature grasp till 1 year</li> <li>• Poor manipulation of objects till 1 year</li> <li>• Eating with excessive spillage after 15–18 months</li> <li>• Excessive clumsiness after 2 years</li> <li>• Assistance in dressing beyond 3 years</li> <li>• Uncontrolled scribbling beyond 3 years</li> <li>• Difficulty buttoning the shirt by 4–5 years</li> </ul>
Speech delay	<ul style="list-style-type: none"> <li>• No babbling: 12 months</li> <li>• No pointing or gesturing: 12 months</li> <li>• No single words: 16 months</li> <li>• No two-word phrases: 24 months</li> <li>• Unintelligible speech: 24 months</li> <li>• Regression of language skills: any age</li> <li>• Loss of language or babbling</li> <li>• Loss of social skills</li> </ul>
Cognitive delay	<ul style="list-style-type: none"> <li>• Difficulty in following simple instructions</li> <li>• Poor comprehension skills</li> <li>• Difficulty in learning new skills</li> <li>• Poor expressive language</li> <li>• Poor memory recall and actual sequence of events</li> <li>• Behavioral problems</li> <li>• Academic lags</li> <li>• Slow in activities of daily living</li> <li>• Poor self-help and increased dependency</li> </ul>

**Table 3** Tools for evaluation of early developmental delay

Domain	Screening tool	Confirmatory test
Motor delay	<ul style="list-style-type: none"> <li>• Developmental observation card (DOC; 1 month to 1 year)</li> <li>• Trivandrum developmental screening chart (TDSC; 1–2 years)</li> <li>• Denver developmental screening test (DDST; 1–6 years)</li> </ul>	<ul style="list-style-type: none"> <li>• Developmental assessment scale for Indian infants (DASII)</li> <li>• Clinical adaptive test (CAT)</li> </ul>
Early language delay	<ul style="list-style-type: none"> <li>• TDSC</li> <li>• DDST</li> <li>• Early language milestone (ELM) scale</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical linguistic and auditory milestone scale (CLAMS)</li> <li>• Receptive and expressive emergent language scale (REELS)</li> </ul>
Cognitive or adaptive delay	<ul style="list-style-type: none"> <li>• TDSC</li> <li>• DDST</li> <li>• Parents evaluation of developmental status (PEDS)</li> </ul>	<ul style="list-style-type: none"> <li>• DASII</li> <li>• Seguin Form Board (SFB)</li> <li>• Raval-Vineland Social Maturity Scale (&gt; 2 years)</li> </ul>

in presence of microcephaly, hepatosplenomegaly, petechial rash, jaundice and chorioretinitis.

Biochemical tests are indicated in children suspected to have amino acidopathy, organic aciduria, galactosemia, phenylketonuria, homocystinuria, urea cycle defects, mitochondrial disorders



and mucopolysaccharidoses. The confirmatory tests for these disorders include enzyme studies in lymphocytes, fibroblasts and other tissues.

## MANAGEMENT

Multidisciplinary consultation is needed for a comprehensive evaluation and management of children with GDD. The aim being goal-driven, therapeutic interventions act as a conduit to long-term community-based rehabilitation and educational resources. Multiple allied health services, such as physical therapy for gross motor, locomotion and balance; occupational therapy for fine motor, activities of daily living (ADL), feeding; speech and languages pathologists for speech therapy and psychologists for cognition, social and behavioral issues are required.

### Early Intervention

Development of the brain continues postnatally and is influenced by extrinsic environmental factors as well as *preprogrammed* genetic factors. Postnatal growth continues into adulthood but it is most rapid and pliable during first few years of life. An outcome of a developmentally delayed child can be improved by modifying the environment. Neuroplasticity is the primary principle for the early intervention program. Neuroplasticity refers to the changes that occur in the organization of the brain as a result of experience. The reorganization is done via the mechanism of axonal sprouting. Therefore, earlier the intervention, better will be the outcome. This is the main principle of early intervention therapy.

The intervention team consists of medical specialists and the rehabilitative team wherein preliminary developmental tests are performed to establish the diagnosis. Early intervention therapy with a home-based program—is more beneficial if started in the first few months of the life, especially less than 6 months. The stimulation is done in areas of visual, tactile, auditory, sensory, head movement, head holding and babbling. Specific management should focus on nursing, feeding and positioning of the child. Antispasticity medications, antiepileptic drugs, orthosis, splints, corrective surgeries, assistive technologic devices should be considered based on needs of the individual child. Rehabilitative services are provided as individual, group or as a home-based program.

Physical therapists use isometric exercises for strengthening, flexibility of muscles and increasing the range of movements. Gait training and bracing is done to improve locomotion and posture maintenance. Occupational therapy consists of developmental therapy and functional therapy for ADL skills.

### Neurodevelopmental Therapy

It originated from Bobath and Bobath in 1940s. The *Classic* neurodevelopmental therapy (NDT) was based on the principle that the CNS dysfunction is the primary cause of movement, posture and development. The normal development was promoted through strict adherence to a normal development sequence and was originally developed for children with cerebral palsy. The contemporary NDT focuses on functional tasks and skills with the normal developmental sequence used as a general guide and less relied upon. It has a broader focus, with CNS as only one of the many systems that impact movement and development.

### Sensory Integrative Treatment

It is based on the premise that the brain processes internal and external sensory information and organizes it for an appropriate response. Deficits in the ability to integrate sensory information can be remediated with guided sensory inputs to elicit an adaptive response such as proprioceptive, tactile, and vestibular stimuli.

The other interventional approaches include aquatic therapy, cognitive orientation to daily occupational performance, constraint to induced movement therapy, hippotherapy and others.

## IN A NUTSHELL

1. Global developmental delay refers to a significant delay in two or more developmental domains in young children under 5 years of age.
2. Prevalence of GDD varies from 2.5% to 10% as reported in different studies in the world.
3. The etiology of GDD includes a wide spectrum of genetic, prenatal, perinatal and postnatal factors. However, in a significant number of cases exact etiology cannot be established.
4. In India, perinatal causes remain major etiological diagnosis in majority of children with GDD.
5. Evaluation of a child with GDD includes detail history-taking, observing the baby in a child-friendly environment, and conducting accurate general physical and neurodevelopmental examination. Team of several health professionals is essential to ensure a complete and thorough evaluation.
6. Neurodevelopmental assessment is essential in all children with GDD. Vision and hearing is mandatory in each case. Various screening and confirmatory tests are now available in India.
7. Laboratory tests include neuroimaging, hormonal tests, cytogenetic studies, bacteriological and microbiological tests for infectious causes and tests for metabolic disorders. Laboratory test should be carefully selected, based on history and clinical examination.
8. Management of a child with GDD includes early intervention therapy, behavioral therapy and counseling of the family regarding diagnosis, risk of recurrence, and possible outcome. Specific pharmacotherapy may be indicated in some children having GDD with neurological disorder.

## MORE ON THIS TOPIC

- American Academy of Pediatrics Committee on Children with Disabilities. Developmental surveillance and screening of infants and young children. *Pediatrics*. 2001;108:192-6.
- American Psychiatric Association: Diagnostic Statistical Manual of Mental Disorders. 5<sup>th</sup> ed. Arlington, VA: American Psychiatric Association; 2013.
- Ellioth H, Shevell MI. Global developmental delay and mental retardation/intellectual disability. In: Swaiman KF, Ashwal S, Ferreiro DM, Sclor NF. *Swaiman's Pediatric Neurology Principles and Practice*. 5<sup>th</sup> ed. Philadelphia: Elsevier; 2012. pp. 554-74.
- Jennifer K, Angela C, Shashidhar G. Developmental delay: timely identification and assessment. *Indian Pediatr*. 2010;47:415-22.
- Martin T, Meghan K. Developmental screening and assessment: infants, toddlers and preschoolers. In: William B, William L, Allen C, Allen R, Heidi M. *Developmental-Behavioral Pediatrics*. 4<sup>th</sup> ed. Philadelphia: Elsevier; 2009. pp. 785-96.
- Myriam S, Michael S. Genetics and the investigation of developmental delay/intellectual disability. *Arch Dis Child*. 2014;99:386-9.
- Nair MKC, George B, Padmamohan J, et al. Developmental delay and disability among Under-5 children in a rural ICDS block. *Indian Pediatr*. 2009;46:S75-8.
- Shevell M. Global developmental delay and mental retardation or intellectual disability: conceptualization, evaluation, and etiology. *PCNA*. 2008;55:1071-84.
- Shevell MI, Majnemer A, Rosenbaum P, Abrahamowicz M. Etiologic determination of childhood developmental delay. *Brain Dev*. 2001;23:228-35.
- Tirosh E, Michael J. Global developmental delay and mental retardation—a pediatric perspective. *Dev Med Res Rev*. 2011;17:85-92.

## Chapter 20.5

# Intellectual Disability

Suja Koshy

Intellectual disability (ID) is the most common developmental disorder with deficits in cognitive functioning (IQ < 70) and adaptive skills originating before the age of 18 years. Children with intellectual disabilities are below average in intelligence, have limitations in their intellectual functioning and also have difficulties in coping up with the challenges associated with daily life, i.e., to communicate, socialize or take care of their everyday needs.

It includes a heterogeneous group of conditions ranging from *children with severe developmental disabilities* who need constant support to *children with only mild delays*. Though ID is different from global developmental delay (GDD), GDD is often a precursor to ID. GDD is the term applied to age less than 5 years; significant delay (performance two standard deviations or more below the mean on age-appropriate, standardized norm-referenced testing) in two or more of developmental domains including gross/fine motor skills, speech/language, cognition, social/personal, activities of daily living (ADL). *Intellectual disability* is a term applied to age more than or equal to 5 years and manifesting before age 18 years, historically referred to as *mental retardation*; intellectual functioning level (IQ) less than 70–75 and significant limitations in two or more adaptive skills.

There is no single characteristic feature, prognosis or cause for ID. The medical model looked upon intellectual deficit as an illness, but today the educational model looks upon it as a developmental disability where there is new emphasis on the rights of the child. Today, ID is not considered a static disorder, but a dynamic condition dependent on the etiology and available environmental supports.

### TERMINOLOGY

Though the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has replaced *mental retardation* with *intellectual disability* (intellectual developmental disorder), as of 2014, the old term is still used by the World Health Organization (WHO) in the International Classification of Diseases (ICD)-10 codes. "A condition of arrested or incomplete development of the mind, which is especially characterized by impairment of skills manifested during the developmental period, skills which contribute to the overall level of intelligence, i.e., cognitive, language, motor and social abilities. Retardation can occur with or without any other mental or physical condition." [Source: Chapter V, *Mental and behavioral disorders (F00-F99)*, p. 176 *The ICD-10 Classification of Mental and Behavioral Disorders, Clinical descriptions and diagnostic guidelines*. WHO, 1996. Reprinted with permission] In the next revision, the ICD-11 is expected to replace the term *mental retardation* with *intellectual disability*. Unfortunately, the term *mental retardation* is still used sometimes in professional medical settings in India and some parts of the world.

### DEFINITION

Different definitions of the term; intellectual disabilities' have been accepted professionally. In India, *mental retardation* means a "condition of arrested or incomplete development of mind which is specially characterized by subnormality of intelligence" as per

the Persons with Disabilities (Equal Opportunities, Protection of Rights and Full Participation) Act, 1995. No doubt, the use of the term *mental retardation* is still in use in India and the content of the definition really points to the long overdue need for reviewing this definition.

The widespread definitions used are given by the American Association on Intellectual Developmental Disabilities (AAIDD), IDEA, WHO and the American Psychological Association (APA). The definition as given by IDEA is "significantly subaverage general intellectual functioning existing concurrently with deficits in adaptive behavior and manifested during developmental period, that adversely affects a child's educational performance". (Source: *National Dissemination Center for Children with Disabilities, NICHCY*)

The AAIDD definition (2010) of intellectual disability is "a disability characterized by significant limitations in both intellectual functioning and in adaptive behavior, which covers many everyday social and practical skills. This disability originates before the age of 18." (Source: *Schalock et al, 2010*).

Hence, it can be seen that through the years, disagreement was seen with respect to the definitions of intellectual disabilities. Some definitions relied on:

- IQ scores alone to classify individuals with intellectual disability,
- only adaptive behaviors for classification and
- both IQ scores and measures of adaptive behavior.

But today, there is more consensus and the common elements of the definitions are:

- The onset period of intellectual disabilities as being the developmental period (i.e., before 18 years)
- Impairments evident in both cognitive functioning and adaptive skills.

The DSM-5 definition focuses toward identifying limitations, whereas the AAIDD (2010) focuses on detecting current abilities and strengths of individual that facilitate rehabilitation. AAIDD stresses that additional factors must be taken into account, such as the community environment, linguistic diversity, cultural differences typical of the individual's peers and culture while defining and assessing ID.

Due to the paradigm shift from the medical model to the educational model, professionals have realized the need to have more effective systems of identification and classification for providing more effective educational and rehabilitative interventions to children with intellectual disabilities.

### CLASSIFICATION OF INTELLECTUAL DISABILITIES

Intellectual disabilities exist along a continuum with the degree varying from person to person, and it can be classified as mild, moderate, severe or profound. Looking from the clinical perspective, the two major categories of intellectual disabilities are as follows:

1. Syndromic, characterized by associated clinical, radiological, metabolic or biological features
2. Nonsyndromic forms of ID in which the cognitive impairment represents the only manifestation of the disease.

The boundaries between the syndromic and nonsyndromic forms are not very stringent, as in both these types there is association of several genes.

The other major ways of categorizing groups of ID are as:

- metabolic syndromes,
- syndromes with ID and
- associated malformations/dysmorphism and syndromes with ID and neurological/neuromuscular symptoms.

From the educational perspective, there has been a paradigm shift in the way children with intellectual disabilities are classified. The ICD-10 is the most widely used classification system across all member countries of the WHO 2007 (**Fig. 1**). But unfortunately, the IQ-based classifications are not helpful for intervention planning. Presently rather than emphasizing IQ-based subgroups (mild, moderate, severe and profound), professionals are encouraged to describe needed *appropriate supports* to improve adaptive functioning for individuals with ID (**Table 1**). The various levels of severity are defined on the basis of adaptive functioning rather than IQ scores, because the adaptive functioning determines the patterns and level of supports required (i.e., intermittent for mild, limited for moderate, extensive for severe and pervasive for profound). Moreover, IQ measures are less valid in the lower end of the IQ range. However, others opine that to provide appropriate services, it is vital to emphasize the child's capacity level (intellectually and adaptively).

## EPIDEMIOLOGY

Intellectual disability prevalence rates vary according to the definitions and classification system being used. Worldwide prevalence of ID is approximately between 2.5% and 3% of the general population. Other specialists argue that the prevalence is lower as ID is not only determined by the child's individual IQ score alone, and the adaptive functioning may not be impaired (as many children with 50–70 IQ scores may not show significant deficits in adaptive functioning). In India, no reliable prevalence data is available due to lack of national level population-based study. Small epidemiological studies in India indicate 2–3% of our population of children have ID, i.e., 1 in 800 livebirths. However, a wide discrepancy in incidence of ID has been reported, from around 1/1000 to 32/1000. Among those with a diagnosis of ID, mild ID affects about 85% of the population, moderate ID about 10%, severe ID about 4%, and profound

ID about 2%. About 0.5% children are severely intellectually disabled due to etiological medical causes. Additionally, there are 1.6 children with Down's syndrome per thousand newborns. The incidence of congenital hypothyroidism (CH) is quite high with 1 in 1000 cases.

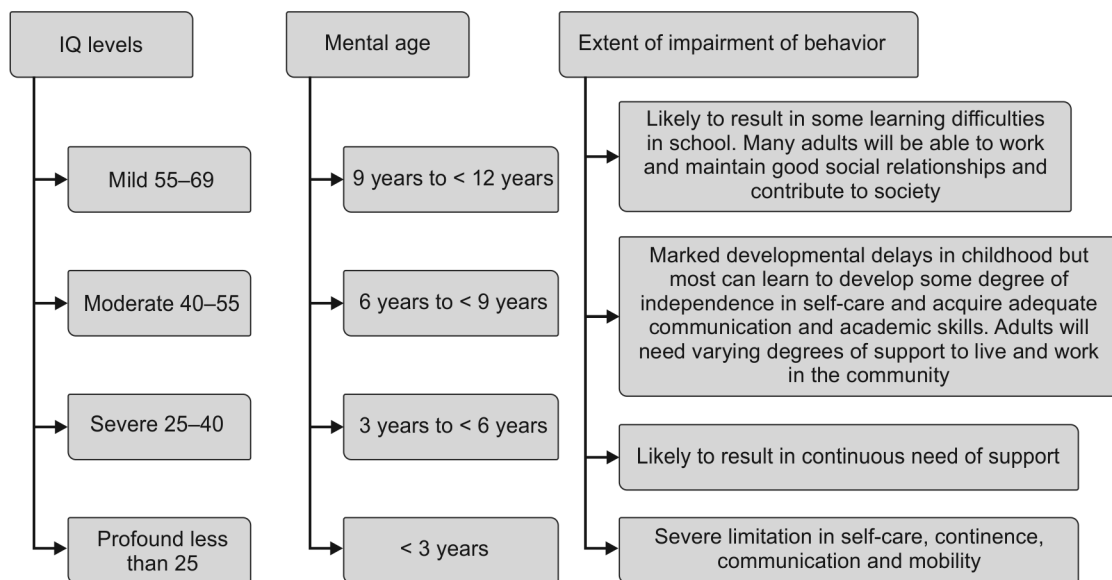
The proportions of ID have been reported to be higher in males, especially in mildly intellectually disabled individuals. This could be due to more incidences of congenital anomalies and more premature births in boys. Another reason is the presence of X-linked forms of ID. The prevalence of males to females is 2:1 in intellectual disabilities necessitating intermittent supports and 1.2:1 in intellectual disabilities needing extensive supports, due to sex-linked disorders like fragile X syndrome. The prevalence peaks at 10–14 years of age as children with intellectual disabilities requiring intermittent supports are identified considerably later than those with more severe impairments.

The prevalence of emotional, behavioral and psychiatric disorders is three- to fourfold greater in persons with ID.

## ETIOLOGY

There are innumerable causes of intellectual disabilities, and determining the exact cause of ID is very difficult. The causes are more understood in more than 70% of children with severe intellectual disabilities, whereas causes in 40–50% cases remain idiopathic. In two-third of the cases of mild ID and one-third of the cases of severe ID, no causes are found.

The causes can be diverse from *genetic and metabolic disorders* to trauma to brain at birth or at later ages. A child can develop ID due to prenatal, perinatal or postnatal causes (**Table 2**). Perinatal causes have been found to be the most common cause of ID. Of these, genetic factors play an important role in the etiology of 30–50% cases of ID. Chromosomal abnormalities like Down's syndrome and fragile X syndrome are the most diagnosable genetic causes of ID.



**Figure 1** Classification of severity of intellectual disability

Source: Adapted from Chapter V, Mental and Behavioral Disorders (F00–F99), pp.177–180. The ICD-10 Classification of Mental and Behavioral Disorders, Clinical Descriptions and Diagnostic Guidelines. WHO, 1996. Reprinted with permission from the publisher.

**Table 1** Intellectual disability (ID) and adaptive functioning

Definition	Adaptive skills are defined as practical, everyday skills needed to function and meet the demands of one's environment, including the skills necessary to effectively and independently take care of oneself and to interact with other people.				
Domains	Conceptual language, functional academics, telling time, ability to learn and remember information Social—interpersonal skills, following rules (turn-taking during games), social-problem solving, empathy, making friends Practical—personal self-care, home-living, health and safety, recreational activities, occupational skills.				
Assessment of adaptive behavior	Standardized adaptive rating scales Semi-structured clinical interviews Observation at home/school				
Adaptive behavior at each level of severity of ID		Mild ID (85%)	Moderate ID	Severe ID	Profound ID
Conceptual	Ability to think, learn and remember	Concrete thinking. Lacks abstract thinking. Inability to generalize	Inability to think logically	Limited ability	Visual-spatial skill at concrete level present
	Reading, writing, counting, solving Maths problems	Difficulty in coping with academics. Requires more time and practice to master academics Can generally learn reading, writing and math skills between the 3rd and 6th standard levels.	Can achieve preacademic skills at slow pace. Unlikely to go beyond 2nd standard level Academics	No understanding of written language. Unable to read or write. Functional academics not readily developed	Functional academics not readily developed
	Understanding language and speaking	Concrete and immature language	Simplistic usage of grammar	Difficulty pronouncing words. Limited vocabulary Understands simple language and gestures	Likely to have little or no speech, and will rely on gestures, facial expression
Social	Interpersonal skills	Difficulty in developing and keeping friends. Immature social judgement. Gullible	Generally rejected. No age-appropriate social skills	Extremely isolated. Relationships with family/familiar people	Relationships with family
	Understanding others	Difficulty in understanding social cues	Limited social understanding	Social understanding significantly impaired	Social understanding significantly impaired
Practical	Self-help skills	Age-appropriate skills in childhood. Look after themselves	Needs assistance (extended instruction) in caring for self	May lack self-help skills	Needs 24-hour care and support for self-care
	House work	Performs house work (shopping, money) with additional time, instructions and reminders	Chores left half done	Performs simple tasks in closely supervised settings	Some can perform simple tasks in closely supervised and sheltered settings
	Travel	With guided instructions, can use transportation reasonably well	Can learn to use public transport to travel to familiar places	Restricted to home	Restricted to home
	Occupational skills	Performs semi-skilled jobs	Can do semi- or unskilled jobs. Faces difficulty at workplace	Not employable	Homebound

There is an evidence also that various *environmental factors* contribute to ID. Recent research has revealed that the causes in India are mainly due to:

- Serious postnatal infections like encephalitis and meningitis during childhood
- Malnutrition (micronutrient deficiencies)
- Illness during pregnancy and birth-related causes (4%). The most common perinatal cause is neonatal complications due to anoxia, premature birth or low birthweight
- Serious illnesses during childhood (48.6%)
- Serious lead-poisoning and other toxic exposures can cause serious cerebral damage, which is irreversible
- Grave head injuries (falling from table, open window, balcony and stairs) can lead to cognitive impairments
- Environmental neglect and physical trauma in children who are physically abused can also cause cognitive impairments
- In many cases, the cause is unknown (22.4%).

## **PATHOGENESIS**

No specific neuropathologic correlates of ID have been documented. It occurs due to mutations in single genes that code for enzymes which results in abnormal or reduced enzyme activity. It is accepted that ID can stem from two broad mechanistic themes: dysfunction of neurodevelopmental programs and alterations in synaptic organization and plasticity.

One to five percent of nonsyndromic ID are inborn errors of metabolism. The most common inborn error of metabolism associated with ID is phenylketonuria (PKU) which has an average worldwide estimated prevalence of 1:10,000. The most common single chromosomal cause of ID is Down's syndrome. The most common form of X-linked intellectual disability, fragile X syndrome has prevalence of approximately 1:2,500 individuals. Children with Prader-Willi syndrome and Angelman syndrome also have ID.



**Table 2** Causes of intellectual disabilities

Prenatal	Chromosomal disorders	<ul style="list-style-type: none"> <li>• Down syndrome (Trisomy)</li> <li>• Fragile X-syndrome</li> <li>• Prader-Willi syndrome</li> <li>• Angelman syndrome</li> <li>• Williams syndrome</li> </ul>
	Inborn errors of metabolism	<ul style="list-style-type: none"> <li>• Phenylketonuria</li> <li>• Galactosemia (carbohydrate disorder)</li> </ul>
	Developmental disorders of brain formation brain formation	<ul style="list-style-type: none"> <li>• Hydrocephalus</li> <li>• Idiopathic microcephaly</li> <li>• Spinal bifida</li> </ul>
	Maternal illness	<ul style="list-style-type: none"> <li>• Rubella</li> <li>• HIV</li> <li>• Diabetes mellitus</li> <li>• Hypothyroidism</li> </ul>
	Embryonic teratogen exposure	<ul style="list-style-type: none"> <li>• Maternal substance use</li> <li>• Fetal alcohol syndrome</li> </ul>
	Acute placental insufficiency	<ul style="list-style-type: none"> <li>• Toxemia/eclampsia</li> <li>• Placenta hemorrhage</li> </ul>
	Chronic placenta insufficiency	<ul style="list-style-type: none"> <li>• Maternal diabetes</li> <li>• Erythroblastosis</li> </ul>
	Difficult or complicated delivery (Intrauterine disorders)	<ul style="list-style-type: none"> <li>• Prematurity</li> <li>• Breech</li> <li>• Multiple gestation</li> <li>• Obstetrical trauma</li> </ul>
Perinatal	Neonatal complications	<ul style="list-style-type: none"> <li>• Anoxia</li> <li>• Septicemia</li> <li>• Severe jaundice</li> <li>• Hypoglycemia</li> </ul>
	Head injuries Infections	<ul style="list-style-type: none"> <li>• Falls and accidents</li> <li>• Encephalitis</li> <li>• Meningitis</li> <li>• Measles</li> <li>• Rubella</li> </ul>
Postnatal	Degenerative disorders Seizures Toxic-metabolic disorders Severe and prolonged malnutrition Environmental deprivation	<ul style="list-style-type: none"> <li>• Rett syndrome</li> <li>• Infantile spasms</li> <li>• Chronic exposures to lead/mercury</li> <li>• Protein-calorie (Kwashiorkor, marasmus)</li> <li>• Child abuse and neglect</li> </ul>

During development, neurogenesis and cell migration occur in a tightly controlled spatiotemporal manner, during which neurons form intricate axonal and dendritic connections. Small disruptions in any of these processes during development can lead to cognitive dysfunction in children.

Defects in the control of neuronal number, from excess or defects in germinal epithelial proliferation can lead to disorders. Microcephaly is known to be associated with mutations in at least 4 genes (*MCPH1*, *ASPM*, *CDK5RAP2* and *CENPF*), all associated with cell division and cell cycle regulation.

## CLINICAL FEATURES

The presenting signs and symptoms may vary as per the level and the etiology of ID and include delay in language, cognitive skills and adaptive skills. The signs for severe and profound level of ID may be obvious from birth itself, whereas for mild degree of ID, it may be noticeable only by 3–4 years.

**Language delay** Most common clinical presentation in these children is delay in receptive and expressive language. Developmental history might reveal that the infant did not babble till 12 months, or at 2 years has still not spoken anything, and may

have started speaking between 3 and 6 years. Expressive language even at 12 years may be limited to simple two- to three-word sentences. Some parents may show apprehensions about the child being hearing impaired.

**Fine motor/adaptive delay** Noteworthy delay noticeable in ADL, such as toileting and self-feeding. Drooling may be observed even at the time of physical examination. Parents might complain of child being messy while eating.

**Gross-motor delays** Slight delays in gross-motor development are seen. Oro-motor disorders (drooling) seen more in children with moderate, severe and profound levels of intellectual disabilities. The child with ID may be clumsy with poor motor co-ordination.

**Neurologic and physical abnormalities** About 25–30% of children with intellectual disabilities develop epilepsy by childhood. Indian studies reveal that high proportions of children with ID have had history of neonatal seizures.

**Associated behavioral manifestations** Complaints of difficult temperaments, irregular sleep habits, hyperactivity may

come up in the history-taking. The children with intellectual disabilities requiring extensive supports often have associated impairments like 10% are hearing impaired, 20–25% are visually impaired, 33% have seizure disorders, 30–60% of children with severe intellectual disability have cerebral palsy, 4–18% have a co-occurring psychiatric disorder like schizophrenia, depressive disorder, phobic disorder or generalized anxiety disorder. Communication impairments and ADHD are some associated problems related to severe ID. A number of children with ID are persistently overactive, impulsive and distractible with short attention span. Respiratory diseases are a leading cause of early deaths in children with ID due to problems of posture, feeding and swallowing. These associated impairments may create dilemma in differentiating ID from other developmental disabilities.

A tall stature may suggest fragile X syndrome, whereas short stature may suggest a genetic disorder, fetal alcohol syndrome or hypothyroidism. A short stature along with some of the characteristics (flat broad face, oval-shaped eyes, flattened nasal bridge, brachycephaly, small oral cavity with short roof and protruding tongue, epicanthic folds, upward sloping palpebral fissures, redundant loose neck skin, single palmar crease, wide gap between first and second toes, fifth finger clinodactyly) may indicate the possibility of the child having Down's syndrome. Common features of children with fetal alcohol syndrome include growth deficiency, widely spaced eyes with narrow eyelids, long smooth philtrum, thin upper lip, short nose, epicanthal folds, small head circumference, underdeveloped jaws with malocclusion, hyperactivity and attention problems.

## DIFFERENTIAL DIAGNOSIS

The conditions that could be mistaken for intellectual disabilities are listed in **Box 1**. Though a child with cerebral palsy also may show average to severe impairment in areas of motor development and expressive language, there is generally no cognitive limitation in a child with cerebral palsy. Similarly, a child with communication disorder shows severe delay in expressive and receptive language without major cognitive limitation.

Children should be referred for a hearing and vision test to rule out problems of hearing and vision. Approximately one-fourth of the children with isolated ASD have an occipitofrontal circumference greater than the 97th percentile which becomes apparent by 3–4 years. A full evaluation of the child will help sort this out. At times, repeated evaluations may be needed to determine the primary developmental disability.

When a school age child is referred, the presenting problem may be poor academic performance. In such situations, the differential diagnosis should include problems like ADHD, learning disabilities and language disorders.

Hearing problems, specific language problems and Autism spectrum disorders may be confused with ID in young children, or may coexist with ID.

### BOX 1 Differential diagnosis of intellectual disability

- Autism spectrum disorder
- Child with hearing impairment
- Cerebral palsy
- Communication disorder
- Child with borderline intellectual functioning
- Child with learning disabilities
- Specific language problems
- Child with cultural deprivation/lack of stimulation.

## MAKING THE DIAGNOSIS

Intellectual disability could be suspected in children significantly below the normative developmental milestones for their age. Today, the diagnosis of ID is based on three main criteria: (1) significant subaverage general intellectual functioning; (2) limitations in adaptive behavior in at least two of the following skills: communication, self-care, home living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and (3) onset of the symptoms before 18 years of age. A large percentage of children diagnosed with GDD may eventually meet the diagnosis of ID. Among the professional organizations, there is a consensus that accurate diagnosis of intellectual disability requires clinical judgment based on comprehensive three basic criteria:

1. Evidence of general low intellectual functioning level (approximately two standard deviations or more below the mean as compared to children of their own age) measured by standardized intelligence tests;
2. Concurrent deficits/impairments in adaptive functioning in at least two of the following areas, (communication, self-care, home living, social/interpersonal skills, functional academic areas, leisure, health and safety; and
3. Onset is before the age of 18 years for both intellectual and adaptive deficits (**Table 3**).

Goal of diagnosis should not be to *label* or finding the cause, but to identify strengths and plan intervention and provide optimal support to the child (**Fig. 2**). An intelligence test alone cannot diagnose intellectual disabilities in children. Child should also have a testing in adaptive behavior. Child with IQ score of above 70 may still have severe problems in other areas of functioning. Early diagnosis by the pediatrician can provide the opportunity for early referral for intervention.

## Developmental Screening

The aim of developmental screening tool is to identify children who need more comprehensive evaluation. Unfortunately, developmental screening tools are not widely used in pediatric practice as it is time-consuming with no monetary benefit. After developing rapport with the child and making the child comfortable, a thorough physical examination can be done (with accurate measurements of growth parameters, including head circumference). Assess the functioning of vision, hearing and motor function. Look for any dysmorphism and congenital anomalies. This should be followed by a complete neurodevelopmental assessment.

It is prudent for the pediatrician to become familiar with some of the following developmental screening tests which were discussed in Chapter 20.3.

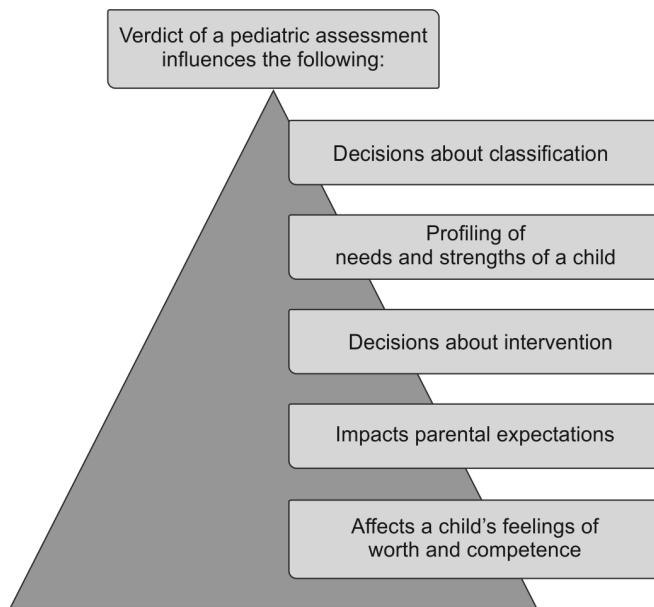
- Denver Developmental Screening Test: Denver II (DDST-II, 1992) (Revised)
- Neonatal Behavioral Assessment Scale, Brazelton (NBAS or BNBAS)
- Bayley Scales of Infant Development (Bayley-III) (BSID, Bayley 1993)
- Developmental Assessment Scales for Indian Infants (also referred to as Phatak's Baroda Screening Test) 2nd Edition (DASI-II, 1997)
- Trivandrum Development Screening Chart (TDSC) (0–6 years), 2013

Amiel-Tison and Hammersmith neonatal neurological screener are tests that can predict neurodevelopmental disability. Amiel-Tison test is comparable to BSID and is useful for motor developmental disability. Hammersmith neonatal neurological screener is a simple test which assesses the baby's reflexes,

**Table 3** Intellectual functioning and adaptive behavior

Intellectual functioning	Adaptive behavior
<p><b>Intellectual functioning</b>—also called intelligence—refers to general mental capacity, such as learning, reasoning, problem-solving, and so on</p> <p>One way to measure intellectual functioning is an IQ test. Generally, an IQ test score of around 70 or as high as 75 indicates a limitation in intellectual functioning</p>	<p><b>Adaptive behavior:</b> Adaptive behavior is the collection of conceptual, social and practical skills that are learned and performed by people in their everyday lives</p> <p><i>Conceptual skills:</i> Language and literacy; money, time and number concepts, and self-direction</p> <p><i>Social skills:</i> Interpersonal skills, social responsibility, self-esteem, gullibility, naivete (i.e., wariness), social problem-solving, and the ability to follow rules/obey laws and to avoid being victimized</p> <p><i>Practical skills:</i> Activities of daily living (personal care), occupational skills, healthcare, travel/transportation, schedules/routines, safety, use of money, use of telephone</p>

Source: Schalock et al (2010). Reproduced with permission from American Association on Intellectual and Development Disabilities.

**Figure 2** Assessment of a child with intellectual disability

movements, posture and tone, movement, orientation/behavior and abnormal patterns. It can be administered easily in an OPD ward. If two items are in the shaded areas, the neonate should be sent for detailed evaluation.

Check for coordination of the child while the infant reaches out to toys, etc. Unusual muscle movements like spasmus nutans (periodic head nodding, occasional abnormal positioning of the neck) is sometimes seen in decreased IQ. If diffuse or focal abnormalities are seen in the detailed neurological screening, then it indicates the need for neuroimaging.

### Developmental Surveillance

Today, developmental surveillance is replacing the concept of developmental screening. *Developmental surveillance*, an important function of the pediatrician, is a flexible, continuous process which includes eliciting and attending to parental concerns, obtaining relevant developmental history, making accurate observations, record keeping of surveillance and sharing concerns with multidisciplinary team. Utilize the immunization contact days or follow-up appointments for developmental surveillance. In 2013, Indian Government launched the *Rashtriya*

*Bal Suraksha Karyakram* (RBSK) aimed at screening over 270 million children from 0 to 18 years for four Ds: Defects at birth, Diseases, Deficiencies and Development Delays including Disabilities.

Pediatricians should increase interaction with the parents so as to listen actively regarding the children's development, which will help them to gain more insight into the behavioral indicators.

- Studies indicate that parental apprehensions about the child's development are highly predictive of true problems. For example, delay in motor milestones and speech delay are developmental concerns which may be voiced by parents during the early years.
- Concerns taken casually by the pediatrician can lead to substantial delay in early diagnosis.
- Recently screening tools have been developed that respond to parental concerns. By using these tools, parents become active participants in the care of their child.
- In the West, use of *parents' evaluation of developmental status* (PEDS) has been recommended for screening of all children. The parent is asked questions to elicit their concerns. For example, the pediatrician may say "Please tell me any concern about your child with regard to learning, development and behavior" or "Do you have any concern about how your child uses his hands and fingers to do things?" The responses given by the parents are then categorized into significant and nonsignificant concerns (depending on the developmental domain and age of the child) as per the guidelines of PEDS.

However, in India, a very different situation prevails. Some uneducated parents believe that the doctor is the enlightened one who guides the parents and hence may not raise any concerns from their side. At other times, parental concerns are ignored or not given enough weightage by some professionals. Indian research reveals that PEDS is not an alternative to standardized developmental testing.

### INVESTIGATIONS

#### Laboratory Tests

Genetic testing has evolved greatly, but a judicious choice of most useful and cost-effective tests has to be made. When laboratory tests are advised, counsel the family patiently and appropriately about possible outcomes of the tests. As compared to standard karyotyping and fluorescence in situ hybridization (FISH) assays, chromosomal arrays are highest yielding tools where the cause is unknown. The two common types of arrays are comparative genomic hybridization (CGH) and single-

nucleotide polymorphism (SNP). G-banded karyotyping detects in 2–4% of cases, FISH in 2.4–3.5%, and CGH and SNP has yield of 10–30%.

## Neuroimaging

Neuroimaging is recommended for children with abnormal head growth. Magnetic resonance imaging (MRI) is more sensitive than CT scans in detecting brain abnormalities related to developmental delays due to intracranial pathology and structural abnormalities. Electroencephalography (EEG) can be recommended for seizure disorders. Brain scans of children with fragile X show abnormalities of the prefrontal cortex, caudate nucleus and cerebellum.

## Metabolic Testing

Blood and urine tests are done in suspected cases, especially when there is a family history of ID. Urine tests recommended for PKU for early diagnosis, which in turn helps the newborn to grow up with normal brain development. A *musty odor* of the baby's sweat and urine (due to presence of phenyl acetate), is one of the prominent signs of the presence of PKU.

## TESTS OF INTELLIGENCE AND ADAPTIVE SKILLS

The multidisciplinary assessment approach to ID should also include a battery of intelligence tests to assess a child's ability to think abstractly, learn and solve problems. A child may have ID if the IQ test results are 70 or below. It is vital to recognize the cultural implications while doing intelligence testing.

### Commonly used Definitive IQ and Social Maturity Tests

*Wechsler Intelligence Scale for Children*® (WISC®-IV, 2003) (6 years and 16) WISC scores yield an overall intelligence quotient, called the full scale IQ. The main advantage of this test is a separate verbal and performance IQ.

*Wechsler Intelligence Scale for Children*® Fifth Edition (WISC®-V) (age range: children aged 6:0–16:11, paper-pencil and digital format).

*Wechsler's Intelligence Scale for Children*® (WISC®) *Indian Adaptation*, AJ Malin, (5–15 years) Test similar to original version of WISC but adapted to Indian child.

*Stanford Binet-Kamat test of intelligence* (3–22 years) Includes items related to vocabulary, language development, sentence building, similarities and differences, analogies, sentence repetition, auditory perception and visuospatial coordination ability.

*Bhatia's battery of performance test* This is frequently used with children (even the semiliterate and hearing impaired). It consists of five subtests: Koh's block design, Alexander's pass-along test, pattern drawing, digit span and picture construction test.

*Seguin Form Board* A nonverbal test for assessing the eye-hand co-ordination, shape concept, visual perception and cognitive ability. It is given to children from birth to 5 years and takes about 20 minutes to administer.

*Raval's Vineland Social Maturity Scale* (birth to 15 years) Measures the adaptive skills of children from 1 year to 15 years. The information is collected from the parents/caregivers who are familiar with the behavior of the child. The domains assessed by this scale are communication (receptive, expressive and written), socialization (interpersonal relationships, play and leisure time, coping skills), and motor skills. Scoring is not as easy as the original test and few items are culturally irrelevant. The scale yields

a social age which can be converted to a *social quotient* (SQ) score calculated as follows:

$$SQ = \frac{\text{Social Age}}{\text{Actual Age}} \times 100$$

## Tests of Adaptive Functioning

Diagnostic and Statistical Manual of Mental Disorders and ICD-10 indicate that adaptive skills need to be measured in addition to IQ testing.

*Vineland Adaptive Behavior Scales* (VABS) (birth to age 90): The most widely used instrument is the VABS, 2nd Edition (Sparrow, Cicchetti, and Balla, 2005). Adaptive functioning is measured in four domains (*communication, daily living skills, socialization and motor skills*). It gives the adaptive behavior composite score and the maladaptive behavior domain.

The different degrees of intellectual disability which are diagnosed are generally diagnosed at different ages of growth. For example, mild intellectual disability is generally diagnosed in school years through deficits shown while processing novel or complex information in academic tasks; while moderate intellectual disability may be diagnosed by 3–4 years through cognitive/social adaptive/language deficits. Severe intellectual disability can be easily diagnosed by one year through the dysmorphic features associated with medical conditions, low Apgar scores, poor feeding, hypoglycemia, hypothermia and presence of seizures.

## MANAGEMENT

### Sharing the Diagnosis and Psychoeducation

*Sharing of diagnosis* with the parent is a skill that a pediatrician needs to develop.

- Break the news to parents about the condition as promptly as possible after the diagnosis.
- Assign sufficient time for this session as families will always recall the way in which they were informed of their child's diagnosis.
- Counsel the parents together with sensitivity, empathy and present information, in an uninterrupted and non-rushed manner.
- Help to educate parents about intellectual disabilities as it empowers them to become advocates for the child in the society.
- Explain the diagnosis in simple helpful language to the parents, emphasizing the prognosis. They need to be told it is incurable and clarify the term *developmental delay*, as parents frequently misinterpret this as meaning the child has the ability to catch up.
- Ample time should be scheduled to discuss the findings and to allow for questions, which will be numerous. The family should be encouraged to write a list of questions for further communication with the physician.
- Enlighten families regarding the intervention and management options available. Guide them to seek early intervention after screening and assessment.
- All through this interaction, it is important to help the parents talk about their own feelings.

### Planning for the Intervention

Development of a comprehensive intervention plan is essential with inputs from multidisciplinary team of professionals (special educators, speech therapist, and occupational therapist) as many of the children with intellectual disabilities also have associated problems. This plan is called the individualized support plan (ISP)



or individualized therapy plan (ITP) which maximizes functioning through the strength model. All through the intervention, the child should be the center/focus with the professionals coming in or going out as per the needs of the child. AAIDD definition of ID is more often used toward identifying abilities which in turn facilitates rehabilitation.

### Early Intervention

Early intervention is crucial and it includes infant stimulation, speech and language therapy, physiotherapy, occupational therapy, parent counseling and training. A developmental model focuses on early, continuous intervention along with positive supports. Early intervention helps to alter the developmental trajectories by minimizing secondary complications.

Though the medical doctor is the first person usually to disclose the ID in young children, most do not refer these children for early intervention. Explaining about early intervention gives reassurance to the parents. National Institute for the Mentally Handicapped (NIMH) has exclusive units for early intervention and parent training.

### Functional Assessment

The importance of assessment for teaching by the teacher has come to the focus in India in recent years. An informal functional assessment guide for all disabilities has been developed (NCERT, 1990) for use by teachers. In addition, educational assessment tools for these children, such as Madras Developmental Programming System (MDPS, 1991), an adaptation of Minnesota Developmental Programming System, Indian adaptation of Portage Guide to Early Education (1987) and Functional Assessment Checklists (1994) by NIMH are popularly in use in India. Another assessment scale developed by NIMH is called *behavioral assessment scale* for Indian children with MR which is available for making objective assessment for planning training programs. The linguistic, sociocultural practices vary from region to region in India and there is a trend in various states to develop functional assessment tools suitable to their region. Finally, assessments must also assume that limitations in individuals often coexist with strengths, and that a person's level of life functioning will improve if appropriate personalized supports are provided over a sustained period.

The Functional Assessment Checklists (NIMH) have the items described in terms of activities rather than skills for early monitoring. Periodic quarterly assessment provision is made and the checklists are separately developed for children from pre-primary to prevocational levels (age range of 3–18 years). Separate checklist for profoundly intellectually disabled children in the name of care group is provided for these children.

### Educational Placement

Guide the parents to select the appropriate educational interventions. Brochures giving information about a list of centers/schools, and support groups could be distributed to the families. Educational facilities in India range from special schools to inclusive schools. A central issue in intervention of these children is whether they should be placed in special schools or for inclusive education in regular schools and provided additional supports. This decision will depend on the individual needs of the student.

A significant objective of these schools is to provide education for adaptive functioning. Adaptive behavior is referred to as the effectiveness with which the individual copes with the nature and social demands of the environment. These children need help with skills needed to live, work, and play in the community. Teachers

and parents can help a child work on these skills at both school and home. Training needs to be provided in the following areas:

- Taking care of personal needs (dressing, bathing, going to the bathroom)
- Health and safety
- Home living (helping to set the table, cleaning the house, or cooking dinner)
- Communicating and interacting with others
- Social skills (manners, getting along in a group, playing a game)
- Reading, writing and basic math
- As they get older, skills that will help them in the workplace.

### Vocational Training

Never underestimate the abilities of children with intellectual disabilities. Though many may need constant medical care and support, many can also function independently as adults. Develop the vocational skills of the youth with intellectual disabilities so as to increase their employability. Let them work in sheltered workshops or under supervision. This will aid in leading a fulfilling and independent life.

### Behavior Therapy

Behavior disorders are frequent in these children and can create problems in their everyday life. Most common of these disorders are agitation, self-injurious behavior (self-hitting, head banging) sleep disturbances (night-waking, early waking), ADHD and aggression (kicking, hitting, biting, breaking windows, screaming). About 20–35% of them also have a comorbidity of psychiatric etiology. Behavior assessment scale for Indian children (BASIC-MR) can be used to quantify the behavioral problems before giving the intervention. Self-injurious behavior, temper tantrums and aggression can be handled by using behavioral approach. Pharmacological treatment is effective for ADHD.

### Family Counseling

Empowering parents through parent education helps them to understand the needs of their child; assist the child in the learning process; handle the associated problems; and do advocacy for their children.

Significant aspect in the management of a child with intellectual disabilities is parental support. No doubt that ID is considered a static disorder, but the needs of the child and the family are bound to change from time to time. As the child grows older, the goals need to be reassessed and more information may be necessary to be given to the parents. As the case may be, the intervention plans may also need to be modified. Encouraging the parents to come in to the hospital/clinic for future clarifications and support is also very crucial. Providing them with supports in the society is also important.

### Nutritional Counseling

In galactosemia, treatment with a galactose-free diet prevents life-threatening liver failure, but despite good diet control, a majority of children may develop speech delay, low IQ scores and ataxia.

### Medical Intervention

No specific pharmacologic treatment is available for the cognitive impairment in the child. Medications, if prescribed, need to be targeted toward associated problems or comorbid associations. For example, a child with Down's syndrome may be vulnerable to infections and may also need supportive therapy or treatment for, hearing and vision problems, digestive problems, cardiac problems, lung defects, epileptic seizures and thyroid problems.

Inform the parents about the associated conditions that the child may have. Therapies such as speech therapy, occupational therapy or physiotherapy may be recommended as per the individual needs of the child. In some cases, prescription of anticonvulsant medications for seizures may be needed. Involving a speech therapist, a physiotherapist or an occupational therapist may be necessary.

### Leisure and Recreational Needs

In addition to the educational needs, it is very imperative to address the social and recreational needs of the child with intellectual disabilities. The goals of the leisure and recreational program are to support these persons to participate in meaningful recreation, leisure and volunteer activities of their choice. Encourage them to indulge in play activities (physical coordination, weight management and cardiovascular fitness).

### PROGNOSIS

The prognosis for children with intellectual disabilities depends on the underlying cause, the degree of the ID and the presence of the associated medical conditions. Children with intellectual disabilities reach their milestones as per the degree of the disability that the child has.

Individuals *requiring intermittent supports* reach the usual milestones, but they do it at their own pace. With supportive special education, speech therapy, medical care along with love and support from the family, they can be helped to develop functional literacy (until 5th or 6th std. level). They can be helped to reach their potential, gain economic and social independence with periodic supervision. Life expectancy is not adversely affected. Children with Down's syndrome generally live actively up to 50 years and beyond.

For intellectually disabled individuals *requiring limited supports*, the goal of education is to enhance the adaptive skills and vocational skills. Academically, they can reach up to second std. level. They may be trained to do specific job and will be able to work in sheltered workshops.

For individuals with ID *requiring extensive or pervasive support*, they function at preschool level, and will need extensive, continuous support through their lives. Having associated conditions like cerebral palsy or sensory impairments will also impact their adaptive functioning. They continue to live with their parents/siblings, as they need lot of support for their everyday living and for their severe medical problem.

In the West, the median life expectancies are 74 years, 67 years, and 58 years for people with mild, moderate and severe levels of intellectual disabilities. No such data is available for the Indian population.

### PREVENTION

#### Primary Prevention

It seeks to prevent the onset or occurrence of the problem. Advances in medical technology can aid in prevention as follows:

##### Immunization

Vaccination of girls with rubella vaccine should be encouraged to prevent fetal rubella occurring in the first trimester of pregnancy. Rh immune globulin (RhoGAM) usage for Rh positive pregnant women can prevent intellectual disabilities. Usage of Hib vaccine for preventing Hib meningitis can also prevent innumerable cases of intellectual disabilities in children.

#### Genetic Counseling

Family history indicates intellectual disabilities among family members. Consanguineous marriages have high chances of manifesting metabolic disorders with recessive inheritance. Late motherhood has high chances of a child being born with Down's syndrome. Genetic testing by amniocentesis and chorion villus sampling (CVS) could reduce the incidence of intellectual disabilities.

#### Obstetric Supervision

During labor, good obstetric supervision is essential to prevent occurrence of birth asphyxia, injuries, jaundice and sepsis.

#### Screening and Surveillance

Under the RBSK, which is a new initiative of the Ministry of Health and Family Welfare, 2013, it is mandatory to screen for *Down's syndrome* for all children between birth and 18 in the rural and urban slum groups. Regular pediatric surveillance is needed for the child at risk.

#### Awareness Training Programs

Educate young mothers about the harmful impact of intake of alcohol as fetal alcohol spectrum disorder is the most common known preventable cause of ID. Toxic exposure through environmental pollutants (e.g., lead poisoning) and through maternal substance abuse are avertable causes that can be fought with education and training. During pregnancy, good antenatal care, avoidance of teratogenic drugs, hormones, iodides and antithyroid drugs is needed. Healthy diet with folic acid in the diet reduces the chance of ID in the fetus. Prevent use of lead-based painted toys. Awareness on early detection in rural and urban areas will be of assistance in the *at risk* children to get the right support and intervention at the accurate time.

#### Secondary Prevention

Secondary prevention efforts should be directed to children who are born with a condition that might otherwise result in intellectual disabilities.

- Intellectual disability due to PKU can be easily prevented by a simple blood test followed up by phenylalanine-restricted diet. Most children with PKU who receive treatment have normal intellectual development. The incidence of PKU is highest in Turkey (1 in 2,600 births), whereas it is 1 in 18,300 births in India. Since the incidence of PKU is low in India, neonatal screening is not cost-effective or recommended.
- Incidence of CH is quite high (1 in 1,000 to 1 in 4,000). Cases of CH can be prevented by newborn screening and use of thyroid hormone replacement therapy. Indian babies ideally should be screened for CH. Newborn screening is making its progress in India. Kerala has started screening for 5 disorders from February 2013, and Gujarat is beginning to follow this trend.
- Use of surgery for implants for hydrocephalus.
- Empowering the child and the families with ID will help in stress reduction among the caregivers.

#### Tertiary Prevention

Measures are taken to reduce or limit impairments and disabilities, and to promote the patients' adjustment to *irremediable conditions*. Tertiary prevention seeks to limit the adverse effect of an existing problem while maximising the child's potential. Early intervention is the kind of tertiary intervention that has to be promoted for children with intellectual disabilities.

### IN A NUTSHELL

1. Intellectual disability is defined as consistently subaverage intellectual functioning accompanied by impairments in both cognitive functioning and adaptive skills with the onset before 18 years.
2. Early screening helps to anticipate associated comorbidities and help families to seek early intervention, which will ensure development of full potential of these children.
3. Recommend hearing tests as language delays can also be due to other developmental disabilities like hearing impairment, autism.
4. Abnormal dysmorphic features may or may not be significant predictors.
5. Magnetic resonance imaging and EEG yield specific diagnosis only in 7–8%. Patient management is not enhanced with MRI and CT scans of Down's syndrome, fragile X syndrome and hence need not be recommended in all cases of ID. Utility of CT or MRI scan is unclear when no neurological signs are present or when head circumference is normal. Chromosomal arrays are the highest yielding tools for ID of unknown etiology and are preferred over karyotyping and FISH assays.
6. Good history-taking and thorough physical examination can lead to diagnosis in most cases with intellectual disability.
7. Counsel the parents together with sensitivity, empathy and present information, in simple helpful language to the parents, emphasizing the prognosis.
8. Interventions which range from medical therapies to education to support groups will improve the quality of life of the child/family.

### MORE ON THIS TOPIC

- Belanger SA, Buret S, Gauthier M. Behavior disorders in children with an intellectual disability. *Paediatr Child Health*. 2012;17:84-8. From: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3299352/#lpo=21.4286>.
- Habela CW, Hamosh A. (2013). Genetic testing for intellectual disability: a role in diagnostic evaluation. *Contemporary Pediatrics*. From: <http://contemporarypediatrics.modernmedicine.com/contemporary-pediatrics/news/RC/genetic-testing-intellectual-disability-role-diagnostic-evaluation?page=full>. Accessed April 20, 2014.
- Harris JC. Intellectual disability: understanding its development, causes, classification, evaluation and treatment. Oxford: Oxford University Press; 2006.
- Heward W. *Exceptional Children: An Introduction to Special Education*, 7th ed. Ohio: Merrill Prentice Hall; 2003.
- Jain S, Chowdhury V, Juneja M, et al. Intellectual disability in Indian children: experience with a stratified approach for etiological diagnosis. *Indian Pediatr*. 2013;50:1125-30.
- Johnson CP, Walker WO, Palomo-González SA, Curry CJ. Mental retardation: diagnosis, management and family support. *Curr Probl Pediatric Adolescent Health Care*. 2006;36(4):126-65.
- Lakhan R. Behavioral management in children with intellectual disabilities in a resource-poor setting in Barwani, India. *Indian J Psychiatry*. 2014;56:39-45.
- Rehabilitation Council of India. (2007). Status of Disability in India. *Mental Retardation*, Vol. 5. From: <http://www.rehabcouncil.nic.in/writereaddata/mr.pdf>. Accessed March 28, 2014.
- Schalock RL, Buntinx WHE, Borthwick-Duffy S, et al. Intellectual disability: definition, classification, and systems of supports, 11th ed. Washington, DC: American Association on Intellectual and Developmental Disabilities; 2010.
- Weis R. *Introduction to Abnormal Child and Adolescent Psychology—examining childhood psychopathology from a developmental perspective*, 2nd ed. Los Angeles: Sage Publications; 2014.

## Chapter 20.6

# Visual Impairment

Nikhil Rishikeshi, Sucheta Kulkarni

Visual impairment is defined as a functional limitation of the eye(s) or visual system and can manifest as reduced visual acuity or contrast sensitivity, visual field loss, photophobia, diplopia, visual distortion, visual perceptual difficulties, or any combination of the above. These functional limitations can result from congenital (e.g., prenatal or postnatal trauma, genetic or developmental abnormalities), hereditary (e.g., retinitis pigmentosa or Stargardt macular degeneration), or acquired conditions (e.g., ocular infection or disease, trauma, age-related changes, or systemic disease).

An impairment of the visual system present at birth, or developing shortly thereafter, can adversely affect development. Visually impaired children are often developmentally delayed in the areas of gross and fine motor skills and perception. For students, the inability to read standard-sized print, to see the chalkboard, overhead projection, or the computer, or to discriminate color can have a significant impact on their educational development. A visual impairment can cause disability by significantly interfering with one's ability to function independently, to perform activities of daily living, and/or to travel safely through the environment.

Specific problems include, but are not limited to, loss of the ability to read, inability or limitation with respect to driving, difficulty performing work-related tasks or leisure activities, and/or inability to recognize faces of familiar people. When these disabilities limit personal or socioeconomic independence, a visual handicap exists.

The primary justification for early identification of visual impairment in infants relates to its impact on the psychomotor development, cognitive achievements and social/emotional development. Delayed identification and management of visual impairment may impede the child's ability to adapt to family and community life and may mimic or cause behavioral problems.

## DEFINITION

The term *visual impairment* refers to a functional limitation of the eye(s) or visual system due to a disorder or disease that can result in a visual disability or a visual handicap. For example, retinitis pigmentosa (a disorder) can result in reduced visual acuity (an impairment in vision). A visual disability is a limitation of the ability (ies) of the individual (in this example, the inability to read small print or night blindness), and a visual handicap refers to a limitation of personal and socioeconomic independence. Simply put, a visual impairment may be considered as vision inadequate for an individual's needs.

## Severity of Visual Impairment

The World Health Organization (WHO) classifies levels of visual impairment based on visual acuity and/or visual field limitation, and defines blindness as profound impairment (this can refer to blindness of one eye or blindness of the individual). The WHO definition of blindness specifies visual acuity less than 20/400 and/or remaining visual field less than 10 degrees in the better seeing eye. Visual acuity of 20/70–20/400 (inclusive) is considered moderate visual impairment or low vision (**Table 1**). The National Eye Institute defines low vision more loosely, as a visual impairment not correctable by standard glasses, contact lenses, medication or

**Table 1** Categories of visual disability (classification currently in use)

Category	Better eye*	Worse eye*	Percentage impairment
Category 0	20/30–20/60	20/80–20/120	20
Category I	20/60–20/120	20/200 to nil	40
Category II	20/130–20/300 or field of vision 100–200	20/400 to nil	75
Category III	20/400–20/1,200 or field of vision 100	20/8,000 to nil	100
Category IV	20/8,000 to nil or field of vision 100	20/8000 to nil	100
One-eyed persons	20/20 20/8,000 to nil or field of vision 10–30 degrees		

\*With correcting lenses

surgery, that interfere with the ability to perform activities of daily living.

The existing classifications do not consider loss of function due to hemianopia, loss of contrast sensitivity, photophobia, visual distortion, diplopia, or visual perceptual difficulties. A classification system that considers the functional loss of the patient, rather than simply visual acuity or field loss, has been recommended.

The International Classification of Diseases-10 (ICD-10) International Classification of Impairments, Disabilities and Handicaps (ICIDH) has been developed to take into account these and other relevant factors. According to ICD-10, there are four levels of visual function: normal vision; moderate visual impairment; severe visual impairment; and blindness. Moderate visual impairment combined with severe visual impairment is grouped under the term *low vision*: low vision taken together with blindness represents all visual impairment. Many visually impaired individuals do not meet the current criteria for legal blindness and thus are not entitled to benefits and services that would seem appropriate. This notwithstanding, visual acuity, visual field, and contrast sensitivity are the most clinically useful quantifiers of visual impairment. Often, more than one function is affected.

## PREVALENCE

An estimated 19 million children are visually impaired worldwide. Of these, 12 million children are visually impaired due to refractive errors, a condition that could be easily diagnosed and corrected. 1.4 million are irreversibly blind for the rest of their lives. Approximately, 1.4 million children aged 0–14 years are blind, defined as a corrected visual acuity in the better eye of less than 3/60 (Thylefors, Négrel, Pararajasegaram, and Dadzie; World Health Organization, 2009). It is important to know that 80% of all visual impairment can be cured.

## ETIOLOGY

Worldwide, vitamin A deficiency is still a very important cause of childhood blindness. Predominant causes of blindness among children in the poorest countries of the world include: corneal scarring due to vitamin A deficiency, measles infection, ophthalmia neonatorum, and the effects of harmful traditional eye remedies. More than 12 million children age 5–15 are visually impaired due to uncorrected refractive errors as a result of near-sightedness, far-sightedness, or astigmatism (WHO, 2009). Refractive errors if not corrected at the right time can lead to amblyopia.



## Amblyopia

It refers to partial or complete loss of vision in one eye caused by conditions that affect the normal development of vision without any structural or organic ocular defect. It has a devastating effect on development of binocular single vision and stereopsis. In amblyopia, the brain favors one eye over the other. The other eye is ignored. It is not adequately stimulated and the visual brain cells do not mature normally. Amblyopia is the most common cause of monocular blindness, partial or complete blindness in one eye. Amblyopia affects 2-3% of children in the world.

Causes include strabismus, ptosis of one eyelid, stimulus deprivation amblyopia, disease of the cornea, congenital cataract, and injury to the eye of a young child. Any pathology that affects the normal development of the visual system causes irreversible visual loss, i.e., amblyopia if not treated very early and very aggressively.

All it takes for prevention of this potentially severe visual impairment is early detection and management by treatment of the causes—spectacles or contact lenses/occlusion or patching therapy/surgery.

## Cortical Visual Impairment

It is a form of visual impairment caused by a brain problem rather than an eye problem [the latter is sometimes termed *ocular visual impairment* when discussed in contrast to cortical visual impairment (CVI)]. Some people have both CVI and a form of ocular visual impairment.

Cortical visual impairment is also sometimes known as cortical blindness, although most people with CVI are not totally blind. The term neurological visual impairment (NVI) covers both CVI and total cortical blindness. Delayed visual maturation, another form of NVI, is similar to CVI, except the child's visual difficulties resolve in a few months. Though the vision of a person with CVI may change, it rarely if ever becomes totally normal. The major causes of CVI are as follows: asphyxia, hypoxia, developmental brain defects; head injury; hydrocephalus and infections of the central nervous system, such as meningitis and encephalitis.

Various causes of visual handicaps are discussed in detail elsewhere in this book (see Section 48 on eye and its diseases).

## BRUCKNER TEST (RED REFLEX TESTING)

Red reflex testing is vital for early detection of vision and potentially life-threatening abnormalities such as cataracts, glaucoma, retinoblastoma, retinal abnormalities, systemic diseases with ocular manifestations, and high refractive errors.

The American Academy of Pediatrics currently recommends red reflex assessment as a component of the eye evaluation in the neonatal period and during all subsequent routine health supervision visits.

## MANAGEMENT

Management goals and strategies have to be realistically and meticulously crafted to suit every individual, depending on the following: degree of visual impairment, disability, or handicap; underlying cause of visual impairment and prognosis; patient's age and developmental level; overall health status of the patient; other physical impairments which may affect the ability to participate in vision rehabilitation; patient's adjustment to vision loss; patient's expectations and motivation; and patient's (cognitive) ability to participate in the rehabilitation process.

Early diagnosis and referral to tertiary eye care centers cannot be stressed enough. Rehabilitation of the child at all levels and stages of development is of paramount importance. Prescription of appropriate spectacles, occlusion therapy for amblyopia (lazy eye), medical or surgical management as indicated and low visual aids form the pillars of management of all of these conditions. Children with visual impairment who do not improve even after prescription of optimum spectacles or contact lenses/surgery wherever needed, or even after necessary amblyopia therapy, need to be encouraged to make full use of whatever residual visual acuity is present with the help of a phenomenal range of low visual aids, hand held magnifiers, stand magnifiers, monocular and binocular telescopes.

### IN A NUTSHELL

1. There is a wide plethora of conditions that cause visual impairment in children.
2. Most causes of childhood blindness are preventable if recognized and treated early.

## MORE ON THIS TOPIC

Nelson LB, Olitsky SE. *Harley's Pediatric Ophthalmology*. Philadelphia: Lippincott Williams and Wilkins; 2005.

Wright KW. *Pediatric Ophthalmology for Pediatricians*. Baltimore, MD: Williams and Wilkins; 1999.

## Chapter 20.7

# Hearing Impairment

Neelam Vaid

Hearing loss is the most common sensory deficit in humans today. As per World Health Organization (WHO) estimates in India, there are approximately 63 million people, who are suffering from significant auditory impairment; this places the estimated prevalence at 6.3% in Indian population. Four of every thousand children in India have severe to profound hearing loss. This is much more than other conditions for which neonates are routinely screened such as congenital hypothyroidism, phenylketonuria and other inborn errors of metabolism. As per National Sample Survey Organization (NSSO) survey, currently there are 291 persons per one lakh population who are suffering from severe to profound hearing loss. Of these, a large percentage is children between the ages of 0–14 years. It is indeed a big challenge to provide education and employment to this large population. There are only 540–550 special schools catering to 3% of children with hearing impairment, in India.

### DEVELOPMENT OF HEARING

The anatomical parts of the ears develop in the first 20 weeks of intrauterine gestation. The organ of Corti is differentiated to such a degree that by 20 weeks the fetus can hear and respond to fluid borne sounds. At about 25 weeks of gestation the auditory system is functional. The period from 25 weeks of gestation to 5–6 months of age is the most critical for the development of hearing as unlike

the visual system the auditory system requires external stimulation for development.

The most intensive period of hearing and speech and language development is the first 3 years of life when the brain neuroplasticity is optimum. By 6 months of age, most children recognize the basic sounds of their native language.

### Hearing and Speech and Language Milestones

Hearing is critical to development of speech and language and learning. It is imperative that pediatricians know about the normal milestones related to hearing and speech. These too should be addressed during routine visits by the child and the family. An outline is provided by the American Speech, Language and Hearing Association (**Table 1**). A detailed description is available at <http://www.asha.org/public/speech/development/chart.htm>.

### HEARING IMPAIRMENT

It is defined as the inability to perceive or identify sound due to auditory problems. It can be bilateral or unilateral. Depending on the magnitude of hearing loss it is classified as mild (26–40 dB), moderate (41–55 dB), moderately severe (56–70 dB), severe (71–90 dB) or profound hearing loss (+91 dB; **Fig. 1**). Hearing loss up to 10–15 dB is normal.

### Types of Hearing Impairment

Depending on which part of the auditory system is affected, hearing loss can be of three types:

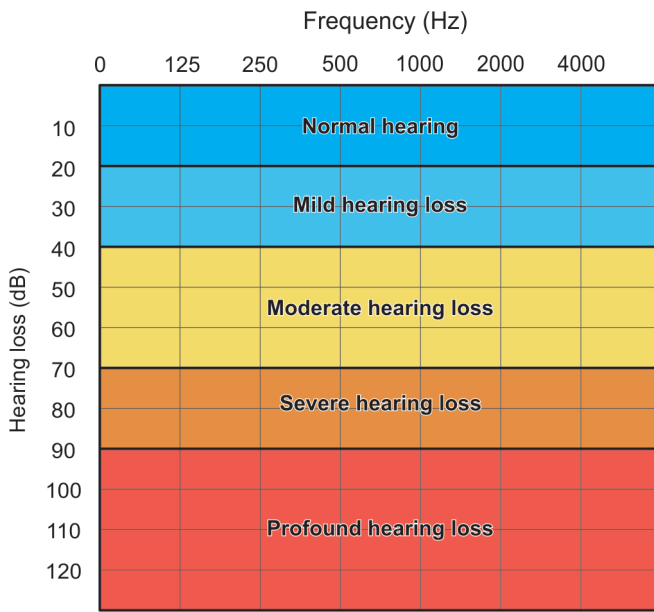
#### Conductive Hearing Loss

This is due to a problem in the outer and/or the middle ear. The common causes are: (a) Otitis media—associated with temporary

**Table 1** Milestones of hearing, speech and language

Hearing	Speech and language
Birth–3 months <ul style="list-style-type: none"> <li>Startles to loud sounds</li> <li>Quiets or smiles when spoken to</li> <li>Seems to recognize your voice and quiets if crying</li> <li>Increases or decreases sucking behavior in response to sound</li> </ul>	Birth–3 months <ul style="list-style-type: none"> <li>Makes pleasure sounds (cooing, gurgling)</li> <li>Cries differently for different needs</li> <li>Smiles when sees you</li> </ul>
4–6 months <ul style="list-style-type: none"> <li>Moves eyes in the direction of sounds</li> <li>Responds to changes in tones of your voice</li> <li>Notifies toys that make sounds</li> <li>Pays attention to music</li> </ul>	4–6 months <ul style="list-style-type: none"> <li>Babbling sounds more speech-like with many different sounds, including p, b and m</li> <li>Vocalizes excitement and displeasure</li> <li>Makes gurgling sounds when left alone and when playing with you</li> </ul>
7 months to 1 year <ul style="list-style-type: none"> <li>Enjoys games like peek-a-boo and pat-a-cake</li> <li>Turns and looks in the direction of sounds</li> <li>Listens when spoken to</li> <li>Recognizes words for common items, like <i>cup</i>, <i>shoe</i>, <i>juice</i></li> <li>Begins to respond to requests (<i>Come here</i>, <i>Want more?</i>)</li> </ul>	7 months to 1 year <ul style="list-style-type: none"> <li>Babbling has both long and short groups of sounds, such as <i>tata</i>, <i>upup</i>, <i>bibibibi</i></li> <li>Uses speech and non-crying sounds to get and keep attention</li> <li>Imitates different speech sounds</li> <li>Has one or two words (bye-bye, dada, mama), although they may not be clear</li> </ul>
1–2 years <ul style="list-style-type: none"> <li>Points to a few body parts when asked</li> <li>Follows simple commands and understands simple questions (<i>Roll the ball</i>, <i>Kiss the baby</i>, <i>Where's your shoe?</i>)</li> <li>Listens to simple stories, songs and rhymes</li> <li>Points to pictures in a book when named</li> </ul>	1–2 years <ul style="list-style-type: none"> <li>Says more words every month</li> <li>Uses some 1–2 word questions (<i>Where kitty?</i>, <i>Go bye-bye</i>, <i>What's that?</i>)</li> <li>Puts 2 words together (<i>more cookie</i>, <i>no juice</i>, <i>mommy book</i>)</li> <li>Uses many different consonant sounds at the beginning of words</li> <li>Vocabulary of 200 plus words</li> </ul>
2–3 years <ul style="list-style-type: none"> <li>Understands differences in meaning (<i>go-stop</i>, <i>in-on</i>, <i>big-little</i>, <i>up-down</i>)</li> <li>Follows two requests (<i>Get the book and put it on the table</i>)</li> </ul>	2–3 years <ul style="list-style-type: none"> <li>Has a word for almost everything</li> <li>Uses 2–3 word <i>sentences</i> to talk about and ask for things</li> <li>Speech is understood by familiar listeners most of the time</li> </ul>

Source: American Speech, Language and Hearing Association (ASHA).



**Figure 1** Categorization of hearing loss

and fluctuating hearing loss. Medical therapy and/or surgical intervention can reverse this hearing loss; (b) Impacted wax/cerumen; and (c) Congenital aural atresia—this is a failure of development of the external and middle ear and is commonly associated with microtia (small ears) or absent pinna. This may have associated cardiac and renal anomalies.

### Sensorineural Hearing Loss

This is due to a problem in the inner ear, i.e., the cochlea or the auditory nerve and its central connections. This type of hearing loss is usually permanent and irreversible. 21% of congenital sensorineural loss is caused by inner ear dysplasia which is due to genetic abnormalities. These include rudimentary otocyst, cochlear aplasia/hypoplasia, cystic cochleovestibular anomaly, Mondini deformity, X-linked deafness, large vestibular aqueduct syndrome, and cochlear aperture anomalies.

### Mixed Hearing Loss

This is a combination of both conductive and sensorineural hearing loss.

## Etiology

### Congenital Hearing Impairment

*Genetic factors* contribute to more than 50% of congenital hearing loss and could be syndromic (30%) or nonsyndromic (70%). The word syndromic implies an association of hearing impairment with other clinical distinctive features. These can be inherited in an autosomal dominant, autosomal recessive, X-linked recessive or mitochondrial pattern. More than 300 syndromes are associated with hearing impairment.

*Intrauterine factors* (8%) such as toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus and herpes (TORCH) infections, human immunodeficiency virus, maternal diabetes, toxemia of pregnancy and consumption of certain toxins by the mother, e.g., alcohol, cocaine or ototoxic drugs, e.g., streptomycin during pregnancy can cause hearing impairment.

*Perinatal causes* (12%) of hearing impairment are prematurity, low birthweight (< 1,500 g), birth hypoxia, severe hyperbilirubinemia and sepsis.

### Acquired Hearing Loss

Acquired hearing loss can be due to otitis media, meningitis, head trauma, autoimmune factors, encephalitis, and other. In children, otitis media and bacterial meningitis are the most common cause of postnatal deafness. In *H. influenzae* meningitis, 40% of survivors will have some degree of hearing impairment. 4% of these will develop profound hearing loss. Associated seizures, cranial nerve neuropathy, prolonged hospitalization, delay in treatment for more than 48 hours and low sugar in cerebrospinal fluid are predictors for the development of hearing loss in patients with meningitis. Patients with *S. Pneumoniae* meningitis are predisposed to develop obstruction of the cochlea (labyrinthitis ossificans). This can begin as early as 2 weeks after the attack of meningitis. It increases with time and is usually bilateral.

No etiology is found in 20–30% children and these are labeled as *idiopathic*. Conditions with a high risk of associated hearing impairment are listed in **Box 1**.

### Effects of Hearing Impairment on Development

Hearing impairment affects speech and development in following ways:

- There is a delay in the development of receptive and expressive communication skills.
- This leads to delayed speech and language development which has a detrimental effect on the academic performance of the child.
- The children become socially isolated and frustrated. They have a poor self-esteem.
- This results in limited vocational options for these individuals as most professions need competent communication skills today.

Some of the psychological problems associated with hearing impairment are behavioral issues, low self-esteem, depression and introversion. Behavioral problems like aggression or hyperactivity are due to internal issues like depression, anxiety and inability to communicate. These children are usually described as shy/introverts. This is because communicating takes a lot of effort on their part. Children with sensorineural hearing loss have higher rates of behavioral issues (30–38%) than normal hearing children (3–18%).

Permanent childhood hearing loss, therefore, has major developmental impacts on children's literacy, psychosocial functioning and academic achievement (JCIH 2000). Children with hearing loss who begin intervention earlier have significantly better developmental outcomes than similar children who begin intervention later. Research shows that children diagnosed with hearing loss receiving intervention before 6 months of age achieve hearing and speech skills comparable to their normal peers.

## NEONATAL HEARING SCREENING

*Hearing loss is a neurological emergency as the child has already lost 20 weeks of intrauterine auditory stimulation. Learning to listen is time-bound as the child has a limited window to catch up with the normal hearing peers, i.e., 0–3.5 years.*

Early detection of hearing loss is essential to ensure that hearing impaired children get equal opportunities as their normal hearing peers. Without such programs, the average age of diagnosis of hearing impairment is 24 months, resulting in significant delays in speech language, social, cognitive and emotional development. Mild and moderate hearing loss is often undetected until school age. Nagapoornima et al. have reported a high incidence of hearing impairment, 5.60/1,000 in a standardized neonatal population at risk and not at risk. This warrants urgent implementation of neonatal hearing screening in India.

**BOX 1 Conditions with high-risk of hearing impairment**

1. Caregiver concern regarding hearing, speech, language or developmental delay
2. Family history of permanent childhood hearing loss
3. Neonatal intensive care of more than 5 days or any of the following regardless of length of stay: extracorporeal membrane oxygenation, assisted ventilation, exposure to ototoxic medications (gentamycin and tobramycin) or loop diuretics (furosemide/lasix), and hyperbilirubinemia that requires exchange transfusion
4. In utero infections, such as cytomegalovirus, herpes, rubella, syphilis and toxoplasmosis
5. Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits and temporal bone anomalies
6. Physical findings, such as white forelock, that are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss
7. Syndromes associated with hearing loss or progressive or late-onset hearing loss, such as neurofibromatosis, osteopetrosis, and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielsen
8. Neurodegenerative disorders, such as Hunter syndrome, or sensory motor neuropathies, such as Friedreich ataxia and Charcot-Marie-Tooth syndrome
9. Culture-positive postnatal infections associated with sensorineural hearing loss, including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis
10. Head trauma, especially basal skull/temporal bone fracture that requires hospitalization
11. Chemotherapy.

Overall known risk factors are present in only 50% of infants born with hearing loss. Also mild and moderate hearing loss is often undetected until school age. Therefore, universal neonatal hearing screening (UNHS) has replaced selective or high-risk screening. Most UNHS programs aim for screening by 1 month, confirmation of diagnosis by 3 months and intervention by 6 months. The American Academy of Pediatrics, Joint Committee on Infant Hearing (2007) recommends the 1–3–6 timeline. Hearing screening should be completed by 1 month of age. Those who fail the initial screening should undergo detailed audiologic evaluation by 3 months of age and intervention done not later than 6 months of age. The recommended protocol for healthy babies is shown in **Flow chart 1**. An important point is that to be considered as pass, both the ears must pass screening. High-risk babies and neonatal intensive care unit graduates have a high incidence of auditory neuropathy and delayed onset or progressive hearing loss which needs to be constantly monitored.

Screening can be done by *otoacoustic emission* (OAE) and/or automated auditory brainstem response (AABR) testing. OAE are generated by the outer hair cells of the cochlea in response to auditory input. AABR evaluates the auditory pathway from the external auditory canal to the brainstem. There have been numerous studies comparing OAE only, AABR only and two steps testing using OAE initially followed by AABR. The referral rate is lesser with the two-step protocol using OAE and AABR than a single step OAE program—1.8–5.8%. Using AABR alone had the lowest referral rate, i.e., less than 2%, however, had the highest cost per screening. Regardless of the screening results, all children should be constantly monitored for the development of age appropriate

auditory and communication skills. Any delay in these skills needs detailed evaluation by an audiologist.

## WORKUP OF A CHILD WITH HEARING IMPAIRMENT

The management of a child with hearing impairment involves a team comprising of an otorhinolaryngologist, pediatrician, audiologist, radiologist, clinical geneticist, child psychologist and speech and language pathologist. The recommended steps are outlined:

1. Detailed history taking with special focus on the high-risk factors, antenatal and perinatal details, consanguinity, history of hearing impairment in any other family members and history of any serious illness requiring hospitalization and administration of intravenous drugs.
2. Examination of the child to look for any syndromic features associated visual/motor/neurological development issues.
3. Examination of the ear, i.e., *otoscopy*. It is imperative to rule out the presence of wax or any acute/chronic infection in the ear which needs to be addressed before further management. Any associated anomalies in the ear, nose and throat region like aural atresia, cleft lip and/or palate, facial skeletal deformities and adenoid enlargement need to be ruled out.
4. Diagnostic audiology should be provided by an audiologist with experience in the evaluation of neonates and young children. The aim is to provide the following information: (a) Confirm the presence/absence of hearing impairment; (b) Assess the degree of hearing loss; (c) Determine which part of the auditory system is affected; and (d) Determine which frequencies are affected.

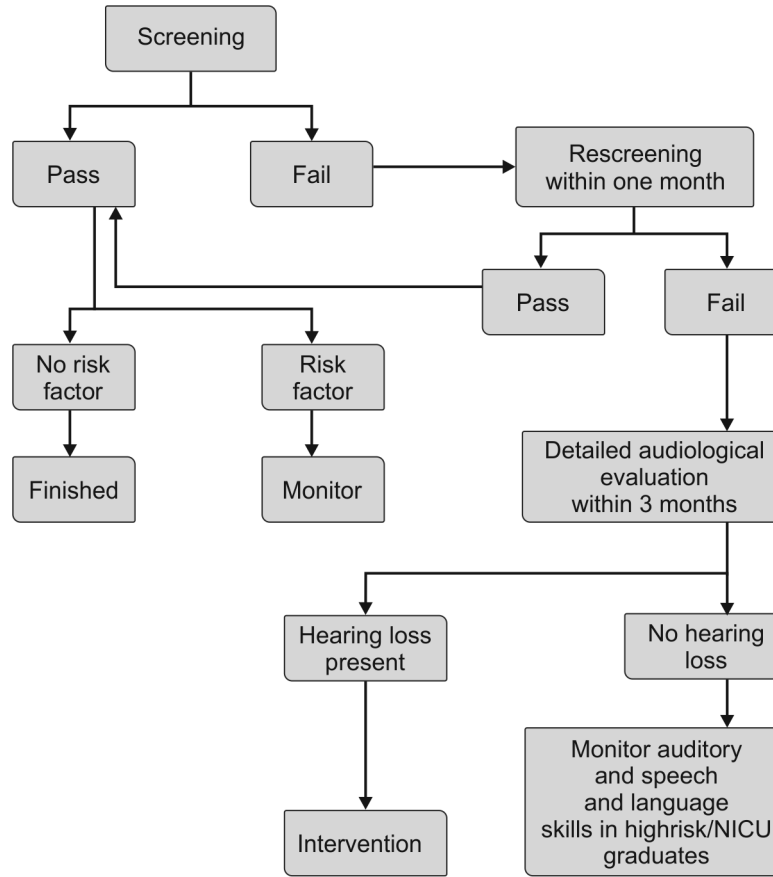
The Clinical Practice Guidelines recommended by the American Academy of Audiology for the assessment of auditory function in children has mentioned the following evaluations: (a) behavioral observation; (b) visual reinforcement audiometry; (c) conditioned play audiometry—frequency specific stimuli and speech audiometry; (d) physiologic assessment—impedance audiometry and OAE; and (e) electrophysiologic audiometry—auditory brainstem response (ABR) and auditory steady state response (ASSR). This is known as the *test battery* approach, i.e., all the above-mentioned tests are incorporated to confirm results. The gold standard of hearing measurement is behavioral assessment. The appropriate behavioral procedures depend upon the child's development, cognitive level and motor and visual development.

5. Anatomy of the ear is evaluated using dual modality radiological assessment comprising of both low dose high resolution computed tomography/cone beam computed tomography and magnetic resonance imaging.
6. Evaluation of the developmental age of the child by a developmental pediatrician and a child psychologist to rule out global developmental delays and look for other associated problems, like autism, learning disabilities and behavioral issues.
7. Complete assessment by a speech and language pathologist about the communicative skills of the child.

## TREATMENT

Intervention depends on the etiology of hearing impairment. Conductive hearing loss caused by disorders in the external and/or middle ear respond to medical and/or surgical line of management. Children with sensorineural hearing loss and congenital aural atresia need different auditory prosthesis, such as hearing aids/cochlear implants/bone anchored hearing aids (BAHA)/middle ear



**Flow chart 1** Neonatal screening for detection of hearing loss

Abbreviation: NICU, neonatal intensive care unit.

implants with therapy focused on developing their listening and speech and communicating skills. The choice of auditory prosthesis is dependent on the degree of hearing loss and the etiology.

### Hearing Aids

Children with mild to moderate hearing loss benefit from appropriately fitted hearing aids. A hearing aid is an electroacoustic device that amplifies sound. It is recommended to fit hearing aids in both the ears of children with hearing impairment to give them the benefit of binaural hearing.

### Cochlear Implants

These are a proven option for children with bilateral severe to profound hearing loss. A cochlear implant consists of an internal part which is surgically inserted and an external part which looks like a hearing aid. The technology converts acoustic signals to electrical signals and directly stimulates the surviving spiral ganglion cells in the cochlea. US Food and Drug Administration (FDA) permits implantation in children over the age of 12 months. Cochlear implantation is contraindicated in the presence of active middle ear disease and absent cochlear development. Till recently absence of the cochlear nerve was an absolute contraindication, however, certain studies are showing limited benefits with the cochlear implants in this subgroup of patients.

### Bone Conduction Hearing Aid

These are indicated for children with conductive or mixed loss due to abnormalities in the external or middle ear not amenable to ear surgery, e.g., severe congenital aural atresia or children in whom hearing aids are not feasible, e.g., chronically discharging ears. These are also an option in children with single-sided deafness. These can be done in children more than 5 years of age. Younger children are given a soft band which functions like a BAHA till they can undergo surgery.

### Active Middle Ear Implants

These are indicated for children with mixed/conductive hearing loss. These require great caution on the part of the surgeon due to the risk to the facial nerve in cases with aural atresia. Presently being done in Europe only, as this surgery in the US on children is still not approved by US FDA.

### Auditory Brain Stem Implants

It is a device which provides some level of hearing in people without a functioning cochlear nerve. These are indicated in children with absent cochlear nerves and severe labyrinthitis ossificans where cochlear implantation is not possible. As on now these are being implanted in children only in Europe.

## IN A NUTSHELL

1. Hearing loss is the most common sensory deficit in children.
2. Early detection and intervention ensure development of near normal speech and language for children with hearing impairment.
3. Diagnostic audiology should be provided by an audiologist with experience in the evaluation of neonates and young children. The aims are to: (a) confirm the presence/absence of hearing impairment; (b) assess the degree of hearing loss; (c) determine which part of the auditory system is affected; and (d) determine which frequencies are affected.
4. Behavioral observation, visual reinforcement audiometry, conditioned play audiometry, physiologic assessment—impedance audiometry and OAE, and electrophysiologic audiometry—ABR and ASSR constitute the *test battery* approach for diagnosis of hearing impairment.
5. Universal neonatal hearing screening needs to be implemented in India.

## MORE ON THIS TOPIC

- Cole E, Flexer C. Children with Hearing Loss: Developing Listening and Talking, Birth to Six. San Diego, CA: Plural Publishing; 2007.
- Durieux-Smith A, Fitzpatrick E, Whittingham J. Universal newborn hearing screening: a question of evidence. *Int Journal Audiol*. 2008;47:1-10.
- Graven SN, Browne JV. Auditory development in the fetus and infant. *Newborn and Infant Nursing Reviews*. 2008;8:187-93.
- Lin HC, Shu MT, Lee KS, et al. Comparison of hearing screening programs between one step with transient evoked otoacoustic emissions (TEOAE) and two steps with TOAE and automated auditory brainstem response. *Laryngoscope*. 2005;115:1957-62.
- Lalwani AK, Casteleine CM. Cracking the auditory genetic code: nonsyndromic hereditary hearing impairment. *Am J Otol*. 1999;20:115-32.
- Morton CC, Nance WE. Newborn screening: a silent revolution. *New England J Med*. 2006;354:2151-64.
- Mehl AL, Thomson V. Newborn hearing screening: the great omission. *Pediatrics*. 1998;101:E4.
- Nagapooranima P, Ramesh A, Srilakshmi, et al. Universal hearing screening. *Indian J Pediatr*. 2007;74:7-11.
- Sennaroglu L. Cochlear implantation in inner ear malformations—a review article. *Cochlear Implants Int*. 2010;11:4-41.
- Sharma A, Dorman MF, Spahr AJ. A sensitive period for the development of the central auditory system in children with cochlear implants: implications for age of implantation. *Ear Hear*. 2002;23:532-9.

## Chapter 20.8

# Cerebral Palsy

Sharmila Banerjee Mukherjee

Cerebral palsy (CP) is the most common cause of chronic motor disability in childhood. In 2007, an international committee described CP as *a group of permanent disorders of movement and posture, causing limitation of activity, attributable to nonprogressive disturbances that occurred in the developing fetal or infant brain, often accompanied by disturbances of sensation, perception, cognition, communication and behavior, epilepsy and secondary musculoskeletal problems*. The Surveillance of Cerebral Palsy in Europe (SCPE) group recognizes five key elements defining CP: (1) an umbrella term, (2) permanent but not unchanging, (3) disorder of movement and/or posture and of motor function, (4) due to a nonprogressive interference, lesion or abnormality and (5) affecting the immature brain.

Cerebral palsy is a clinical phenotype of various types and degrees of motor impairment due to heterogeneous causes, resulting in a permanent single-time insult to the developing brain. Though the insult itself is nonprogressive, manifestations change due to natural progression, influence of intervention and/or development of complications.

### EPIDEMIOLOGY

In developed countries, systematic and valid epidemiological information is easily available. The Centers for Disease Control and Prevention (CDC) reports CP in 3.6/1,000 with a boy/girl ratio of 1.4:1. A prevalence of 2–3 cases of CP/1,000 livebirths has been reported from other countries. Over the years, studies have either shown a static trend or a minor increase probably reflecting increased survival of very premature babies. Community-based statistics are not available from developing countries including India.

### ETIOLOGY

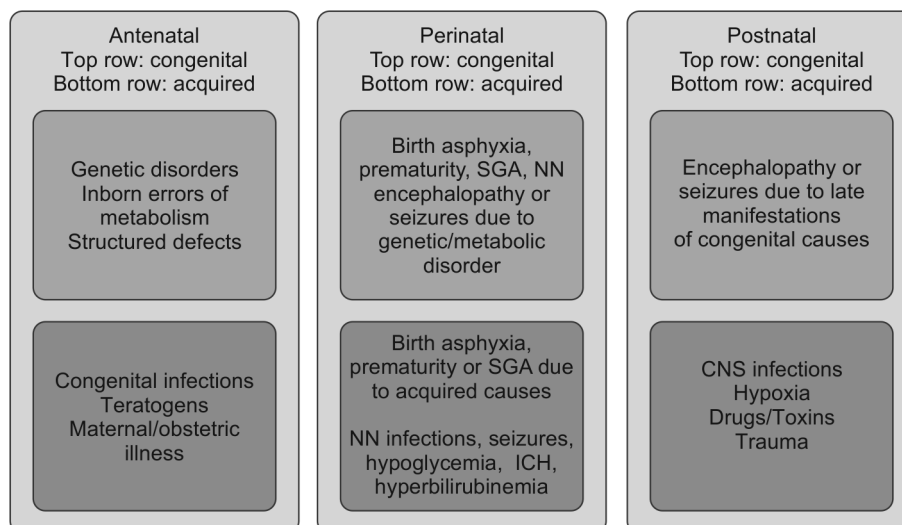
The primary insult to the developing brain is categorized as congenital, acquired or combined. This can be hypoxic, ischemic,

infectious or inflammatory, irrespective of cause. Timing of this insult can be antenatal, perinatal or postnatal. Although apparently synonymous, the difference is appreciable in **Figure 1**.

Earlier hypoxic injury at birth was thought to be the commonest cause of CP. Now it has been conclusively proven that it is responsible for less than 10% of cases. In 2003, the International Cerebral Palsy Task force criteria update added four essential criteria for defining an intrapartum event sufficient enough to cause CP: (1) metabolic acidosis with pH less than 7.2 and base deficit of greater than or equal to 12 mmol/L in fetal umbilical cord arterial sample at delivery; (2) early onset of moderate or severe neonatal encephalopathy in babies greater than or equal to 34 weeks' gestation; (3) spastic quadriplegia or dyskinetic CP; and (4) exclusion of identifiable causes (trauma, coagulation disorders, infectious conditions or genetic disorders). The SCPE states that in the absence of obvious insult at birth or later the underlying etiology may be considered antenatal. Precise etiology cannot be identified in 20–30% cases.

Certain factors have been found to have significantly higher associations with CP which may be causative. These can be preconceptional (fertility treatment), antenatal (neonatal stroke due to factor V Leiden, multiple pregnancies, maternal pre-eclampsia), natal (maternal hypotension, premature separation of membranes, low placental weight, low Apgar scores) and postnatal [requirement of admission in a neonatal intensive care unit (NICU), neonatal sepsis and respiratory disease].

In developed countries, most cases of CP are attributable to antenatal causes and preterm neonatal survivors. Associated factors are assisted conceptions and multiple pregnancies. In developing countries, although antenatal causes are maximal, the proportion of acquired causes is relatively more in contrast to developed countries. Indian data of a large cohort of children with CP over 10 years from the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh revealed majority to be term deliveries, 59.8% due to congenital causes, 17.8% acquired and 22.4% combined. In the acquired group, 57.4% were due to central nervous system (CNS) infections, 30% bilirubin encephalopathy (mostly Rh incompatibility), 7.4% late hemorrhagic disease of the newborn or intracranial bleeds and 5.2% due to hypoglycemia/head injury. Compared with the results of an earlier study cases associated with prematurity, low birthweight, neonatal jaundice and birth asphyxia had increased significantly.



**Figure 1** Congenital and acquired causes of cerebral palsy according to timing of insult to the immature brain (antenatal, perinatal and postnatal)

## PATHOGENESIS

The basic pathophysiology is a cascade of harmful events that often begin in utero and continue during and after delivery. It depends upon underlying etiology, mechanisms of injury (hypoxic-ischemic or inflammatory), timing of insult, gestational age (< 34 weeks or older), neuroanatomical structure affected and genetic predisposition. A simplified version is depicted in **Flow chart 1**.

Any significant ischemic-hypoxemic insult triggers an excitotoxic cascade that causes secondary energy failure in the mitochondria. Hypoperfusion provokes protective redistribution of blood to the brain, heart and adrenals. When reperfusion occurs secondary to compensatory mechanisms, there is a massive influx of free oxygen radicals and calcium ions in the affected areas due to damaged ion channels. This ionic imbalance causes neuronal membrane depolarization and glutamate transporter failure in the presynaptic glia that normally removes glutamate from the synaptic cleft. When the increased synaptic glutamate spill over into the extracellular spaces, excitatory glutamate N-methyl-D-aspartate (NMDA) receptors get stimulated, which cause release of more free radicals and worsen the oxidative stress. Enzyme-mediated cellular damage and release of proapoptotic cytochrome C and apoptosis-inducing factors stimulate pathways leading to neuronal apoptosis. Lactic acid accumulation disrupts the mitochondrial respiratory chain. The cumulative effect is apoptosis and necrosis of brain cells with glia being more susceptible than neurons. The inflammatory cascade is triggered by maternal infection and makes the brain more sensitive to hypoxemic-ischemic injury.

The immature brain (< 34 weeks' gestation) is more prone to injury and oxidative stress. This is reflected in the characteristic magnetic resonance imaging (MRI) findings of *white matter damage of immaturity* (WMDI) seen in preterm babies with CP. The most common autopsy findings in the premature brain are subependymal, intraventricular or leptomeningeal hemorrhage.

In contrast, in term babies, brain structures rich in excitatory synapses like the deep basal ganglia, para-rolandic cortex and posterior putamen are more vulnerable to injury.

Genetic factors may contribute to susceptibility to inflammatory response. Male neurons in culture are more sensitive to death from exposure to NMDA and nitric oxide (NO) radicals and more vulnerable to autophagy than female neurons. This could be why CP is more common and more severe in boys. Functional polymorphism in the interleukin-6 gene has been associated with CP in term babies.

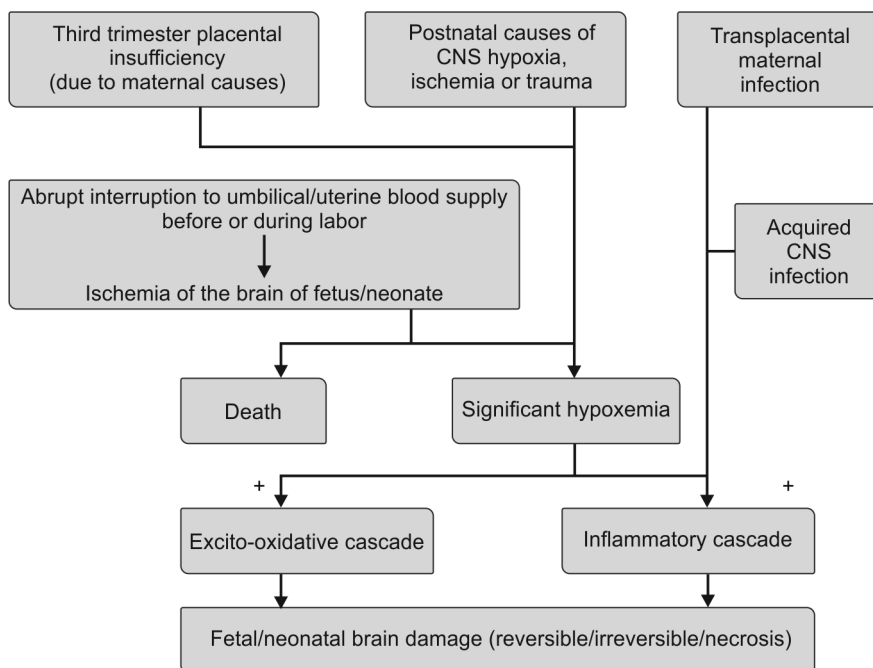
## CLASSIFICATION

This provides description of nature and severity and information regarding healthcare needs, thus enabling monitoring of change in individuals and comparison of data from different centers. The *topographic classification* is based on the distribution pattern of limb involvement, the *physiological classification* is based on the type of motor abnormality and the Swedish and SCPE classification systems combine both (**Table 1, Fig. 2, and Flow chart 2**).

In developed countries, spastic CP is seen in 85% (diplegia 35%, quadriplegia 20%, hemiplegia 25%) and extrapyramidal in 5%. Indian data reports 73% spastic (quadriplegic 51.5%, diplegic 34.5%, hemiplegic 13.8%), 7% dyskinetic/athetoid, 11.2% hypotonic/ataxic and 8.8% mixed.

In 2001, the International Classification of Functioning, Disability and Health (ICF) for developmental disabilities introduced the concept of defining impairment in body function and/or structures, limitation of activity, restriction in participation and environmental factors. **Flow chart 3** exemplifies ICF in a child with CP. The Gross Motor Function Classification Scale (GMFCS) (**Fig. 3**) and Manual Ability Classification scale (MACS) rate dysfunction in terms of overall mobility and upper limb function respectively (**Table 2**). The main drawback of these systems is that they cover only one aspect. A multiaxial classification essential for holistic understanding and appropriate management will be discussed later in this chapter.

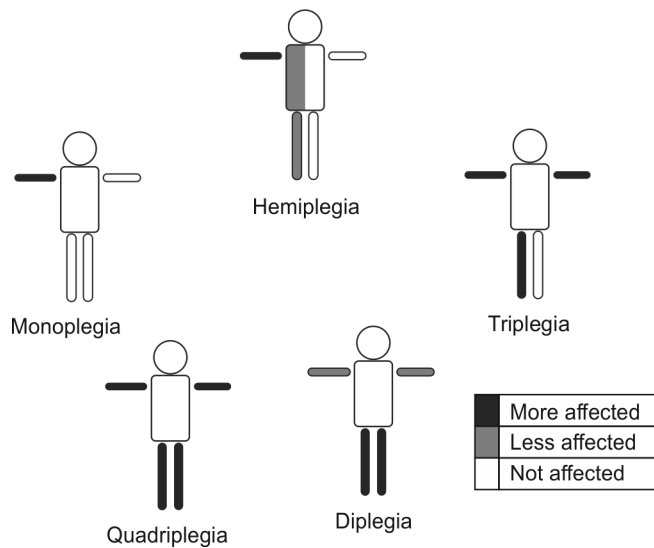
**Flow chart 1** Pathogenesis of brain damage in cerebral palsy





**Table 1** Topographic, physiological and modified Swedish classification systems of cerebral palsy

Topographic classification	Physiological classification	Modified Swedish classification
Quadriplegia	Spastic	Spastic
Hemiplegia	Quadriplegia	Tetraplegic
Diplegia	Hemiplegia	Hemiplegic
Monoplegia	Diplegia	Diplegic
Triplegia	Extrapyramidal	Ataxic
	Mixed	Dyskinetic
		Choreoathetotic
		Dystonic

**Figure 2** Topographical classification of cerebral palsy

## CLINICAL MANIFESTATIONS

The diagnosis of CP is purely clinical.

### Presenting Complaints

One would assume that this would be primarily motor-related like delayed motor milestones, locomotor difficulties or abnormal movements. However, comorbid conditions commonly associated with CP may be equally or more incapacitating. The presenting complaints reported in the Indian study were developmental delay (88%), seizures (34.7%), problems of gait and posture (22.8%), speech delay (9.5%) and problematic behavior (5.9%).

### Motor Manifestations in Established Cerebral Palsy

It is easy to make a diagnosis by 18–24 months when decreased motor power is accompanied by the following easily recognizable signs:

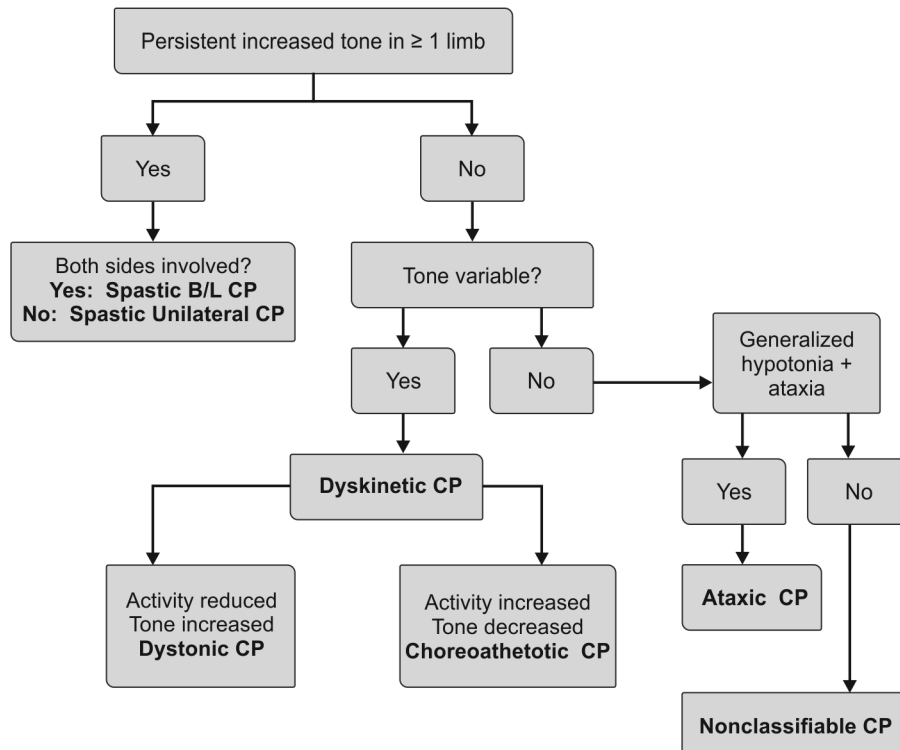
**Abnormal tone** Increased (spastic), decreased (ataxic) or variable (dyskinetic).

**Abnormal gait** Crouched (hip flexion, knee flexion and ankle dorsiflexion) and circumductive.

**Abnormal limb positioning** Characteristic upper limb postures are elbow flexion with pronation of forearm, flexion of the wrist and fingers and thumb in palm (**Figs 4A to C**). The lower limbs exhibit equinovag, equinovarus and pes valgus, flexion of the knees and hip subluxation (characterized by pelvic obliquity). Excessive adductor spasm causes scissoring.

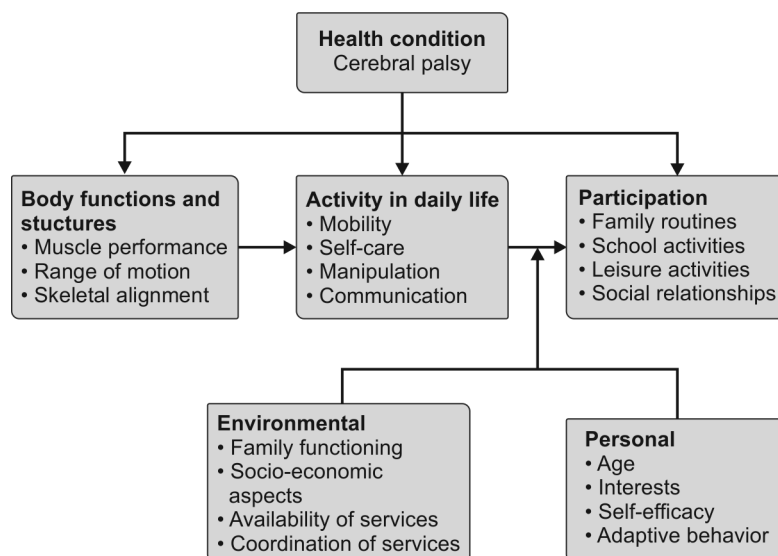
**Abnormal movements** Choreoathetosis, dystonia or both.

**Abnormal reflexes** Hyperreflexia of deep tendon reflexes, persistence of neonatal reflexes, persistent extensor plantar reflexes and failure of appearance of postural reflexes.

**Flow chart 2** Surveillance of Cerebral Palsy in Europe (SCPE) algorithm for classification of cerebral palsy

Source: Surveillance of cerebral palsy in Europe (SCPE): a collaboration of cerebral palsy surveys and registers. Dev Med Child Neurol. 2000;42:816–24. With permission from John Wiley and Sons Inc: USA.

**Flow chart 3** The International Classification of Functioning, Disability and Health (ICF) framework applied to a child with cerebral palsy



Source: Reproduced with permission from WHO.

**Table 2** Manual Ability Classification System (MACS)

Level	Description of manual ability
I	Handles objects easily and successfully
II	Handles most objects but with somewhat reduced quality and/or speed of achievement
III	Handles objects with difficulty; needs help to prepare and/or modify activities
IV	Handles a limited selection of easily managed objects in adapted situations
V	Does not handle objects and has severely limited ability to perform even simple actions

Source: Reproduced with permission from Ann-Christin Eliasson and Peter Rosenbaum, Can Child Centre for Childhood Disability Research, Ontario.

Note that this is applicable for children with CP between 4 and 18 years. The cumulative manual ability of both hands is considered while staging.

### Manifestations in Evolving Cerebral Palsy

Recognition of this stage requires experience, keen observation and clinical acumen. Symptoms like delayed milestones, slightly more than normal tightness or limpness of the body or limbs appreciable while diapering or dressing the infant, difficulties in breastfeeding, repetitive tongue movements, impaired hearing or vision, squint or recurrent regurgitation may be indicative of evolving CP. One must keep a high degree of suspicion, especially in *at high-risk* babies (NICU graduates) and do a detailed developmental evaluation looking for any abnormal or asymmetrical patterns of movement or position while performing the developmental maneuvers (Table 3). Sometimes it is difficult to differentiate slight abnormalities from normal variation or transient tone abnormalities that can occur around 4–5 months of age. In these circumstances, parents should not be needlessly alarmed without justification. At the same time, it is extremely important for intervention to be started. Parents should be sensitively explained that the mild abnormalities detected may be a false alarm but nevertheless will require intervention and close follow-up for a few months.

### Changing Manifestations of Cerebral Palsy

This occurs due to natural progression of the primary injury, which although static in nature gets modified by the naturally ongoing maturation of the CNS (i.e., hypotonia evolving into spasticity due to the normal ongoing myelination) or age-dependent recognition of symptoms (speech delay or cognitive impairment becoming appreciable when child is older).

#### Nonmotor Manifestations

These are frequently seen in CP either due to the primary insult or secondary to other factors. Children with CP usually have multiple comorbid conditions that require documentation and monitoring for optimal management (Table 4). An individual's problem chart should record details of the following:

**Cognitive impairment** Global developmental delay/intellectual disability or learning disability manifests as delayed milestones and scholastic underachievement. This gets confounded by sensory impairments and motor restriction which lead to limited cognitive stimulation and experiential learning.

**Behavioral issues** These may be severe enough to interfere with daily functioning. They may be due to primary defects, drug side effects or faulty parenting practices.

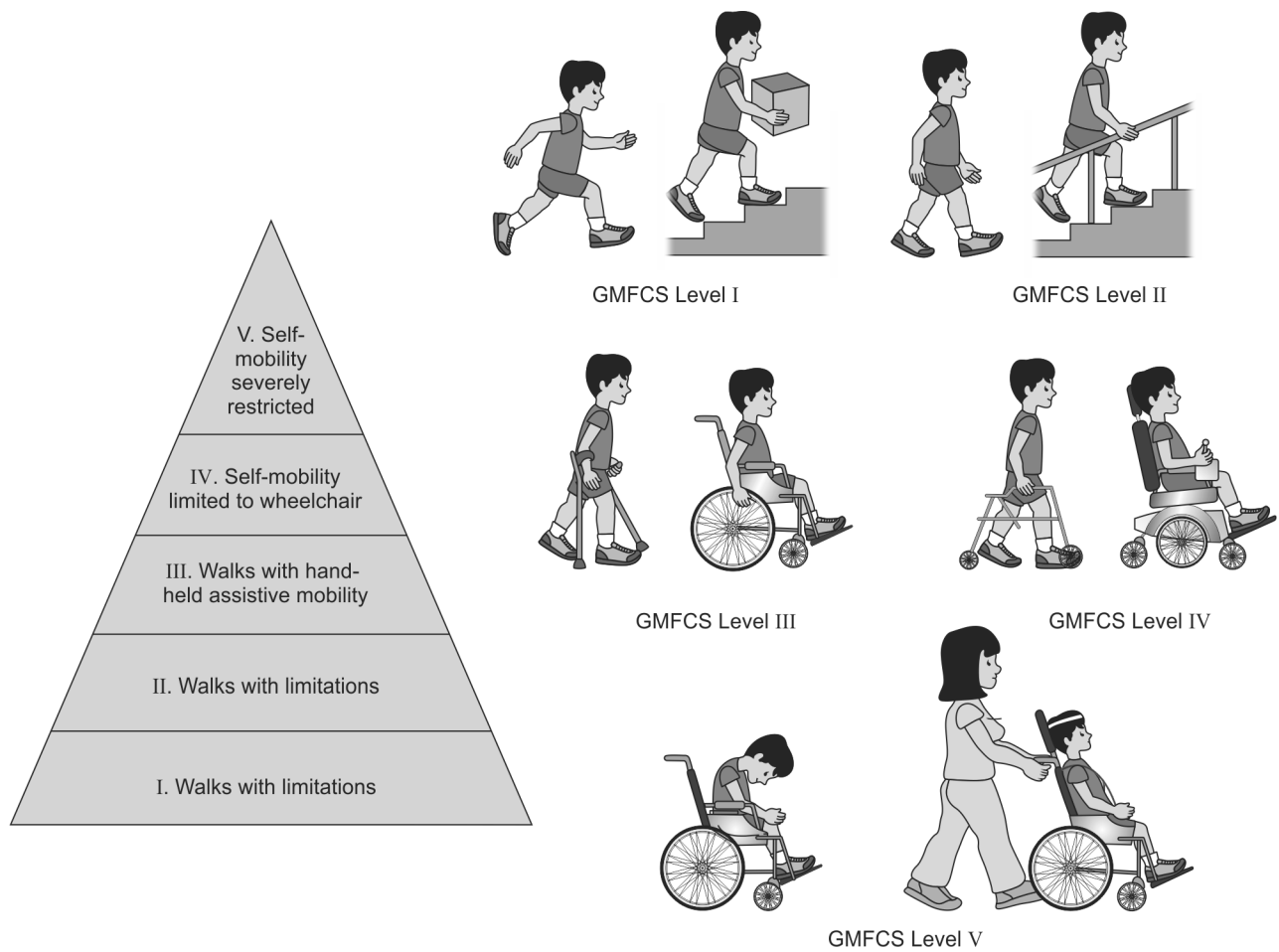
**Epilepsy** Nearly one-third have epilepsy with onset within the first 2 years. Generalized tonic-clonic seizures are most frequently seen. Seizure control often requires multiple anticonvulsants.

**Speech and language problems** These arise due to cognitive defects, hearing impairment or dysfunctional speech areas. Articulation defects are due to oromotor dysfunction and pseudobulbar palsy.

**Sensory impairment** These include cortical blindness, hearing impairment, perceptual deficits oromotor hypersensitivity and sensory disintegrative dysfunction.

**Ocular manifestation** These include strabismus, refractory errors, optic atrophy, nystagmus and visual impairment.

**Gastrointestinal problems** Poor dental hygiene, gastrointestinal motility disorders, gastroesophageal reflux (GER) and constipation are common.



**Figure 3** Levels of the Gross Motor Function Classification Scale (GMFCS)

Source: Reproduced with permission from Palisano et al. Dev Med Child Neurol. 1997;39:214-23.

Can Child: www.canchild.ca; Illustrations: © Kerr Graham, Bill Reid and Adrienne Harvey—The Royal Children's Hospital, Melbourne.



**Figures 4A to C** Upper limb positions seen in cerebral palsy: (A) Flexion of wrist with slight splaying of fingers; (B) Pronation of forearm; (C) Flexion of fingers

Source: Dr Srishti Goel.

**Feeding problems** Difficulties in chewing and swallowing, choking, excessive drooling and food aversion can be due to causes like oromotor dysfunction, abnormal perioral sensory awareness, poor head stability, inability to self-feed and gastroesophageal reflux disease (GERD).

**Macronutrient and micronutrient deficiencies** This is attributable to decreased intake. Vitamin D deficiency is due to nonambulation, anticonvulsants, low sun exposure and poor calcium intake.

**Pain** This manifests as excessive crying or irritability. Causes are chronic muscle spasm, orthopedic complications, undetected dental problems, constipation and GERD.

### Orthopedic Complications

These include the following:

1. **Low impact fractures:** Due to associated severe osteopenia.
2. **Secondary abnormalities:** Spasticity results in disuse atrophy, joint contractures and limb length discrepancy. Deformities like femoral anteversion, external tibial torsion, talipes equinovagum and hip subluxation are referred to as *lever arm disease* due to a malaligned bony lever that impairs muscle function and affects gait. Hip subluxation occurs due to femoral neck valgus, persistent anteversion, soft tissue contractures and acetabular deformity. Lumbar scoliosis is seen in less than 10% of ambulatory children and 30–40% of nonambulatory children.

**Table 3** Signs indicative of early CP while performing developmental maneuvers

Developmental maneuvers	Significant findings
Supine	<ul style="list-style-type: none"> <li>• Head persistently in midline</li> <li>• Limbs unduly extended with persistent fisting of one or both hands</li> <li>• Reduced and/or asymmetrical spontaneous movements</li> <li>• Not tracking till 180° by 12 weeks</li> <li>• Not turning head to sound</li> </ul>
Prone	<ul style="list-style-type: none"> <li>• Head to side, not in midline by 12 weeks</li> <li>• Chin not raised off plane of surface by 6 weeks</li> <li>• Face not at 45–90° and no weight-bearing on forearms by 12 weeks</li> <li>• Pelvis still not flat by 12 weeks</li> <li>• Knees drawn under abdomen without extension of legs &gt; 6 weeks</li> </ul>
Pull to sit	<ul style="list-style-type: none"> <li>• Pronounced head lag</li> <li>• Spasm of hamstring felt in popliteal space and feeling of resistance with flexion of knees</li> <li>• Entire body rising spontaneously to feet</li> </ul>
Held sitting	<ul style="list-style-type: none"> <li>• Inability to lift chin up intermittently</li> <li>• Rounding of back pronounced</li> </ul>
Held standing	<ul style="list-style-type: none"> <li>• Unable to lift chin up momentarily beyond 8 weeks</li> <li>• Unable to bear weight at all</li> <li>• Abnormal degree of plantar flexion</li> </ul>
Ventral suspension	<ul style="list-style-type: none"> <li>• Excessive head lag with limbs hanging limply OR</li> <li>• Advanced head control—head above level of plane with increased extension of lower limbs</li> </ul>
Axillary suspension	<ul style="list-style-type: none"> <li>• Abnormal/asymmetrical extension of lower limbs</li> <li>• Abnormal adduction/scissoring of lower limbs</li> <li>• Feeling of sensation of slipping</li> </ul>

3. *Tertiary abnormalities:* These result from compensatory mechanisms adopted to overcome spasticity and secondary abnormalities in order to achieve ambulation, i.e., hamstring and recti femori involvement results in compensatory hip over-abduction and circumductive gait.

## Clinical Manifestations According to Cerebral Palsy Subtype

### Spastic Quadriplegic Cerebral Palsy

This is the most severe form with high association with intellectual disability, epilepsy, microcephaly, squint/visual impairment, pseudobulbar palsy, speech abnormalities and deformities (**Fig. 5**).

*Spastic diplegic cerebral palsy* This is most commonly seen in preterm babies (85%). Initial indicators are difficulties in diapering and *commando crawl* (self-propulsion by use of arms). Intellectual disability and epilepsy are less common but learning disability or sensory problems may be present.

*Hemiplegic cerebral palsy* Early indicators are persistent fisting, cortical thumb, hand preference in infancy and circumductive gait. As they grow older, asymmetry of posture and limb position become obvious (**Fig. 6**). Epilepsy and intellectual disability are relatively common.

*Dyskinetic cerebral palsy* Initially hypotonicity gradually evolves into dystonia, rigidity and abnormal postures. Intellectual disability and epilepsy are less common but commonly associated

speech difficulties, tongue thrust and drooling are often mistaken for severe cognitive impairment.

*Ataxic cerebral palsy* This is caused by cerebellar injury that affects the whole body. It is characterized by hypotonia, difficulty with balance and motor coordination and tremors.

*Mixed cerebral palsy* This is a combination of both spastic and extrapyramidal CP.

## CLINICAL EVALUATION

Preliminary evaluation comprises of a detailed history, general physical examination, extended neurological assessment, developmental assessment and evaluation of nature and severity of comorbidities and complications (**Table 5**). All children should be referred to other specialists.

## INVESTIGATIONS

### For Determining Etiology

Individualized, targeted and sequential investigations ensure a higher etiological yield.

*Neuroimaging* The pattern, extent and severity of lesions may determine etiology and timing of insult. MRI is preferable over computed tomography (CT) scan (except where cranial calcification is anticipated). **Table 6** illustrates the commonly known MRI-topographic-etiology correlates. Further investigations are planned accordingly. MRI findings in the European study were WMDI (42.5%), basal ganglia lesions (12.8%), cortical/subcortical lesions (9.4%), malformations (9.1%), focal infarcts (7.4%), miscellaneous (7.1%) and normal (11.7%). Indian literature reported hypoxic-ischemic changes (35.7%), periventricular leukomalacia (PVL) (13.4%), cerebral malformations (7.4%), nonspecific cerebral atrophy (12.8%), basal ganglia changes (5.8%) and others (11.5%). This corresponds to the difference in etiologies.

*Metabolic investigations* When the MRI is normal but there is clinical suspicion of a metabolic disorder according to history or examination (spastic diplegia or choreoathetoid CP without definite etiology), standard metabolic investigative protocol should be followed.

### Assessment of Comorbidities

*Cognitive impairment* Administration of specific validated psychometric diagnostic scales by a clinical psychologist.

*Behavioral issues* Determine parental responses to inappropriate behavior. If maladaptive behavior very severe, frequent, refer to clinical psychologist.

*Nutritional assessment* Assessment of dietary and water intake and investigations for micronutrient deficiencies including vitamin D levels annually.

*Others* Visual, hearing, speech and language assessment. Speech and language pathologist evaluation that should include a feeding assessment. Radiographs of affected joints, both hips at 18–24 months (subluxation may not be clinically apparent) and spine to exclude scoliosis. Orofacial evaluation is important.

## FINAL DIAGNOSIS

This should be multiaxial with the following components: physiological, topographic, ICF/functional and neuroradiological classification, etiology, timing of insult, comorbid conditions, complications and nutritional status. This helps in planning management, counseling, monitoring progress and prognostication. Certain conditions that mimic CP are given in **Table 7**. These can usually be excluded by a detailed evaluation.



**Table 4** Example of a problem chart of a child with cerebral palsy

Name: <u>Anant</u> Age/Sex: <u>4 Y/M</u> Classification of CP: <u>Spastic Quadriplegic CP, GMFCS V, MACS_V</u> Neuroradiological classification: <u>Extensive WMDI and cortical lesions</u> Causation and timing: <u>Perinatal-neonatal meningitis, hypoglycemia</u> Nutritional status: <u>Protein energy malnutrition grade IV, anemia</u>						
Problems	Details	1° cause	2° cause	Test	Intervention/referral	Outcome
Motor disability	Spastic Q. paresis	CP	Contractures		OT/PT/orthopedic	
Cognitive impairment	Global developmental delay	CP	Decreased stimulation	Psychometric assessment	Clinical psychologist	
Behavior problems	Temper tantrums		Overindulgence	Behavior charting	Parental counseling	
Epilepsy	GTCS	CP		MRI brain EEG	ACT started	
Speech and language	Delayed speech	CP	? hearing delay		Speech therapist	
Sensory impairments	? decreased hearing	CP		BERA	To be referred to ENT for ruling out wax	
Ocular	Squint, ? impaired vision	CP			Pediatric ophthalmologist	
GIT problems	Constipation		Reduced water and roughage intake	Monitor daily intake	Counsel	
Feeding issues	Swallowing difficulty	CP		Feeding assessment		
Micronutrient/macronutrient deficiencies	PEM IV Anemia		Reduced + deficient oral intake	Type of anemia, Cal/SAP/Vit. D levels	Calorie dense, frequent small meals Supplements	
Pain	Excessive crying ?		Contracture		OT	
Orthopedic complication	Dynamic contractures				Orthopedic consult	
Others						

Abbreviations: CP, cerebral palsy; OT, occupational therapy



**Figure 5** Spastic quadriplegic cerebral palsy: note the position of upper limbs and lower limbs in the recumbent position  
Source: Dr Srishti Goel.

## MANAGEMENT

Intervention should start the moment CP is diagnosed or suspected. Without intervention the natural course is rapid deterioration of gait and motor function. Goals are enhancing acquisition of new skills, treating comorbid conditions and decreasing complications. Ideally it should be done by a multidisciplinary team (rehabilitative, medical and surgical) in a single center (**Fig. 7**). Any member can act as a team-leader whose responsibilities are mainly ensuring team coordination, scheduling group discussions on progress and appointments and updating the management chart (**Table 4**). The various modalities are discussed below:

### Physiotherapy

It involves repetitive exercises directed at a specific muscle group with a joint above and below (**Figs 8A to D**). This should be done



**Figure 6** Spastic hemiplegic cerebral palsy: note the asymmetry of position of right upper limb with flexion at elbow joint and slight flexion and splaying of fingers. The child is standing with legs wide apart  
Source: Dr Srishti Goel.

at least thrice a day with complete range of movement. It also includes the equipment required to develop strength and motor skills required in sitting, standing, balancing, etc., and control of

**Table 5** Components of an in-depth evaluation of a child with cerebral palsy

Component	Salient aspects to be evaluated
History	Parental concerns (presenting complaints) Motor manifestations Comorbid conditions Bladder and bowel habits Dietary and water intake and feeding Developmental history: all domains Histories pertaining to etiology (antenatal, natal, postnatal) Family history (3° pedigree tree)
General physical examination	Anthropometry especially for microcephaly, wasting and stunting Dysmorphology Neurocutaneous markers Amiel-Tison angles (by a goniometer) Orthopedic complications (joints, spine)
Extended neurological examination	Posture, alertness and interest in surroundings Cranial nerve examination Observe posture and gait Observe movements: range, symmetry, abnormality Tone: feel muscles, shake limbs, observe resistance to passive movements Reflexes
Developmental examination	Developmental maneuvers Cross check accuracy of developmental milestones elicited
Assessment of oromotor function	Interference of primitive reflexes with feeding Tongue weakness, tongue thrust and jaw thrust Difficulty in closing mouth, sucking and swallowing Uncoordinated mandible and tongue movements Tonic bite reflex Hyperactive gag reflex Neck hyperextension

movement (**Fig. 9**). The basic principle is encouraging movement that is as normal as possible, maintaining correct positioning in activities of daily living (ADL) and reducing inappropriate postures (**Figs 10A and B**). Recently the American Academy of CP and Developmental therapy stated that apart from decreasing abnormal joint motion and limiting contractures, physiotherapy (PT) had no long-term benefit for children with severe disease or beyond 4–7 years.

### Occupational Therapy

It includes instruction and use of techniques and adaptive equipment to develop skills required for ADL (**Figs 11A and B**). The aim is increasing functional skill and independence. Devices can be mobility-assistive like wheelchairs, crutches and customized orthoses (ankle-foot orthosis, knee orthosis, knee-ankle-foot orthosis). They can also be ADL-assistive like devices that enable feeding (cup handle, spoon handle), dressing (Velcro straps, zipper pull), grooming (adapted toothbrush, comb) and bathing (long-handled sponge). Feeding management is especially important and includes the use of shallow spoons, feeding of soft textured food or small pieces of solids with special techniques (placing food in the middle of tongue, applying pressure on the jaw while chewing to keep mouth closed to minimize tongue thrust and encourage swallowing, rubbing the gums before meals for perioral desensitization). Strategies to maximize arm and hand function in hemiplegic CP have been developed.

*Constraint-induced movement therapy (CIMT)* Movement of the affected side is constrained with casts so that the impaired limb is forced to perform under motivation repetitively. However, it proved to be frustrating and demotivating for the child and failed to address bimanual deficits and coordination defects.

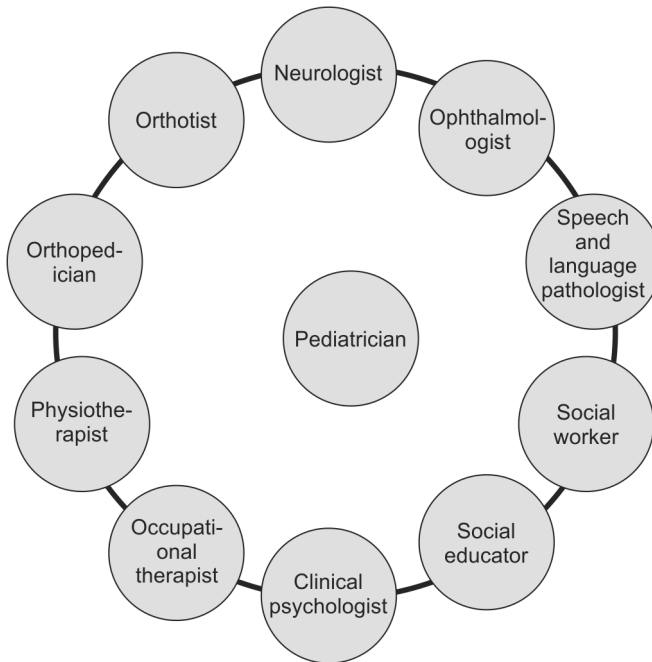
*Hand-arm bimanual intensive therapy (HABIT)* Bimanual coordination is improved by performance of bimanual activities without a physical restraint in a similar environment. The task is

**Table 6** MRI-topographic-etiology correlates in cerebral palsy (CP)

Topographic classification	MRI findings	Common etiologies
Diplegic CP	White matter damage of immaturity (WMDI): periventricular leukomalacia, posterior > anterior Periventricular cysts/scars in WM Enlargement of ventricles Squared posterior ventricles	Prematurity Ischemia Infection Metabolic
Quadriplegic CP	Cortical-subcortical lesions Extensive WMDI Multicystic encephalomalacia Cortical malformations	Ischemic injury Infection Endocrinal Metabolic Genetic/developmental
Hemiplegic CP	Asymmetric WMDI Stroke (in utero/neonatal) Focal infarct (cortical/subcortical) Cortical malformation	Thrombophilic disorder Infection Genetic/developmental PV hemorrhagic infarction
Dyskinetic CP	Basal ganglia lesions in different combinations Symmetrical scars in putamen and thalamus Scars in globus pallidus, hippocampus Scars in GP, putamen, caudate, brainstem No lesions	Severe birth asphyxia Kernicterus Mitochondrial Genetic/metabolic disorders

**Table 7** Differential diagnoses of cerebral palsy (CP) based on stage and type

Evolving CP	Established cerebral palsy			
	Spastic quadriplegic CP	Spastic diplegic CP	Extrapyramidal CP	Ataxic CP
Musculodystrophies (when predominantly motor delay) Global developmental delay (when $\geq 1$ domain affected)	Post-traumatic, atlanto-axial instability, neural tube defects, Pelizaeus-Merzbacher disease Peroxisomal disorders	Arginase deficiency, Hereditary spastic familial paraparesis, Juvenile metachromatic leukodystrophy	Primary neurotransmitter deficiencies, Dopa responsive dystonia, Primary dystonias, glutaric aciduria type I	Neurodegenerative causes of ataxia

**Figure 7** Members of a multidisciplinary team involved in management of cerebral palsy

demonstrated to the child who is then encouraged to perform it with positive reinforcement. If the child tries to compensate with the unaffected extremity, the activity is stopped and the process repeated.

### Speech Therapy

Parents are instructed on how to: (1) provide a stimulating environment conducive for speech and communication; (2) help in exercises for improving muscle tone of tongue and throat that result in decreasing drooling; and (3) dealing with feeding problems. Communication can be augmented with technologically advanced devices like specialized keyboards, talking typewriters, electronic speech-generating devices and specially adapted computers.

### Management of Spasticity

Indications of treating spasticity include impairment in muscle function, pain, secondary orthopedic complications or interference in care. This is achieved by the following:

**Physical therapy** Night splints and orthotics provide passive stretch.

**Drugs** The practice parameter for pharmacological treatment of spasticity in CP recommends botulinum toxin A for localized spasticity and considers diazepam and tizanidine for short-term treatment of generalized spasticity. It states that there is

insufficient data to support or refute the use of phenol, alcohol, or botulinum toxin B in the former and for dantrolene or baclofen (oral/intrathecal) in the latter. Details of drugs are given in **Table 8**.

**Surgery** Selective dorsal rhizotomy is a laminoplasty of L1-S1 with selective section of 20–40% of the dorsal rootlets. Indications include pure spasticity, good selective motor control, adequate muscle strength, 4–7 years age and spastic diplegia. Long-term complications have caused it to fall into disrepute.

**Age-dependent planning of spasticity reduction** PT or botulinum toxin A is preferred for children less than 4 years. Between 4 and 7 years options include management of generalized spasticity. Beyond 7 years the development of severe *lever arm disease* or contractures make these modalities redundant.

### Other Drugs

**Abnormalities of tone or motor movements** Levo-dopa (0.5–2 mg/kg/day), carbamazepine and trihexyphenidyl (0.25 mg/day, BD-TDS) have been used for dystonia. Tetrabenazene (12.5–25 mg/day, BD-TDS), neuroleptics and benzodiazepines have been tried for choreoathetosis, which is difficult to treat.

**Drooling** Anticholinergics like oral glycopyrrolate or transdermal scopolamine may be used if occupational therapy (OT) exercises fail but are limited by side effects (constipation, urinary retention). Local botulinum toxin A in both submandibular and parotid glands has been tried with success.

### Physical, Visual and Hearing Rehabilitation

Hearing and visual aids need to be provided as needed. **Orthopedic management** should be aimed to prevent deformities, improve function and relieve pain.

**Correct muscle imbalance** This can be noninvasive (passive stretching, night splinting, serial casting, localized reduction in spasticity) or invasive (heel-cord tightening, surgical lengthening, tendon transfers).

**Contractures** When dynamic (movable on passive stretching) PT is beneficial, once fixed (immovable) soft tissue release or tendon lengthen without weakening.

**Reconstructive surgery** This is resorted to for restoring muscle balance, releasing contractures and stabilizing joints to improve placement of the hand in space, voluntary grasp, release and pinch functions.

**Corrective surgery** This is required for the 'bony lever disease' described earlier. It is crucial that the individual components are correctly identified. Secondary abnormalities need to be rectified. Interference with tertiary abnormalities results in worsening of function. The **Video Gait Analysis** is an optoelectronic computer-based system that objectively analyzes gait and documents joint movements in multiple planes and levels. It is particularly helpful in preoperatively determining cause of crouch gait (equines/hamstring tightness, lever arm dysfunction), in-toeing (femoral





**Figures 8A to D** Child with spastic quadriparetic cerebral palsy: (A) being held in the recommended position that minimizes abnormal postures of trunk and limbs; (B to D) mother delivering a physiotherapy session

Source: Dr Srishti Goel.



**Figure 9** Child with cerebral palsy undergoing gait training with parallel bars

Source: Dr Srishti Goel.



**Figures 10A and B** Effects of positioning on the posture of a child with CP. (A) Hyperextension of neck, arching of back and extended limbs; (B) Head and neck in proper position with normal flexion being maintained at knees

Source: Dr Srishti Goel.

or tibial torsion), and pes varus (anterior or posterior tibialis dysfunction).

*Orthopedic selective spasticity control surgery (OSSCS) or single event multilevel surgery (SEMLS)* It refers to correction of all deformities (soft tissue and bony) in one hospital admission, requiring single exposure to anesthesia and rehabilitation. Multiarticular muscles





**Figures 11A and B** A customized corner chair to facilitate the sitting position: (A) with a table for promoting eye-hand coordination and hand activities; (B) with a wedge to keep both lower limbs apart  
Source: Dr Srishti Goel.

with limited antigravity action are selectively released and monoarticular antigravity muscles are preserved. The best age for surgery is 4–6 years for lower limb surgery and 6–8 years for upper limb surgery. Unstable lever arm disease must be operated irrespective of age.

### Other Surgical Indications

This includes surgeries for refractory drooling (salivary duct ligation), GERD not amenable to medical management or gastrostomy/jejunostomy for feeding when there is significant malnutrition and failure to establish adequate feeding.

### Dietary Advice

Young children with malnutrition should be given calorie-dense, balanced semisolid diet in small quantities frequently. If older and nonambulatory with adequate nutritional status, calories should be restricted to ~65% to avoid obesity. Adequate water intake should be ensured. Constipation should be treated with fluids, stool softeners, specific PT for increasing bowel motility

and adaptive toilet seats. Micronutrient supplements should be given.

### Special Education

This involves planning of flexible instructional programs based on individual strengths and weaknesses. This employs strategies aimed at developing sensory and perceptual motor skills, language, cognition and memory with reinforcement of learning. They also teach socially acceptable behavior and provide academic instruction in a stimulating learning environment.

### Educational Placement

Children with normal intellect should attend regular schools. Those with borderline intelligence or mild impairment benefit from integrated schooling. Others require special schools and vocational training. Educational placement of children with disabilities is mandatory by Indian law. Institutions are supposed to be equipped with facilities like ramps, lifts, adaptive toilets, etc. Like any other teenager, these children need to be prepared for the various changes and emerging sexuality that occurs during this period.

### Advocacy and Parent Support Groups

Emotional support for the family is important for successful management. Looking after children with CP is stressful and distorts family dynamics. Social workers can help in easing difficult situations and strain on families. Parents should be made aware of parent support groups, disability benefits and the *National Trust for the Welfare of Persons with Autism, CP, mental retardation and Multiple Disabilities Act, 1999*. The latter mandates that all children should receive equal opportunities, protection of rights and full participation in education, employment and others.

### Parental Counseling

Relevant information should be explained sensitively as per the parent's level of understanding. It may take more than one sitting. It is essential to empathize and be realistic without being fatalistic or giving false expectations. In nontechnical language parents need to be counseled about the nature, pathogenesis, comorbid conditions and natural course of CP. Feelings of personal guilt should be

**Table 8** Drugs used to reduce localized and generalized spasticity

Indication	Drug	Mechanism of action	Route	Dose	Side effects
Localized spasticity	Botulinum A toxin	Prevents presynaptic release of acetylcholine at neuromuscular junction	IM, repeated every 4–6 months	Small muscle 1–2 U/kg, large muscle, 4–6 U/kg each Limited to 12 U/kg or a maximum of 400 U per visit	Unwanted paralysis of adjacent muscles, swallowing difficulty, pain, rash, malaise
	5% phenol	Temporary neurolytic agent	Direct into obturator/musculocutaneous nerves	Variable 1–3 mL per nerve	Requires electrical stimulation Lethal if > 8 mg/day
Generalized spasticity	Diazepam	Facilitates GABA-A receptor-mediated presynaptic inhibition	Oral	0.5–0.75 mg/dose, BD-QID	Sedation, tolerance, withdrawal seizures
	Tizanidine	Central alpha-2 noradrenergic agonist	Oral	0.3–0.5 mg/kg/day QID	Dry mouth, somnolence, dizziness, asthenia
	Baclofen	GABA-B agonist	Oral	0.2–2 mg/kg/day BD/TDS	Seizures, headache, urinary retention, insomnia
			Intrathecal	Implanted pump	Constipation, urinary retention, CSF leak, infection
	Dantrolene	Muscle relaxant	Oral	0.5–10 mg/kg/day BD-QID	Sedation, CNS effects, GIT effects

identified and addressed appropriately. Treatment options need to be discussed. It should be emphasized that although not curable, CP is definitely treatable and with appropriate intervention the quality of life can be good. The need for compliance and regular follow-up requires highlighting. At first, contact proper counseling can make a child (parents understand the situation, are willing to start intervention, comply with instructions and come for follow-up) while improper counseling can break a child (parents feel that the situation is hopeless and nothing can be done; so they do not even try).

## MANAGEMENT IN RESOURCE-CONSTRAINED SITUATIONS

The management outlined previously is considered ideal. If such dedicated multidisciplinary centers are not available, pediatricians should ensure that management remains family-centered, competent, comprehensive, compassionate, continuous and community-based. In addition to routine pediatric issues, they must assume the role of team coordinator and counselor. To achieve this, they need to follow the guidelines given below:

1. Have a referral list of competent service providers and establish open communication channels with them. After referral, a management plan can be devised as outlined earlier with their inputs.
2. Discuss treatment options with parents and plan a feasible schedule by categorizing modalities as frequently required (i.e., OT, PT and speech therapy) and not so frequently required (hearing, visual and orthopedic) so that parents feel that it can be adhered to.
3. Determine whether they have understood the therapist's instructions by checking questions and asking them to demonstrate.
4. Advise regarding domiciliary management that can supplement the above. A pediatrician should have working knowledge about the following:
  - i. Proper handling and positioning during ADL. This should be taught to all family members so that caregiving can be shared (**Table 9**). Emphasize avoidance of vigorous oil massages.
  - ii. Providing a stimulating environment. These include use of bright colors, different textures, different voices, exposure to various experiences and people.
  - iii. Promoting speech and communication. These include repeated naming of common objects in the immediate environment. Use simple, direct and brief language that the child understands. Indulge in shared attention activities like looking at picture books with naming. Immediately mimic whatever sound or word the child utters to promote vocal reciprocity.
  - iv. Encourage play in different positions and with other children. Practice holding and releasing toys. Encourage use of both arms and separately.
  - v. Handle behavioral issues like temper tantrums appropriately and consistently. Do not be indulgent simply because the child has a chronic disorder.

## OUTCOME

Understandably, children with CP have higher mortality and morbidity due to various health issues. Poor prognostic factors are spastic quadriplegia, apparent motor delay within 6 months, persistent primitive reflexes by 2 years, inability to sit by 4 years and inability to walk by 7 years. Good prognostic factors include spastic diplegia, head balance in prone position by 9 months, sitting by 2 years, crawling by 30 months, access to early intervention, good family support and absence of comorbidities.

## PREVENTION

**Primary prevention** Improvement in healthcare in antenatal period (supervised pregnancies), during delivery (more trained birth attendants or hospital deliveries, improvement in transport facilities, administration of predelivery steroids in preterm labor, monitoring of high-risk newborns) and neonatal period (educating mothers about personal hygiene and exclusive breastfeeding, discouraging prelacteals, teaching danger signs and promoting healthcare seeking from qualified doctors).

**Secondary prevention** This entails increased sensitization of pediatricians with training in developmental screening and surveillance and implementation of these into the health services so that high-risk children get detected early and timely intervention is started.





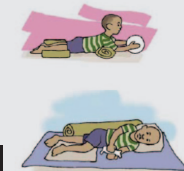
### IN A NUTSHELL

1. Cerebral palsy is the most common cause of chronic motor disability in childhood.
2. Essential criteria that define an intrapartum event sufficient enough to cause CP are metabolic acidosis umbilical cord arterial blood, early onset of moderate or severe neonatal encephalopathy in babies greater than or equal to 34 weeks' gestation, spastic quadriplegia or dyskinetic CP and exclusion of identifiable causes.
3. Hypoxic injury at birth is responsible for less than 10% of cases of CP.
4. Every child with CP requires a detailed history and examination and diagnosis is essentially clinical.
5. Cerebral palsy is characterized by decreased motor power in the presence of abnormal tone, gait, limb positioning, movements and reflexes.
6. The role of investigations is to determine etiology, assess comorbid conditions and assess complications.
7. The final diagnosis should be multiaxial encompassing physiological, topographic, ICF/functional and neuroradiological classification, etiology, timing of insult, comorbid conditions, complications and nutritional status.
8. Evaluation and management should be by a multidisciplinary team (rehabilitative, medical and surgical).
9. Management needs to be family-centered, competent, comprehensive, compassionate, continuous and community-based.
10. Parental counseling is crucial. The first contact interaction can make or break a child.

## MORE ON THIS TOPIC

- Aisen ML, Kerkovich D, Mast J, et al. Cerebral palsy: clinical care and neurological rehabilitation. *Lancet Neurol*. 2011;10:844-52.
- Ashwal S, Russman BS, Blasco PA, et al. Practice parameter: diagnostic assessment of the child with cerebral palsy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2004;62:851-63.
- Johnston MV, Fatemi A, Wilson MA, Northington F. Treatment advances in neonatal neuroprotection and neurointensive care. *Lancet Neurol*. 2011;10:372-82.
- Johnston MV. Cerebral palsy. In: Kliegman RM, Stanton FS, St. Geme JW, Schor NF, Behrman RE. *Nelson Textbook of Pediatrics*. 19<sup>th</sup> ed. New Delhi: Elsevier; 2012. pp. 2061-4.
- Kalra V. Cerebral palsy. In: Kalra V. *Practical Pediatric Neurology*. New Delhi: Arya Publications; 2002. pp. 111-25.
- Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy, April 2006. *Dev Med Child Neurol Suppl*. 2007;109:8-14.

**Table 9** Recommended techniques for physical handling of a child with cerebral palsy

Mode of handling	Description of techniques	Pictorial representation
Positioning in a chair	The child should be positioned symmetrically Rolled up towels can be used for support Feet must be supported, never dangling The position should maximize balance, enable use of hands and promote eye-hand activities A lap board can provide a surface for play	
Carrying	Pick up the child from behind Position arms under the hips so that the child's knees can bend over it Support child's back against your body Wrap your other arm around child's shoulders Carry the child on your hip with both lower limbs around you and the trunk upright	
Lap sitting	Face the child away from you, supporting the back with the trunk of your body Seat the child facing you with legs on either side of your hips First laying the child on his back on your outstretched legs Slowly bend your knees, gradually bringing the child to a sitting position The child's back and head are supported by your thighs	 
Lying down	On stomach: place a roll under child's upper torso On the side: keep both arms forward and bend one hip and knee	

Source: Figures B and C2: Courtesy: Dahlea H. Figures A, C1 and D: Reproduced with permission from Manual—How can you help your child with cerebral palsy? CCBRT and CBM with EU/CBM funding with APDK Kenya. [http://www.globalhelp.org/publications/books/cbm\\_helpchildcerebralspalsy.pdf](http://www.globalhelp.org/publications/books/cbm_helpchildcerebralspalsy.pdf).

Note: Start with the child in a relaxed position and perform all movements slowly.

Singhi P, Saini AG. Changes in the clinical spectrum of cerebral palsy over two decades in North India—an analysis of 1212 cases. *J Trop Pediatr*. 2013;59:434-40.

Singhi PD, Ray M, Suri G. Clinical spectrum of cerebral palsy in North India—an analysis of 1,000 cases. *J Trop Pediatr*. 2002;48:162-6.

Surveillance of Cerebral Palsy in Europe. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. *Dev Med Child Neurol*. 2000;42:816-24.

The Center for Children with Special Needs, Seattle Children's Hospital. *The Critical Elements of Care for Cerebral Palsy*. 5<sup>th</sup> ed. Seattle, WA: Seattle Children's Hospital; 2011.

Werner D. *Disabled Village Children: A Guide for Community Health Workers, Rehabilitation Workers, and Families*. 2<sup>nd</sup> ed. Berkeley, California: The Hesperian Foundation; 2009.

# Section 21 BEHAVIOR AND LEARNING

**Section Editors** Monica Juneja, Devendra Mishra

## Chapter 21.1

### Moral Development

Prahbhjot Malhi, Rajalakshmi Iyer

Moral development plays a significant role in child's life as it lays the foundation for social interactions and helps children adapt to the standards in their environment. The Oxford dictionary defines morality as *principles concerning the distinction between right and wrong or good and bad behavior*. According to Turiel (2002) morality refers to issues of human welfare, justice, and rights that are a function of the inherent features of interpersonal relations. While these definitions hold good for all societies, one needs to distinguish between morality and social conventions and norms. Social conventions and norms are culture dependent and can alter the interpretation of morality. However, it is important to keep in mind that morality is more universal and cuts across cultures.

#### THEORIES OF MORAL DEVELOPMENT

Moral development actually begins very early and is greatly influenced by parenting styles and highly susceptible to modification by the social milieu the child grows in. Moral values include sharing, cooperation, moral reasoning, empathy and autonomy. These values develop over the years in children and these are influenced by home, school and the neighborhood. Children tend to parallel their parents' actions with respect to moral judgment, and are also influenced by their teachers, the books they read and the outlook of their peer group. For most societies, concern and caring for others, empathy, justice and self-control are important social and moral values and efforts are made to inculcate these values in individuals. Many theorists have attempted to explain how moral development takes place in children and a brief description of the important child development theories is presented below.

#### Piaget's Theory

Jean Piaget was the first theorist to systematically examine moral development in children. Piaget conducted interviews with 5–13 years old children by presenting stories in which characters' intentions about right and wrong actions and the consequences about their actions varied. For example, children were asked which of the two boys was wrong: the one who broke more cups unintentionally or the one who broke fewer cups, but intentionally. According to Piaget, there are two broad stages of moral development. The first stage, heteronomous morality characterizes the thinking of 3–10 years old, wherein children view rules as determined by an external authority like the parents, teachers and God. Younger children accept rules from authority figures without questioning as they have limited cognitive capacity. In this stage, the child who broke more cups, regardless of intention, is judged to have performed a greater transgression. As children grow older,

and mature cognitively they move to the autonomous stage of moral development. In this stage, children do not view rules to be externally determined or universally applicable but rather perceive them as flexible and socially determined. Older children are also more likely to take another person's intent into consideration before making a judgment. Piaget also emphasized the role of peer disagreement in developing perspectives on moral actions. Piaget's theory has been subjected to considerable empirical scrutiny and many authors have found support for his contention that moral understanding is related to children's cognitive development.

#### Kohlberg's Theory

According to Lawrence Kohlberg, children learn their moral values through active thinking and reasoning and moral development follows a series of stages. Children pass through three stages in developing their sense of justice and in the kind of reasoning they use to make moral judgments: (1) the preconventional level, (2) the conventional level, and (3) the postconventional level (**Table 1**). Each of these stages is further divided into two stages.

Kohlberg developed his theory of moral development by presenting a series of hypothetical moral dilemmas to the participants and asked them what the main actor should do and why. Based on their reasoning, respondents were scored on a moral judgment scale to determine their stage of development. The most commonly quoted of these dilemmas was **The Heinz dilemma**:

*In Europe, a woman was near death from a special kind of cancer. There was one drug that the doctors thought it might save her. It was a form of radium that a druggist in the same town had recently discovered. The drug was expensive to make, but the druggist was charging 10 times what the drug cost him to make. He paid \$200 for the radium and charged \$2,000 for a small dose of the drug. The sick woman's husband, Heinz, went to everyone he knew to borrow the money, but he could only get together about \$1,000 which is half of what it cost. He told the druggist that his wife was dying and asked him to sell it cheaper or let him pay later. But the druggist said: "No, I discovered the drug and I'm going to make money from it." So Heinz got desperate and broke into the man's store to steal the drug for his wife. Should the husband have done that?*

#### Level I: Preconventional level (Toddlers—2–3 Years)

**Stage 1—The preconventional level** The punishment and obedience orientation: The child judges what is right and wrong based on the physical consequences of one's actions. If one is punished for an act then it viewed as bad, and acts which are rewarded are perceived as good. This is the most immature level of moral reasoning, because it is characterized by an egocentric emphasis and external determination.

**Stage 2—The instrumental purpose orientation** In this stage, the child views right actions as determined by self-interest. Anything which benefits the child is considered good. The needs of others are very rarely considered in this stage of development, unless they help the child in some way.



## Level II: Conventional Level (Preschool Years—3–6 Years)

*Stage 3—Interpersonal concordance orientation or the good boy, nice girl stage* The child now begins to care about what others think and approval by others becomes important. Obeying social rules, meeting social expectations and maintaining order is considered being moral.

*Stage 4—The social law and order orientation (school years: 7–11 years)* Now, the child begins to think of society as a whole. The maintenance of law and order and a need to maintain a stable social structure shape moral values. Personal gain is considered inferior to what would benefit society as a whole; doing one's duty, respecting authority and keeping up social order take precedence.

## Level III: Postconventional Level (The Autonomous Stage)

The postconventional stage is considered the only truly mature stages of moral reasoning as it is detached from socially dictated rules and focuses on personal principles.

*Stage 5—The social contract-legalist orientation* At this level, personal values and opinions of others begin to gain a place in thinking. While the legal point of view retains its importance, scope for argument outside of it begins to make sense to the child. Although law may be binding, it may need modification to benefit the society as a whole. Justice begins to emerge as an important concept at this stage of development.

*Stage 6—The universal ethical principle orientation* This is the highest stage of morality and characterizes the values and thinking of great philosophers and individuals like Mahatma Gandhi, Martin Luther King and Mother Teresa. It comprises the belief that all people are created equal and that no law which gives justice to one and discriminates against another, is right. There is respect for the basic dignity of all people.

These stages occur in a defined order of transition and one has to pass through a lower stage to reach a higher one. Ordered acquisition of the stages of moral development has been demonstrated in research employing both longitudinal and cross-sectional designs. Additional evidence for the sequential acquisition of moral judgment stages is the strong positive relationship found between moral stage and age. The sequence of development is invariant and children cannot reach the highest level until about age 13 years—primarily because of limitations in cognitive development before that age. In fact, Kohlberg found that only a relatively small percentage of adults rise above the second level of his model and very few people reach the highest level of moral reasoning. Children in industrialized societies move through Kohlberg's moral stages more rapidly than children from nonindustrialized countries.

Moreover, strong cultural differences may emerge of what one considers moral. Indians have been found to be more concerned with issues of care and gave greater priority to interpersonal responsibilities than Americans who in turn are more concerned

with moral rules and issues of justice. Studies show that differences among cultures arise from different moral codes where Indians give priority to social duties, while Americans give priority to individual rights and personal choice. Moreover, Indians perceive interpersonal responsibilities as duties, while Americans see them as more voluntary.

Although Kohlberg's theory contributed substantially to the understanding of moral development, the research support is equivocal. One difficulty with the theory is that knowing right from wrong does not mean that individuals would act in accordance with their moral judgments. Moreover, the theory applies primarily to Western society and cross-cultural research suggests that Kohlberg's theory may not be universally applicable. Some authors, particularly Carol Gilligan, have criticized Kohlberg's moral development theory as being male orientated as it overemphasizes rights and justice which are typically masculine ideals and underemphasizes care and responsiveness which are typically feminine ideals. Although Kohlberg's theory has been revised since it was first published, it still remains one of the most accepted of all theories of moral development and remains the dominant theory in child development literature. The theory of Kohlberg has also been subjected to considerable scrutiny and other models have also been proposed as alternatives, which have endeavored to resolve some of its shortcomings.

## INFLUENCES ON DEVELOPMENT OF MORAL REASONING

### Child-Rearing Practices

Parents can facilitate or impede their child's moral development through role modeling and use of appropriate disciplinary methods and child-rearing practices which combine parental warmth, responsiveness and inductive discipline. Parents who narrate stories with moral implications and engage children in moral discussions encourage the development of morality and prosocial behavior. Parents who consistently use explanations that emphasize taking others' perspective, consequences of one's actions on others in their child-rearing are more likely to inculcate empathy, perspective taking and increased internalization of moral values in their children. Moreover, parents who listen to their children's opinions of moral dilemmas considerably increase their children's moral reasoning ability.

On the other hand, power assertive discipline such as using threats, shaming children and withdrawal of love tend to focus attention to external social expectations and development of morality based solely on fear of external punishment. Physically abused and neglected children engage in more stealing, cheating and show fewer rule compatible behaviors. Maltreated children may also have difficulty in understanding reasons for the morally inappropriateness of their behavior which may result in rigidity in the application of moral rules. Interestingly, evidence indicates that South Asian parents are more likely to use shaming, withdrawal of

**Table 1** Kohlberg's stages of moral development

Level	Stage	Definition
1. Preconventional	Obedience and punishment	Whatever leads to punishment is considered wrong; hence, children avoid punishment and seek out rewards
	Individualism and exchange	Right behaviors are those that are in the best interest of oneself
2. Conventional	Interpersonal relationships	Children believe that holding to social norms is being good
	Authority and social order	Law and order are considered the highest ideals
3. Postconventional	Social contract	At this stage, individuals start to use abstract reasoning to justify behaviors. Moral behavior is based on ethical principles that are comprehensive and universal such as justice, dignity and equality
	Universal principles	Develop internal moral principles

love rather than induction and reasoning as disciplining techniques in their child-rearing practices. Such parenting practices may actually hamper the acquisition of higher moral development in Indian children. Evidence also indicates that Indian children hold obligations to parents as far more important than other moral transgressions. Such findings raise questions about the cultural relevance of the highest stages of Kohlberg's moral development.

### Schooling and Peer Influences

Education has a strong impact on moral development and moral reasoning mainly because it introduces children to social, political and cultural issues which extend beyond personal issues. School also provides children immense opportunities to interact with diverse social groups and participate in academic discussions which encourage perspective taking. In fact, low school attainment, low intelligence and delayed moral judgment are all risk factors for juvenile delinquency.

Peer interactions during the formative years also play an important role in the development of moral reasoning, particularly during adolescent years. Close friendships provide the youth with increased opportunities for mutual perspective taking and enhances moral reasoning. Peer conflict and resolution of conflict with emphasis on compromising and negotiating is particularly important for development of moral reasoning in children.

### Culture and Morality

Moral values, religion and culture are the foundations of Indian society. Initially, the child's moral values closely parallel those taught to him, but with age, children tend to reason out what they believe is just and moral, and why. Evidence indicates that by the preschool years, children across cultural groups and social classes can differentiate moral transgressions, involving harm and unfairness, from social conventions, judging the former to be wrong regardless of external authority and punishment. However, cross-cultural studies have also shown that individuals from traditional cultural settings such as Arab villages and rural Nigeria are relatively reluctant to change their social conventions. Marked cultural differences between Asian and western cultures have been observed in several studies. Indian compared to Americans have been reported to be more oriented toward issues of care and interpersonal responsibilities, while Americans are more concerned with moral rules, issues of justice, individual rights and formal moral obligations. Tangible improvement in Indian children's social, emotional and moral behavior and ability to listen to another's argument have been noted by researchers who have attempted to enhance children's sociomoral reasoning and behavior of Indian children through intervention sessions.

### Implications for Parents and Pediatricians

Parents often turn to pediatricians for help in managing their children's behavioral and emotional problems. Parents actively seek guidance regarding the kind of parenting that can effectively foster positive outcomes in their children, including early internalization of societal values and norms. Thus, it is important for pediatricians to promote positive child-rearing practices that facilitate empathy, perspective taking and moral reasoning. **Box 1** presents some strategies for parents and other stakeholders to guide the moral development of children.

#### BOX 1 Strategies to teach morality to children

- Caregivers need to provide reasonable and rational reasons for rules
- Engage children in conflict resolution which emphasizes perspective taking, negotiation and compromise
- Provide opportunities for discussions which highlight understanding of different viewpoints
- Use positive disciplining techniques
- Encourage participation in youth activities that directly teach concern for others, engage in moral discussions
- Teach children self-control by delaying gratification, resisting temptation and setting limits to behavior.

#### IN A NUTSHELL

1. Moral development begins very early and is greatly influenced by parenting styles and highly susceptible to modification by the social milieu the child grows in.
2. According to Lawrence Kohlberg, children learn their moral values through active thinking and reasoning and moral development follows a series of stages. Children pass through three stages in developing their sense of justice and in the kind of reasoning they use to make moral judgments: (1) the preconventional level, (2) the conventional level and (3) the postconventional level.
3. Rearing practices, culture, morality, peers and schools all can influence the behavioral development of a child.

#### MORE ON THIS TOPIC

- Armon C, Dawson TL. Developmental trajectories in moral reasoning across the lifespan. *J Moral Educ.* 1997;26:433-53.
- Barber BK, Stoltz HE, Olsen JA. Parental support, psychological control, and behavioral control: Assessing relevance across time, culture, and method. *Monogr Soc Res Child Dev.* 2005;70:1-137.
- Dawson TL. New tools, new insights: Kohlberg's moral judgment stages revisited. *Int J Behav Dev.* 2002;26:154-66.
- Eisenberg N. Emotion, regulation, and moral development. *Ann Rev Psychol.* 2000;51:665-97.
- Helwig CC, To S, Wang Q, et al. Judgments and reasoning about parental discipline involving induction and psychological control in China and Canada. *Child Dev.* 2014;85:1150-67.
- Kohlberg L, Ryncarz RA. Beyond justice and reasoning: Moral development and considerations of a seventh stage. In: Alexander CN, Langer EJ. *Higher stages of human development: Perspectives on adult growth.* New York: Oxford University Press; 1990. pp. 191-207.
- Mason MG, Gibbs JC. Social perspective taking and moral judgment among college students. *J Adolesc Res.* 1993;8:109-23.
- Mehta S, Whitebread D. Philosophy for children and moral development in the Indian context. Paper presented at: First Global Conference on Philosophy with Children; 2004. Available from : <http://www.persons.org.uk/ati/education/CP/CP1/mehta%20paper.pdf>. Accessed Nov 11, 2014.
- Miller JG. A cultural perspective on the morality of beneficence and interpersonal responsibility. In: Ting-Toomey S, Korzeny F. *International and intercultural communication annual*, Vol. 15. Newbury Park, CA: Sage Publications; 1991. pp. 11-23.
- Turiel E. *The culture of morality: Social development, context, and conflict.* Cambridge: Cambridge University Press; 2001.
- Volling BL, Mahoney A, Rauer AJ. Sanctification of parenting, moral socialization, and young children's conscience development. *Psychol Relig Spiritual.* 2009;1:53-68.

## Chapter 21.2

# Sleep Hygiene and Disorders of Sleep

Suresh Kotagal

Disorders of sleep are common in childhood. In a questionnaire survey of 332 children of 11 through 15 years of age, Ipsiroglu and associates observed that 28% of the subjects had snoring, insomnia, or a parasomnia. Occurrence of sleep problems in a high proportion of children in India has been documented in both urban and rural children and adolescents. Sleep disorders have a significant effect on the quality of life. Many are also treatable, which underscores the importance of prompt recognition and management. They are equally common in boys and girls. Sleep is also influenced by social and environmental factors, such as use of electronic media late into the night or illicit substance use.

## SLEEP: THE BASIC CONCEPTS

### Sleep Ontogeny

Sleep can be distinguished from wakefulness in a premature infant by 27–28 weeks' postconceptional age. At this age, 80% of sleep is of the active or rapid eye movement (REM) type. During early childhood, there is progressive reduction in REM sleep and a corresponding increase in non-rapid eye movement (NREM) sleep. Contrasting physiologic characteristics of the two types of sleep are shown in **Table 1**. Melatonin, a sleep inducing hormone, is produced by the pineal gland. It acts at the level of the suprachiasmatic nucleus of the hypothalamus to facilitate sleep induction and maintenance.

By 4–6 months of age, NREM sleep becomes fully differentiated into N1, N2 and N3 sleep—this corresponds respectively to light, intermediate and deep stages from the arousal threshold standpoint. The bulk of N3 occurs during the first-third of the night. Growth hormone release is closely linked to N3 sleep, with suppression of the latter leading to impaired growth hormone release.

The physiologic sleep-onset time in elementary school-age children is usually around 8:00 pm–8:30 pm. Around adolescence, there is a physiologic delay in sleep-onset time as it shifts to 10:30 pm–11:00 pm. As a result, they are unable to fall asleep at an earlier hour. When juxtaposed with the need to rise early for high school related activities, it is easy to understand why many teenagers are chronically sleep deprived and consequently show mood swings, impaired attention span, decreased reaction time and increased propensity for accidents.

## Sleep History

The key to evaluating sleep-wake disorders is a good history. The sleep history is provided by the patient, parent, or guardian. It is crucial in arriving at a specific diagnosis. Questions should pertain to:

- The sleeping environment (e.g., crib, bassinet, parent's bed)
- The sleeping position (e.g., prone or supine, semiupright)
- Habitual need for sleep aids (e.g., pacifier, rocking, patting)
- Time of entering bed, time it takes to fall sleep (sleep latency) and time of the final morning awakening (on school nights and during weekends and holidays)
- Sensation of restlessness in the legs before sleep onset, intrusive thoughts or worries that might interfere with sleep onset
- Presence of habitual snoring, mouth breathing, observed apnea, restless sleep, sweating, gastroesophageal reflux, scary dreams and behaviors at night suggestive of seizures or parasomnias
- Behavior during the daytime (irritability, inattentiveness, hyperactivity and sleepiness)
- Number of daytime naps and their duration (physiologic daytime napping is uncommon after age 4–5 years)
- Medications that may affect sleep-wake function (e.g., sedatives, stimulants)
- Interventions that the parents have used to improve the child's sleep
- In adolescents, one should also inquire about activities that might interfere with going to bed at a reasonable hour, such as after-school classes, vigorous exercise, heavy meals, caffeine, cell phones, computers, television, nicotine and illicit substance use late in the evening or close to bed time. Patients with restless legs syndrome may experience an urge to move their limbs, a feeling of *bugs or spiders crawling on their legs* in the evening hours, exacerbation of this discomfort when the limbs are kept still, and experience relief with movement. Daytime sleepiness assessment should include questions about taking involuntary naps in the classroom, automatic behavior, and the impact of sleepiness on driving, cataplexy, hypnagogic hallucinations, medications used to promote alertness, academic function and behavioral and mood problems, and the number of school days missed because of sleepiness.

## Sleep Related Examination

Height, weight and body mass index should be recorded because obstructive sleep apnea (OSA) may be associated with failure to thrive during infancy, and with obesity during adolescence (Arens et al., 2010). The blood pressure should be measured because long-standing and severe OSA can be associated with hypertension. OSA patients may exhibit craniofacial abnormalities such as chronic mouth breathing, micrognathia,

**Table 1** A comparison of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep

Characteristic	REM sleep	NREM sleep
EEG pattern	Low voltage, fast frequencies	Higher voltage, slow frequencies
Chin EMG activity	Absent or intermittent	Continuous
Breathing pattern	Irregular	Regular
Brainstem respiratory response to rise in pCO <sub>2</sub>	Absent compensatory increase in minute ventilation	Preserved increase in minute ventilation
Dreaming	Present	Infrequent

Abbreviations: EEG, electroencephalogram; EMG, electromyogram.



dental malocclusion, macroglossia, myopathic face and midface hypoplasia, deviated nasal septum, swollen inferior turbinates and tonsillar hypertrophy.

## Diagnostic Procedures

### Nocturnal Polysomnography

Polysomnography is useful in evaluating intrinsic sleep disorders such as narcolepsy, OSA, nocturnal spells, periodic limb movement disorder. It consists of simultaneous monitoring of electroencephalogram (EEG), eye movements, chin and leg electromyogram (EMG), nasal pressure, thoracic and abdominal respiratory effort, electrocardiogram (ECG), and oxygen saturation, with synchronized video recording. This is accomplished using digital polysomnogram equipment that records and displays both fast biopotentials like EEG and EMG and slow biopotentials like oxygen saturation and respiratory effort/oronasal airflow (**Fig. 1**). PSG is facilitated by having the parents sleep in the same bedroom as the child as this helps to allay the child's anxiety. Children with Down syndrome, neuromuscular disorders and obesity may exhibit hypoventilation that is characterized by shallow chest and abdominal wall movement, with resultant CO<sub>2</sub> retention. It is therefore important to concurrently record end-tidal CO<sub>2</sub> levels as well. Criteria for the recording and scoring of sleep and sleep related events such as apnea, arousals and periodic limb movements have been published. The following are some common types of respiratory events:

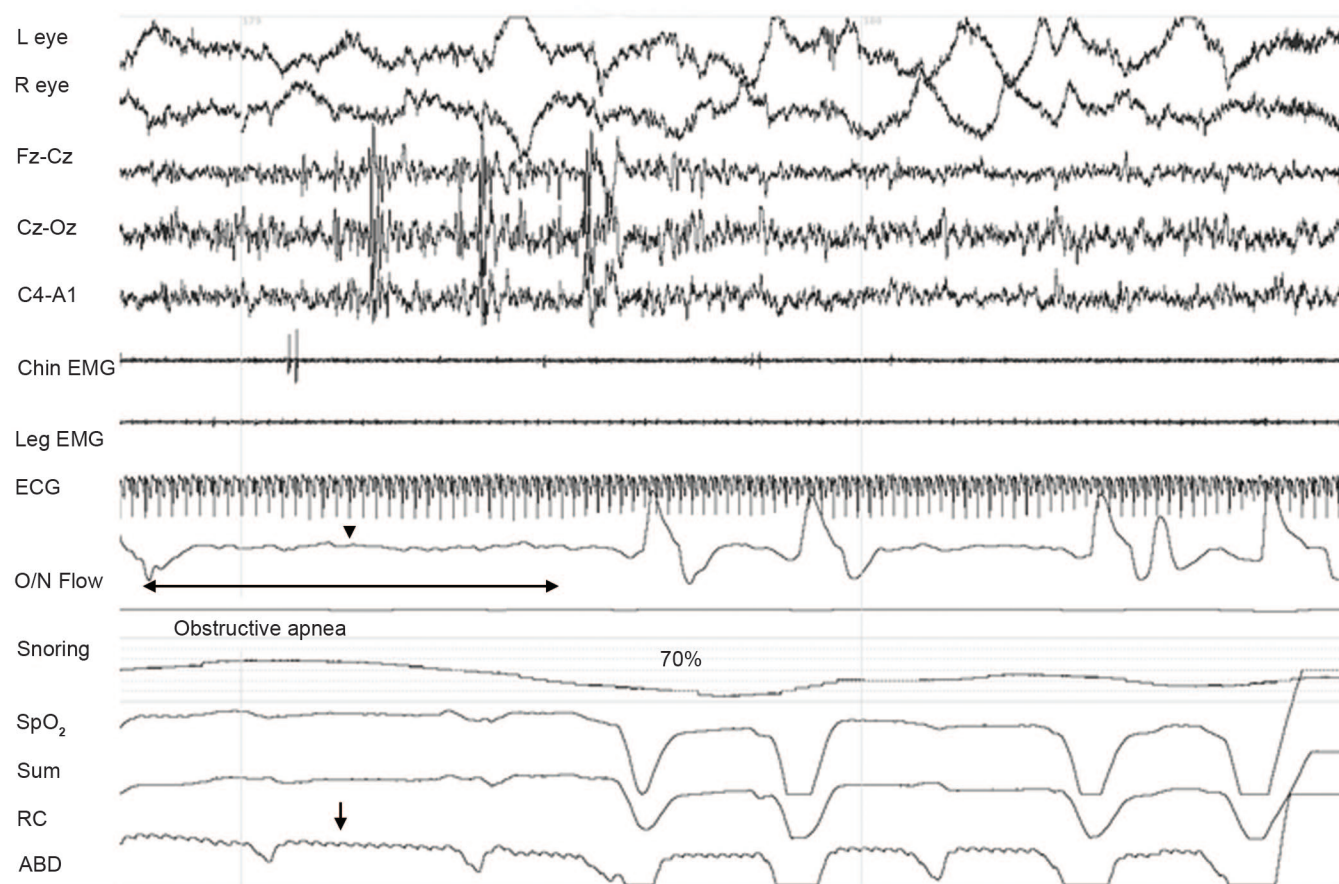
**Obstructive sleep apnea** Loss of oronasal airflow or nasal pressure signal despite persistence of thoracic and abdominal respiratory effort, with 2–3% oxygen desaturation.

**Central sleep apnea** Simultaneous cessation of signal in the oronasal airflow and nasal pressure channels and thoracic and abdominal respiratory effort, with 2–3% oxygen desaturation.

**Mixed sleep apnea** Event initially appears like a central apnea, but there is recovery of chest and abdominal effort before oronasal airflow or nasal pressure signal. Mixed apneas have generally the same significance as OSAs.

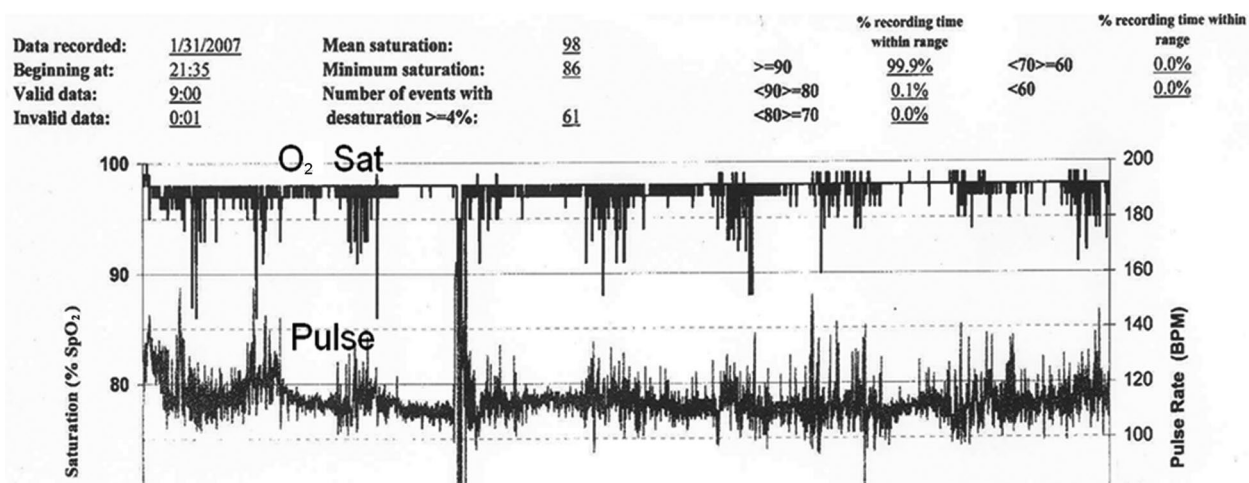
### Oximetry

Sampling of oxygen saturation on an overnight basis is an approximate measure of sleep disordered breathing. The probe for oximetry is placed over a finger. The number of drops in oxyhemoglobin saturation by 4% or more are counted, along with baseline oxyhemoglobin saturation. The normal oxygen saturation is above 92%. The number of oxyhemoglobin desaturations below 92% is about 1/hour of sleep. If the desaturations are increased, this indirectly reflects sleep disordered breathing (central or OSA/lung disease). By correlating it with the clinical history, one can indirectly determine presence and severity of sleep disordered breathing (**Fig. 2**). Advantages of the overnight oximetry is that the test is inexpensive and can be conducted in the home environment. One disadvantage is that motion artefact may lead to suboptimal yield. Another limitation is that oximetry is relatively insensitive,



**Figure 1** Sample of nocturnal polysomnogram, during which electroencephalogram (EEG—Fz-Cz, Cz-OZ, C4-A1), chin electromyogram (EMG), leg EMG, electrocardiogram (ECG), oronasal airflow pattern, snoring, oxygen saturation, summation of rib cage and abdominal respiratory effort, rib cage (RC) motion and abdominal (Abd) wall motion have been recorded. This is a 30-second epoch. Note loss of oronasal airflow during an obstructive apnea episode (down arrowhead) despite persistence of abdominal respiratory effort. This is characteristic of an obstructive apnea episode. There is associated oxygen desaturation to 70%





**Figure 2** Overnight oximetry in a 6-year-old child with habitual snoring and severe tonsillar hypertrophy resulting in obstructive sleep apnea. Note recurrent episodes of drop in oxygen saturation below 90%. The desaturation episodes are most likely occurring during periods of REM sleep. The normal oxygen saturation value is one drop in oxygen saturation of 4% or more per hour of sleep. This patient shows 61 desaturation episodes, with oxygen saturation nadir of 86%. She was referred for tonsillectomy, with significant improvement in her symptoms

and may not pick up mild OSA, being positive only in about 25% of these children.

### Multiple Sleep Latency Test

The multiple sleep latency test (MSLT) assesses how quickly one is able to fall asleep during the daytime and whether transition from wakefulness is into NREM sleep or into REM sleep. It is used for assessing sleepiness in children aged 5 years and above. It consists of providing four daytime nap opportunities at 2-hourly intervals in a darkened, quiet environment, e.g., at 1,000 h, 1,200 h, 1,400 h and 1,600 h. The EEG, chin EMG and eye movements are monitored during each nap opportunity. At each planned nap opportunity, the lights are turned off and the patient is asked to try to sleep. The time from *lights out* to sleep onset is measured and represents the sleep latency. A mean sleep latency is also derived for the four naps. The nap opportunity is terminated either 15 min after successful sleep onset, or at 20 min after *lights out* if the patient does not fall asleep. The mean sleep latency decreases inversely with an increase in the Tanner stage of sexual development, and ranges between 12 min and 18 min (Carskadon, 1982). A mean sleep latency of less than 5 min indicates severe daytime sleepiness; a value between 5 min and 10 min indicates moderate daytime sleepiness. The occurrence of REM sleep within 15 min of sleep onset constitutes a sleep-onset rapid eye movement period (SOREMP). The presence of SOREMPs on two more nap opportunities in conjunction with a shortened mean sleep latency of less than 5 min is highly suggestive of narcolepsy.

Standards have been published for the conduct of MSLT in children.

## SPECIFIC SLEEP DISORDERS

### Apnea of Prematurity

**Epidemiology** This disorder of respiratory control affects 70–90% of premature infants. It may not be present initially at birth, but becomes manifest as the infant matures and is getting ready for discharge from the newborn nursery.

**Pathophysiology** Apnea of prematurity is likely multifactorial and related to immaturity of the structures that regulate respiratory control (ventral brainstem, carotid bodies and cardiorespiratory system). Gradual resolution of the disorder over time (by 48–50 weeks postconceptional age) supports this possibility.

**Clinical features** Patients may show mixed, central or obstructive apneas. There may be recurrent periods of apnea, bradycardia and oxygen desaturation.

**Differential diagnosis** Neonatal seizures, gastroesophageal reflux and structural upper airway lesions (e.g., unilateral choanal atresia) may need to be considered.

**Management** Caffeine citrate a methylxanthine can be used. The recommended dose is 20 mg/kg loading dose intravenously or orally, followed by 5 mg/kg/day by mouth or intravenous route. Improved long-term outcomes from the standpoint of cognitive and motor function have also been reported with caffeine use in the newborn period.

### Congenital Central Hypoventilation Syndrome

This disorder is characterized by defective automatic control of breathing during sleep. Patients generally become symptomatic at birth or shortly thereafter.

**Etiology** Congenital central hypoventilation syndrome (CCHS) is linked to mutations in the homeobox gene *PHOX2B*, which maps to chromosome 4p12, and is transmitted in an autosomal dominant manner. The gene encodes a highly conserved transcription factor. Approximately 92% of primary CCHS patients carry this mutation. About 20% of CCHS patients have coexisting Hirschsprung's disease. There is also an association between CCHS and neural crest tumors like ganglioglioma and neuroblastoma. Frameshift and missense *PHOX2B* mutations predispose to neuroblastoma. It has been postulated that CCHS is a neural crest disorder in which there is defective fetal development as brainstem neurons that regulate chemosensitivity are derived from the neural crest.

**Pathology** Common sites of hypoplasia or neurodegeneration include the arcuate nucleus of the medulla (regulates chemosensitivity), the ventrolateral nucleus of the tractus solitarius, nucleus ambiguus or nucleus retroambiguus, and the nucleus parabrachialis in the dorsolateral pons.

**Clinical features** The respiratory rate and depth are initially normal during wakefulness, but shallow and infrequent breathing, hypercarbia, and oxygen desaturation occur initially during NREM sleep and then during REM sleep. The PaCO<sub>2</sub> is greater than 60 mm during sleep despite absence of pulmonary, neuromuscular or cardiac disease.

**Management** There is no definitive and satisfactory treatment, although acetazolamide and theophylline may enhance chemoreceptivity of the brainstem respiratory neurons. Diaphragmatic pacing and home ventilation via tracheostomy are other therapeutic modalities. Patients may die in infancy or early childhood.

## APPARENT LIFE-THREATENING EPISODES

**Epidemiology** These are defined as episodes that are frightening to the observer and characterized by a combination of apnea, skin color change, marked changes in muscle tone, choking and gagging. The disorder is most prevalent during the first 6 months of life. Apparent life-threatening episodes (ALTEs) are about 14 times more common in preterm infants than those born at full term.

**Etiology** No definite etiology is found in close to 40–50% of cases. Events occurring during wakefulness may be linked to gastroesophageal reflux. OSA, focal seizures, cardiac arrhythmias, congenital heart disease also need consideration.

**Clinical assessment** As with any episodic disturbance of bodily function, a detailed history is important. The body position in which the infant was placed to sleep (supine vs prone), the position in which the infant was found by the parent/guardian, the state of the infant just prior to the event (awake or asleep), presence of head segment automatisms like lip smacking or eyelid fluttering and tachycardia suggestive of seizures, duration of the event, whether or not resuscitation measures were needed and of what type; constipation, nonreactive pupils and weakness (suggestive of infantile botulism), history of gastroesophageal reflux, family history of sudden infant death syndrome, fever and lethargy (suggestive of sepsis), thermoregulation and sweating abnormalities (suggestive of dysautonomia), habitual snoring and mouth breathing (suggestive of upper airway obstruction) should be inquired about. Special attention should be paid to pulse, blood pressure, cardiac and respiratory examination, craniofacial abnormalities, external signs of trauma, mouth breathing, tonsillar hypertrophy, hypotonia, pupil size and reactivity, and motor activity and tendon reflexes.

**Investigations** The most common studies are EEG, magnetic resonance imaging of the head, ECG, echocardiogram, urinary organic acid assay and serum carnitine levels (to rule out medium chain acyl-coA dehydrogenase deficiency) and esophageal pH monitoring (to evaluate for gastroesophageal reflux). Hospitalization during this evaluation process is indicated as it provides the family some time to ask questions of the medical team, learn cardiopulmonary resuscitation techniques and collaborate with the health professionals in the discharge planning process.

**Outcome and management** The recurrence rate for ALTEs may be as high as 60%, with the second event generally occurring within a few days of the initial event. Ultimately there is spontaneous resolution over months. Parents should be familiar with cardiopulmonary resuscitations. Close follow-up is sometimes necessary.

## Obstructive Sleep Apnea

**Epidemiology** Obstructive sleep apnea is characterized by recurrent episodes of oxygen desaturation with simultaneously preserved thoracic and abdominal respiratory effort. Prevalence rate in Western countries is 2–4% of the general population. Habitual snoring, which is the mildest form of sleep related upper airway obstruction, has a prevalence rate of 8–10%. OSA is more common in those born prematurely. It is equally prevalent in boys and girls.

**Etiology** The most common causative factors are adenotonsillar hypertrophy, nasal allergies, exposure to passive smoke, neuromuscular disorders, and craniofacial anomalies like mid-face hypoplasia, retrognathia and macroglossia. Complex upper

airway problems such as unilateral choanal atresia, macroglossia, laryngomalacia, vocal cord paresis, laryngeal clefts, and tracheoesophageal fistula may be observed in infants. Obesity can be a factor in older children and adolescents. Some degree of inflammation and consequent upper airway edema are common and occur from increased vibration of the soft palate and uvula during sleep.

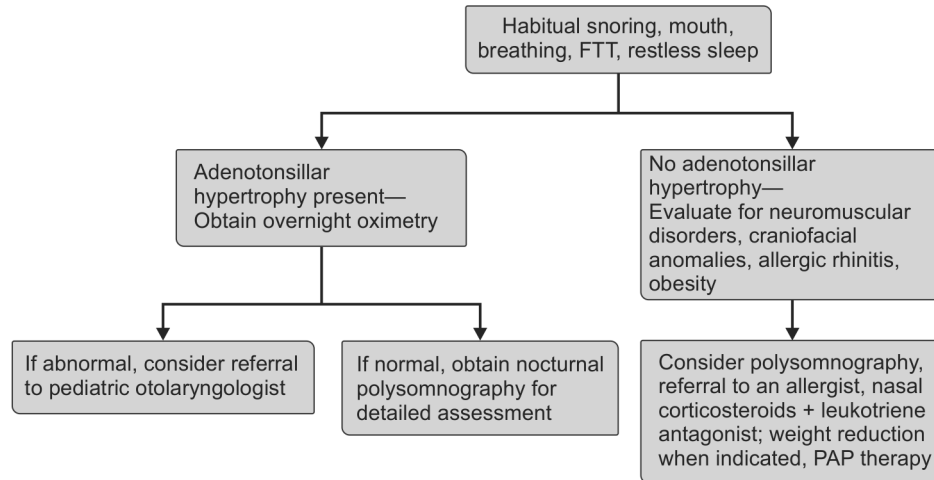
**Clinical features** Sleep is fragmented, with increased frequency of respiratory event related arousals due to episodes of oxygen desaturation. There may be tendency to breathe with the mouth kept partially open, and to manifest restless sleep, excessive sweating while asleep, nocturnal enuresis, sleep walking and waking up in the morning feeling tired. Sometimes an airway protective maneuver such as keeping the neck extended while asleep is observed. Note that infants with hypotonia and weak respiratory musculature do not consistently snore. During the daytime, there may be fatigue, mood swings, irritability and inattentiveness. Failure to thrive may occur in infants from increased energy expenditure for breathing.

**Investigations** Polysomnography is recommended as it helps to differentiate central from OSA, and also helps to assess the severity of OSA. If PSG is unavailable, utilizing overnight oximetry to document recurrent episodes of nocturnal oxygen desaturation is recommended (**Fig. 2**). A sleep specialist (ideal) or pulmonary specialist should be consulted. Patients with confirmed OSA should be seen by an otolaryngologist, and if possible, by an allergist. Direct visualization of the upper airway under anesthesia using flexible endoscopy allows for the detection by the otolaryngologist of areas of narrowing from the nasal passages down to the glottis. Environmental factors that predispose to nasal irritation, such as smoking by parents and relatives should be investigated.

**Management** Adenotonsillectomy is generally the first step in management. Those less than age of 3 years, craniofacial anomalies, or severe OSA should be monitored closely in the hospital for postoperative airway compromise from upper airway edema and swallowing difficulty. The cure rate following adenotonsillectomy varies from 30% to 70%. OSA may persist if there are predisposing factors such as anatomic upper airway abnormalities, obesity, neuromuscular disorders or persistent exposure to cigarette smoke. In case of persistent OSA, consideration is given to use of positive airway pressure (PAP) breathing. This is delivered using commercially available and licensed PAP devices that are connected to nasal or full face mask. The PAP splints the upper airway and thus maintains its patency while asleep. Mild OSA can be treated using a topical nasal corticosteroid combined with a leukotriene antagonist such as montelukast. Smoking parents should be strongly counseled about enrolling in a smoking cessation program. Please also refer to **Flow chart 1** for management guidelines.

## Narcolepsy

**Epidemiology, classification and pathophysiology** Narcolepsy is a primary central nervous system disorder of vigilance. It affects about 1 in 100,000 persons each year. About one-third of all patients with narcolepsy have onset of symptoms prior to the age of 16 years. A distinction is made between narcolepsy *without* cataplexy, and narcolepsy *with* cataplexy (NC). Some patients in the former category will eventually develop cataplexy 5–10 years after initial symptom onset. NC is characterized by positivity for histocompatibility antigen DQB1\*0602 and reduced levels of cerebrospinal fluid (CSF) hypocretin (Orexin). Recent studies implicate T-cell mediated immunity in pathogenesis, with very localized injury/loss of the hypocretin secreting neurons in the dorsolateral hypothalamus.

**Flow chart 1** Algorithm for management of obstructive sleep apnea

Abbreviations: FTT, failure to thrive; PAP, positive airway pressure.

**Clinical features** Hypersomnolence (excessive sleepiness) may be difficult to recognize. In a preschool or elementary school age child, it may manifest as resuming naps which the child had previously outgrown, mood swings and inattentiveness. Cataplexy (episodes of muscle weakness with laughter, anger, or surprise) may be fairly subtle, with only jaw dropping open or slight head roll. Hypnagogic hallucinations (vivid dreams at sleep onset) and sleep paralysis (inability to momentarily move the body at sleep onset); young children do not provide a reliable history of these symptoms. Obesity/overweight and precocious puberty is common in NC at the onset.

**Precipitating factors** These may include a flu-like illness, infectious mononucleosis, or streptococcal illnesses and are encountered in NC.

**Diagnosis** Polysomnography and MSLT are valid after the age of 5 years. Both tests may show sleep-onset REM periods. Further, the MSLT helps to document extreme daytime sleepiness. For younger children less than age of 5 years, one has to rely on documentation of low CSF hypocretin levels.

**Differential diagnosis** Sleepiness and fatigue as a consequence of depression or Kleine-Levin syndrome; use of illicit substances.

**Management** Planned naps at school or upon return home from school for 3–45 min are recommended. Provision of psychological support is very important, especially for teens owing comorbid anxiety and coping issues. Medications for excessive sleepiness include salts of methylphenidate/amphetamine/modafinil or armodafinil. The dosing may need to be 2–3 times per day for effectively controlling sleepiness. For cataplexy, the use of clomipramine/protriptyline, atomoxetine, or fluoxetine is recommended. Patients should be counseled about avoiding driving and use of alcohol. Patient and parents should be informed that narcolepsy is a lifelong disorder. Emotional support through psychological counseling should be provided whenever required.

## Insomnia

Children and adolescents can manifest sleep initiation or sleep maintenance difficulties, or both together. There is a general dissatisfaction about the quality of sleep. Refer to **Tables 2** and **3** for more information.

**Table 2** Some principles of sleep hygiene

Daytime	<ul style="list-style-type: none"> <li>• Try to awaken at approximately the same time, 7 days a week</li> <li>• After age 5–6 years avoid daytime napping</li> <li>• Light exercise in the morning or in the afternoon (not at night)</li> <li>• Avoid caffeine intake in the 2–3 hours before bedtime.</li> </ul>
Night-time	<ul style="list-style-type: none"> <li>• Turn off electronic devices about an hour prior to bed time</li> <li>• Spend the hour prior to bedtime reading your <i>comfort</i> book</li> <li>• Avoid excessive consumption of food or drink before bedtime</li> <li>• If you wake up at night to use the toilet, use only the night light.</li> </ul>

**Table 3** Etiology and clinical features in insomnia

Inadequate sleep hygiene	Use of caffeine, alcohol or nicotine, use of computers, cell phone and television at night; managed with counseling
Restless legs syndrome	Irresistible urge to move the limbs that is worse when legs are kept still, relieved partially by movement; serum ferritin may be low, i.e., below 30 µg/dL; autosomal dominant; treatment is iron supplementation, combined if necessary with gabapentin for a few months
Anxiety	Frequent nightmares, history of emotional trauma or family history of anxiety; both sleep initiation and maintenance difficulty; needs psychological counseling
Depression	Early morning awakenings, dysphoria; needs to see a child psychiatrist
Psychophysiological insomnia	Very concerned about sleep quality (performance anxiety), conditioned arousals, clock watching at night, sleeps better away from bedroom than in it. Restricting total time in bed and psychological counseling are recommended.

## Miscellaneous Entities

*The relationship between sleep and epilepsy* There is a bidirectional relationship between sleep and epilepsy. Sleep deprivation lowers the seizure threshold. Further, OSA increases vulnerability to seizures by leading to sleep fragmentation, which increases vulnerability to seizures. It is a good idea to evaluate patients with poorly controlled seizures for comorbid OSA. Phenytoin can cause lymphoid hyperplasia, including adenotonsillar hypertrophy, that can lead to OSA.

*The relationship between sleep and headache* Sleep deprivation makes patients more vulnerable to breakthrough migraines. The routine counseling of migraine patients should include a discussion about sleep hygiene.

*The relationship between sleep and psychiatric disorders* Frequent nightmares are sometimes marker for underlying anxiety. Also, depression can be associated with insomnia. It is also well known that insufficient sleep contributes to daytime irritability and mood swings. It is a good idea to incorporate sleep hygiene into management of emotional and mood problems of children and adolescents.

### IN A NUTSHELL

1. Problems of sleep-wake function are very common in childhood. Their recognition and treatment can have a significant impact on the quality of life of the child.
2. It is important to incorporate sleep related history and examination into the clinical assessment of children.
3. The prevalence of obstructive sleep apnea (OSA) in infants and children in India is likely underestimated.
4. Adenotonsillar hypertrophy is the most common cause of childhood OSA, followed by craniofacial anomalies, neuromuscular disorders and obesity.
5. Infants with OSA may not snore.
6. Overnight oximetry can be used as a screening tool for severe OSA.
7. Inadequate sleep hygiene is the most common etiology for sleep initiation and maintenance difficulty in adolescents.
8. Causes of excessive daytime sleepiness include inadequate sleep hygiene, depression, drugs, obstructive hypoventilation, narcolepsy and Kleine-Levin syndrome.

## MORE ON THIS TOPIC

- Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, et al. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study. *Am J Respir Crit Care Med*. 2010;182:676-83.
- Gupta R, Bhatia MS, Chhabra V, et al. Sleep patterns of urban school-going adolescents. *Indian Pediatr*. 2008;45:183-9.
- Kotagal S, Chopra A. Pediatric sleep-wake disorders. *Neurol Clin*. 2012;30:1193-212.
- Kotagal S, Nichols CD, Grigg-Damberger MM, et al. Nonrespiratory indications for polysomnography and related procedures in children: an evidence-based review. *Sleep*. 2012;35:1451-66.
- Mindell JA, Kuhn B, Lewin DS, et al. Behavioral treatment of bedtime problems and night wakings in infants and young children. *Sleep*. 2006;29:1263-76.
- Mindell JA, Meltzer LJ, Carskadon MA, et al. Developmental aspects of sleep hygiene: findings from the 2004 National Sleep Foundation Sleep in America poll. *Sleep Med*. 2009;10:771-9.
- Neveus T, Cnattingius S, Olson U, et al. Sleep habits and sleep problems among a community sample of school children. *Acta Paediatr*. 2001;90:1450-5.
- Picchiatti DL, Walters AS. Early manifestations of restless legs syndrome in childhood and adolescence. *Sleep Med*. 2008;9:770-81.
- Pizza F, Contardi S, Antogni AB, et al. Sleep quality and motor vehicle crashes in adolescents. *J Clin Sleep Med*. 2010;15:41-5.
- Ravikiran SR, Kumar PM, Latha KS. Sleep problems in preschool and school aged rural Indian children. *Indian Pediatr*. 2011;48:221-3.
- Van Cauter E, Spiegel K, Tasali E, et al. Metabolic consequences of sleep and sleep loss. *Sleep Med*. 2008;9(suppl 1):S23-8.
- Verhulst SL, Van Gaal L, De Backer W, et al. The prevalence, anatomical correlates, and treatment of sleep disordered breathing in obese children and adolescents. *Sleep Med Rev*. 2008;12:339-46.
- Yang CK, Kim JK, Patel SR, et al. Age related changes in sleep-wake patterns among Korean teenagers. *Pediatrics*. 2005;115(suppl):250-6.



## Chapter 21.3

# Common Behavioral Problems

Praveen Suman

Emotional and behavioral problems are seen commonly during the period of growing up and are due to the stress of development and adaptation to family expectations. These problems are among the most common reasons that children are seen by pediatricians. The age of occurrence of various behavioral problems has been explained on the basis of the *transactional model of development* as the specific problem depends on the developmental phase of the child around that age.

Around 12% children attending pediatric outpatient clinics meet the diagnosis of behavioral and emotional disorders. Worldwide, the community prevalence has been reported to range from 12% to 25%, though Indian studies report a wide range of 2.6–35%. These disorders often lead to distress to the child and family. To help the family, it is important to assess the magnitude of the problem, and identify and address underlying factors causing these problems. Along with the specific interventions, the most critical component is reassuring the parents, as majority of these are transient in nature. However, failure to address these problems may lead to repeat hospital visits, increasing cost, and academic, social, family and economic problems. This chapter provides an overview of common behavioral problems and interventions to manage them (Table 1).

### INFANTILE COLIC

When otherwise healthy infants cry intensely for an excessive duration, they are often referred to as having colic. The time spent crying progressively increases to a mean of approximately 2.5 hours/day during the 2nd month of life and decreases gradually thereafter. The diagnosis of colic requires that the child be otherwise healthy and feeding well. The amount of crying required for a diagnosis of colic is: paroxysms of crying for more than 3 hours a day for more than 3 days/week for more than 3 weeks. Infantile colic is diagnosed only when the baby is otherwise physically healthy and feeding well. Paroxysms are accompanied with facial grimacing, drawing up of legs, arching of back and sometimes passing flatus. The incidence of infantile colic is reported to vary from 5% to 19%, affecting girls and boys equally, and in all ethnic groups and socioeconomic classes.

### Etiology

The etiology of infantile colic is not known but physical problems that can cause excessive crying must be excluded prior to diagnosis of infantile colic.

A number of chronic conditions have been proposed to be the cause of infant colic including cow's milk allergy, lactose intolerance, constipation and gastroesophageal reflux; even though, controlled studies using interventions targeting these problems have not been found to be effective for most infants.

Differences in the temperament of infants with excessive cry from those who cry less have been reported; parents tend to rate these infants as more intense and more difficult to soothe. It has been seen that infants with persistent crying have higher crying-to-fussing ratio than those with less crying. When sucrose solution is administered orally to soothe an infant, the response is poor in infants with colic as compared to those without colic.

### Differential Diagnosis

In a crying infant, before considering the diagnosis of infantile colic, organic conditions should be excluded including infection (especially acute otitis media, meningitis, hidden boils in flexural areas/scalp), corneal abrasion, glaucoma, skull or long bone fracture, incarcerated hernia, supraventricular tachycardia, hair tourniquet and intussusception. Detailed history and physical examination to evaluate for the above-mentioned problems is important. Based on the findings of physical examination, investigations should be done in the form of laboratory tests and radiological investigation. In infants where clinical examination reveals no abnormality, urine examination should be considered to rule out urinary tract infection. In majority of the cases, a close observation of the child during the episode helps in reaching the diagnosis.

### Management

It is important to reassure the parents that their child is healthy and help parents to understand their infant's temperament trait contributing to increased crying. Parents should be counseled that crying is the infant's way of communicating, and it is not necessarily a sign of pain or illness. Parents need to understand that these infants are more difficult to soothe, and thus even when the parent is providing what the infant wants, it may take many minutes before the infant stops crying.

Medications like phenobarbital, simethicone and dicyclomine are not of much use and should be avoided. It is also recommended to avoid soothing of child using excessive shaking, and usage of traditional products like herbal potions, *ghutti*, etc. Dietary changes for the baby (or the mother) are also not of any sustained benefit.

Infantile colic usually disappears by the age of 4–5 months.

### THUMB-SUCKING

Thumb-sucking can be defined as placement of thumb into the mouth for various depths. Thumb-sucking and finger-sucking can more generally be termed as digit sucking. This habit is a concern to specialists in various fields such as pediatricians, psychologists, dentists and speech therapists.

**Table 1** Salient feature of some common behavior problems

Disorder	Age at which considered		Differential diagnosis	Management
	Normal	Abnormal		
Infantile colic	4–5 months	-	Acute gastrointestinal conditions	Parental counseling
Thumb-sucking	1 year	After 5 years	Repetitive behavior	Psychotherapy and reminder therapy
Pica	1 year	After 2 years	In cases of persistence rule out underlying intellectual disability, autism	Parental counseling and multimodal management of associated medical problems
Rumination	-	At any stage	GER	Improve parent–child relationship
Temper tantrums	1–3 years	After 4 years	In cases of persistence rule out underlying intellectual disability, autism	Ignoring undesired behavior

During the 1st year of life, thumb-sucking is considered as normal and usually does not lead to long-term effects. It usually disappears by 3–4 years of age. When this habit persists beyond preschool it is considered as abnormal. This habit needs attention, as otherwise it may lead to dentofacial structure abnormalities.

Thumb-sucking occurs in 23–46% of children aged 1–4 years, but most desist by school-age. If it persists beyond 4 years of age, it is a concern as dental malocclusion, digital deformities, speech difficulties and emotional problems may be associated. Studies have shown the persistence of thumb-sucking in approximately 6% at the age of 11 years.

## Etiology

It can be due to either (1) psychological reasons—due to deep-rooted emotional factor like insecurities, neglect and loneliness experienced by the child; or (2) habitual—the child sucks the thumb as a habit.

## Types of Thumb-sucking

*Type A* Where whole digit is placed inside the mouth with the pad of the thumb pressing over the palate while at the same time maxillary and mandibular anteriors contact is present. This is the most common type and seen in almost 50% cases.

*Type B* In this type thumb is placed into the oral cavity without touching the vault of the palate while at the same time maxillary and mandibular contact is maintained. It is seen in almost one-third of children.

*Type C* Where thumb is placed into the mouth just beyond the first joint and contacts the hard palate and only the maxillary incisors but there is no contact with the mandibular incisors. This is also as common as Type B.

*Type D* Very little portion of the thumb is placed into the mouth. It is seen in 6% of children.

## Diagnosis

Diagnosis is mainly based on the history. Detailed history regarding the frequency, intensity and duration of the habit is to be taken. Enquire about the feeding patterns, parental care of the child and also about other habits. Clinical examination will reveal signs of chronic inflammation on the thumb.

## Treatment

Treatment of thumb-sucking should be considered after 4–6 years of age and when it causes dental problem, digital malformation, or distress to the child. If child is a willing partner, the treatment is more effective.

Psychotherapy is an important part of the treatment which also includes motivation of the child to stop the behavior, by positive reinforcement. Reminder therapy includes various methods which remind the child to stop thumb-sucking. It is of different types:

*Extra oral approach* Using bitter flavored preparation like pepper, quinine or asafetida on the finger.

*Intraoral approach* Orthodontic appliances, which can be removable type (like palatal crib or palatal arc) or fixed type (Upper lingual tongue screens). In resistant cases, fixed intraoral antithumb-sucking appliances are used.

## Pica

Pica is defined as persistent ingestion of non-nutritive substances without an accompanying aversion to food, at an age in which this behavior is developmentally inappropriate. This should persist at least for 1 month to be considered abnormal. It commonly includes

ingestion of dirt, clay, pebbles, chalk, paper, string, ashes, crayons and plastic objects. Ingesting sharp objects such as nails, screws or potentially toxic substances such as medicine, dishwashing fluid can lead to far more serious and potentially life-threatening consequences.

## Prevalence

According to some studies, 10–32% children in the age group of 1–6 years exhibit pica, although an Indian study reported 2% occurrence in those younger than 3 years. The early developmental habit of mouthing objects as an exploratory behavior disappears by 2 years of age. Mental disorders found to have persistent pica more commonly associated with them include pervasive developmental disorders, intellectual disability, schizophrenia, Kleine-Levin syndrome. Children who continue to eat non-food substances on a consistent basis after their 2nd birthday should be evaluated for pica, as well as the presence of developmental disability and a variety of medical conditions with the serious health risks that accompany chronic ingestion of nonfood substance.

## Etiopathology

Cause of pica is unknown. To describe this behavior various theories have been proposed:

*Cultural, ethnic and familial theory* In some cultures there is a custom of eating soil for different illnesses, e.g., morning sickness, which leads to the perception that there is nothing wrong with pica.

*Organic or nutritional theory* Some studies have shown that iron and zinc deficiency increase the craving for nonfood substances. These children get involved in pica to satisfy the craving. However, the prevalence of dietary and mineral deficiencies in children with pica is similar to those without this habit.

*Neuropsychiatric theory* There is a higher incidence of pica among children with many developmental disabilities. Pica is the most common eating disorder in children with developmental disability. It is most frequently observed in those with severe and profound intellectual disability. Children may learn to engage in pica because it provokes adult attention (*positive reinforcement*) or allows escape from a nonpreferred activity (*negative reinforcement*). Pica is also perceived as a sensory activity that the child experiences as stimulating or pleasant.

*Organic hypothesis* Pica may also be explained by this hypothesis whereby genetic disorders such as Prader-Willi syndrome increase the risk of ingesting nonfood substances. Anxiety disorders such as hysteria and obsessive compulsive disorder also have been implicated.

## Diagnosis

It is important to distinguish between stereotyped mouthing of objects by very young children who accidentally ingest them and pica as a behavioral disorder. There can be immediate and long-term effects on health due to pica. The potential for parasitic infections with sequelae of myocarditis, encephalitis and hepatomegaly, and brain damage by intoxicants such as lead from paints and mercury from paper is of immediate concern. Obstruction from an indigestible mass that may cause choking or perforate the stomach or intestine and result in peritonitis is also a possibility.

Except in circumstances involving children and adolescents with autism spectrum disorder and intellectual disability, most cases of pica are easily diagnosed from history from parents. Children may be afraid of disclosing pica because of embarrassment or fear of being punished.

## Management

Educating the parents and child about the dangers associated with placing objects in the mouth is the basic step. Along with this, close supervision of the child by the parents, and making sure that the home-environment is safe for the child are additional measures.

There is no specific medical treatment and the condition often remits spontaneously. Medical management is multimodal in nature. Investigations need to be individualized but may include complete blood count (especially eosinophil count), peripheral smear, serum electrolytes, liver function tests, iron and calcium studies and lead levels. An X-ray abdomen, barium studies or ultrasonography of the abdomen may be occasionally necessary to diagnose obstruction from parasites or bezoars.

Children with lead poisoning may require chelation therapy. Dietary supplements for mineral deficiencies like iron and zinc, if identified, should be addressed, although limited success has been seen in decreasing the behavior. Specific therapies for parasitic infection may be given when required. In cases of obstruction, surgery may be needed.

Multidisciplinary approach involving psychologist, social worker and developmental pediatrician may be required. Psychological interventions are done to modify the behavior. Various behavioral strategies have been described, and very rarely, external devices restricting placement of objects in the mouth may be required for resistant cases. Children with underlying anxiety disorder or obsessive compulsive disorder may need appropriate referrals and medications.

## RUMINATION

Rumination is regurgitation of food which is then partially or completely reswallowed or rechewed. The exact prevalence of eating disorders is not known. It is known that more than 25% of parents are concerned about their child's eating behavior.

## Etiology

Rumination is poorly understood but believed to be self-stimulatory. Infants often initiate rumination by inserting a hand into mouth. They may also bring up the food by thrusting the tongue to the back of the mouth or by contracting their abdominal muscles. It is often associated with child neglect.

## Management

Other causes of vomiting such as gastroesophageal reflux are an important differential diagnosis of rumination. Premature and neurologically fragile infants may require behavioral strategies to decrease overstimulation. The diagnosis of rumination is made by observation. Intervention for children with rumination requires increased nurturing with attention to the infant-caretaker relationship.

## TEMPER TANTRUMS

Temper tantrums are often defined as out of control behavior including screaming, hitting, head-banging and falling down and other violent display of frustration, usually occurring in children of 18 months to 4 years of age. These are emotional outbursts in response to unmet needs or desires in younger children or children with communication difficulty. In extreme case, they may be expressed by vomiting or biting. When the behavior occurs many times a day, lasting 30 min at a time, and is associated with aggression at school and home; it usually requires intervention.

Thus, it is important to find out the frequency, intensity and duration of the behavior.

Temper tantrums have been reported to be present in 22% of normally developing children. In 75.3%, these are present at the age of 3–5 years and, in 20.8% at 6–8 years of age, being least common at 9–12 years (3.9%). They are more common in boys.

## Etiology

Temper tantrums are natural during early childhood. It is a way of communication during the period of developing autonomy and separation from caregivers, and is usually present in children between 1 year and 3 years of age who do not have enough vocabulary to express their feelings. Tantrums gradually decrease by 4–5 years, after which they are uncommon, and need intervention. Being tired, hungry, or sick, can make tantrums worse or more frequent.

Underlying neurological disorders like autism spectrum disorder and intellectual disability also make the child more prone for the persistence of temper tantrums. Underlying precipitants may include frustration, attention-seeking behavior, or unfulfilled demands. Parental factors like excessive disciplining, inconsistent parental attitudes and failure to set limits may also be responsible. Temper tantrums which last for more than 15 min, or occur regularly, or more than thrice-a-day, usually reflect some serious underlying medical, social or emotional problem.

## Management

Detailed history and examination is mandatory to find out if these problems are associated with hunger, fatigue and overstimulation. Exposure to abuse or stress at home may be the reason of persistence of this behavior, which otherwise would have subsided. Thorough physical examination to exclude physical abuse along with neurological and behavioral assessment is important.

Laboratory investigations include screening for iron-deficiency anemia and exposure to lead. Other investigations should be done if there are any clues found on examination.

If the child engages in undesired behavior, parent can ignore the undesired behavior. Undesired behavior is often being reinforced because it results in parental attention. Ignoring the undesired behavior reduces the frequency of that behavior over a period of time, as undesired behavior is no longer reinforced by parental attention. This process is called extinction. It is important to inform parents that with this process, the problem may worsen initially before it improves.

Punishment usually used is verbal reprimand or privilege withdrawal. One of the commonly used punishment strategies for children is time out. It is usually implemented by having a child sit in a chair, stand in the corner or go to the room for brief period usually 1–5 min. Time out facing a corner means that the child has limited access to those around her. Corporal punishment should not be used, though some behavioral techniques may be helpful (Box 1).

### BOX 1 Behavioral techniques that may help to prevent temper tantrums

- Be consistent
- Plan ahead
- Encourage your child to use words
- Let your child make choices
- Praise good behavior
- Distraction from the topic.

### IN A NUTSHELL

1. Behavioral problems are important for the pediatricians as they are common and majority of these patients are likely to present to a pediatrician first, rather than any specialist.
2. Common behavioral problems discussed in this chapter include infantile colic, thumb sucking, pica, rumination and temper tantrums.
3. In many other children attending for other acute or chronic medical conditions, these problems may be present but are not disclosed by parents due to their apparent unimportance or nonseriousness.
4. An integrated behavioral assessment should be routinely done by the pediatrician, so that these problems can be identified and underlying psychological factors addressed or other appropriate advice provided to parents.
5. In occasional patients, referral to mental health professionals may be needed if meeting the criteria for a mental or psychiatric disorder.

### MORE ON THIS TOPIC

Anabrees J, Indrio F, Paes B, et al. Probiotics for infantile colic: a systematic review. *BMC Pediatr*. 2013;13:186.

Bryant-Waugh R, Markham L, Kreipe RE, et al. Feeding and eating disorders in childhood. *Int J Eat Disord*. 2010;43:98-111.

Daniels E, Mandleco B, Luthy KE. Assessment, management, and prevention of childhood temper tantrums. *J Am Acad Nurse Pract*. 2012;24:569-73.

Diwanji A, Jain P, Doshi J, et al. Modified bluegrass appliance: a nonpunitive therapy for thumb sucking in pediatric patients—a case report with review of the literature. *Case Rep Dent*. 2013;2013:537120.

Friman PC, McPherson KM, Warzak WJ, et al. Influence of thumb sucking on peer social acceptance in first-grade children. *Pediatrics*. 1993;91:784-6.

Friman PC, Schmitt BD. Thumb-sucking: pediatricians' guidelines. *Clin Pediatr (Phila)*. 1989;28:438-40.

Herman M, Le A. The crying infant. *Emerg Med Clin North Am*. 2007;25:1137-59.

Juneja M. Childhood behavioral disorders. In: Talukdar B (Ed). *Essentials of Pediatric Neurology*, 2<sup>nd</sup> edn. New Delhi: Academa Publishers; 2009. pp. 236-9.

McCord BE, Grosser JW, Iwata BA, et al. An analysis of response blocking parameters in the prevention of pica. *J Appl Behav Anal*. 2005;38:391-4.

Shamir R, St James-Roberts I, Di Lorenzo C, et al. Infant crying, colic, and gastrointestinal discomfort in early childhood: a review of the evidence and most plausible mechanisms. *J Pediatr Gastroenterol Nutr*. 2013;57(Suppl 1):S1-45.

Tanaka OM, Vitral RW, Tanaka GY, et al. Nailbiting, or onychophagia: a special habit. *Am J Orthod Dentofacial Orthop*. 2008;134:305-8.

Wade S. Infantile colic. *Clin Evid*. 2006;15:439-47.



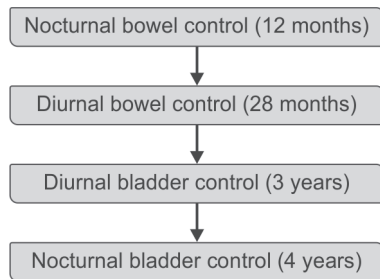
## Chapter 21.4

# Enuresis and Encopresis

Piyush Gupta, Ruchi Mishra

Micturition is an intricate function resulting from a coordinated activity of the muscles of the urinary bladder involving integration of both volitional and autonomic system. In infants, it is primarily under autonomic control and as the child develops this act becomes volitional. It is uninhibited for the first 16 months of life and as the child grows he becomes aware of the sense of bladder fullness and urinary frequency decreases. By 3 years, diurnal control is established and by 4 years most children develop nocturnal control also. Bowel control precedes bladder control in the sequence shown in **Flow chart 1**. Note that proper toilet training is essential for achieving continence.

**Flow chart 1** Sequence of bowel and bladder control



## ENURESIS (BEDWETTING)

Voluntary or involuntary repeated discharge of urine into clothes or bed, after a developmental age when bladder control should be established (usually 5 years), is labeled as enuresis. Bedwetting or urinary incontinence is labeled as enuresis only if urine is being voided twice a week for at least 3 consecutive months, or if it is causing clinically significant distress in the child's life. *Nocturnal enuresis* refers to voiding during sleep, whereas *diurnal enuresis* refers to daytime urination; these may or may not exist together. Approximately 10% of the children with nocturnal enuresis will have diurnal enuresis whereas 50% of children with diurnal enuresis have nocturnal enuresis. Approximately 10% of the 5-year-old, 5% of the 10-year-old and 1% of the 18-year-old children will have nocturnal enuresis.

## Classification

Enuresis may be primary or secondary. *Primary enuresis* is defined as repeated (at least twice a week for at least 3 consecutive months) passage of urine into clothes/bed during night in a child of age more than 5 years, who has never been dry in night. This is three times more common in boys. In *secondary or late-onset enuresis*, the child has been dry for at least 6 months before bedwetting begins again during sleep. In most of these children an underlying organic pathology is detected whereas primary enuresis is mostly idiopathic or behavioral in origin.

*Monosymptomatic (uncomplicated) nocturnal enuresis* involves voiding in the bed at night in the absence of other genitourinary or gastrointestinal symptoms, or daytime symptoms. It accounts for 80–85% of cases of nocturnal enuresis. Another 5–10% of the cases have associated daytime symptoms, such as urgency, frequency, urge incontinence, constipation, or encopresis. These children are labeled as having *polysymptomatic (complicated) nocturnal enuresis*.

## Etiopathogenesis

*Primary enuresis*, though multifactorial, could be related to sleep disorder. There is poor arousability in response to acoustic stimuli. Children are not able to appreciate when the bladder is full during sleep. Small functional bladder capacity and detrusor overactivity may play an important role in pathophysiology of nocturnal enuresis. It is often associated with frequent daytime voiding. Genetic factors include a positive family history in most cases. The risk of a child being affected is 43% if one parent had nocturnal enuresis and 77% if both parents were affected. Approximately 75% of children with nocturnal enuresis have a first-degree relative who had enuresis. Psychological causes may be related to stressors at home or school.

There might be a delay in neurological maturation to control bladder sphincter which is more pronounced in children with mental retardation or spinal cord abnormalities. This is substantiated by the fact that approximately 5% enuretics resolve their symptoms each year without intervention and only about 5% of 10-year-old and 1% of the adolescents remain enuretic.

The following factors have also been implicated in the pathology of nocturnal enuresis: hyposecretion of arginine vasopressin (AVP), decreased responsiveness to low urine osmolality, loss of circadian rhythm of antidiuretic hormone (ADH) secretion. Altered AVP receptor function in the tubule, diminished capacity to be aroused and altered sleep architecture. Less than 3% cases have organic etiology such as obstructive uropathy or urinary tract infections.

Children who undergo training late (after 24 months) are prone to develop late nocturnal bladder control; recommended age to begin toilet training is around 24 months, an age at which most developmentally normal children will be ready to be toilet-trained (**Box 1**). In general, *physiological* readiness for toilet-training occurs at around 18 months of age (can delay defecation or urination sufficiently to get to an appropriate place). However, *cognitive* maturity (to use the potty, to remember to use it, and to resist distraction long enough to complete the process) is usually achieved around 24 months. The *motor skills* needed to get to the bathroom, manage clothes, and sit still on the potty are also important, though parents may assist in some of these.

*Secondary enuresis* Too enthusiastic and immature toilet training can result in secondary enuresis. Other causes include emotional stress, parent child maladjustment, urinary tract infections, diabetes mellitus, or diabetes insipidus. Secondary enuresis is frequently associated with stressful or traumatic events at home or at school or anything related to the daily life of the child.

*Diurnal enuresis* This is more common in preschool girls, is usually due to micturition deferral (waiting till the last moment to pass urine and then being unable to hold any longer), and usually settles by age

### BOX 1 Readiness criteria (when to start toilet training) for a developmentally normal child

- Child stays dry at least 2 hours at a time during the day or is dry after naps
- Bowel movements are regular and predictable
- Facial expressions/posture/words show that your child is about to urinate/defecate
- Child can follow simple instructions and imitates parental behavior
- Child can walk to and from the bathroom and help undress
- Child seems uncomfortable with soiled diapers and wants a clean diaper
- Child asks to use the toilet or potty chair
- Can put on/take off clothes
- Follows parent into bathroom and expresses interest in the toilet.

Source: From AAP Website, from <http://www.pediatrics.org/cgi/content/full/109/3/e48>, and from Am Fam Physician. 2008;78:1059-64.

of 9 years. It is mostly caused by the impaired transition from reflex micturition control of infants to volitionally controlled micturition reflex in adults. Stress incontinence, urinary tract infection, bladder outlet obstruction, ectopic ureter and diabetes are the other causes of diurnal enuresis. Vaginal reflux of urine that seeps out upon rising is common physiological cause in young girls. Psychological causes include constant anxiety, loss of a parent, parental discord and abusive home environment. Some children fail to appreciate the sense of bladder fullness or ignore it while playing. When both diurnal enuresis and nocturnal enuresis are present, abnormalities of the urinary tract or voiding disorders are likely.

Chronic constipation is an important isolated risk factor for enuresis.

## Evaluation

History and examination should be able to rule out the possibility of any underlying neurological disorder, voiding dysfunction, polyuric conditions (diabetes mellitus, diabetes insipidus, chronic renal failure) and bacterial cystitis. Questions should be asked regarding daytime incontinence, urgency, frequency, posturing, infrequent voiding and frequent voiding. Details of sleep pattern, fluid consumption and bowel habits should also be obtained. A *frequency void chart* often helps to differentiate primary nocturnal enuresis from voiding dysfunction. Ideally an input-output chart should be maintained. The normal frequency of daytime void in a child is 4–7 times per day. A frequency of more than eight times or at duration of less than 2 hours is considered abnormal. Look for any deformity of spine or foot; or abnormality of gait. Physical signs of occult spinal deformities such as dimples, tuft of hair, skin discoloration, lipoma and asymmetrical buttocks may be useful. Anal sphincter tone and perineal sensation and reflexes should be assessed. Genital examination is a must for all children. In boys abnormal meatus or abnormal urinary stream should be evaluated. In girls, look for labial adhesions and ectopic ureteral openings.

Investigations for primary nocturnal enuresis involve routine urine examination including osmolality, microscopy, reducing substance and culture. A good *ultrasonogram* (USG) on full bladder can also give a rough estimate of bladder capacity. Postvoid residual urine volume should be assessed during USG to guide regarding presence of voiding-dysfunction. *Urodynamic study* is needed to assess bladder capacity and detrusor pressures in a child who has an abnormal frequency void chart.

## Management

The timing of initiation of treatment for monosymptomatic nocturnal enuresis varies from child to child. The major determinants are whether the child and caregivers view the enuresis as a problem and how strongly motivated they are to participate in a treatment program. Any serious attempts to treat the condition should begin only beyond 7–8 years of age as enuresis interferes with socialization and behavior in older children. Management goal should be aimed at completely stopping the enuresis. After establishing the diagnosis of primary nocturnal enuresis a treatment plan should be discussed with the parent. Cooperation of the child in the management plan is essential.

### Nonpharmacological Measures

These are effective in 30% cases and consist of behavior modification, alarm systems and bladder strengthening exercises.

*Behavioral treatment* is the first mode of therapy for a child with enuresis without any disorder of the genitourinary tract.

- Counseling and reassurance to the family is the most essential step. They need to be assured of the benign nature of the condition and high spontaneous resolution rate.

- Ask the parents to maintain a diary record of dry nights; reward the child for such nights.
- Parents should provide emotional support to the child, not to criticize and changing the bedsheets without child's notice.
- Avoid punitive measures. Positive reinforcement has been shown to have a success rate of more than 85%. Parents should understand that enuresis is not under volitional control so punishment is counterproductive.
- Children should have an early dinner and appropriate fluids with dinner. It is recommended to avoid any form of fluid at least 2–3 hours prior to sleep. Ask the child to void before going to sleep. Ample consumption of fluid in the morning and afternoon reduces the need for significant intake later in the day. Isolated night-time fluid restriction, without compensatory increase in daytime fluid consumption, may prevent the child from meeting his or her daily fluid requirement and is usually unsuccessful.
- Encourage regular daytime voiding schedule, emptying the bladder before going to sleep and getting adequate sleep should also be encouraged.
- Clinicians should also be aware of any comorbid condition like constipation, encopresis, and any psychiatric disturbance. Treating the comorbidity often rectifies the incontinence.
- Repeated waking to void is not helpful, though using an alarm clock to wake the child once, 2–3 hours after falling asleep is indicated. Child should be fully aroused and walk unaided to the toilet to urinate. Advantage of an alarm is that the child becomes aware of a sense of bladder fullness during sleep also.

*Behavior conditioning or alarm system* Behavior conditioning with use of alarms is extremely effective. Enuresis alarms are a first-line treatment for children whose bedwetting has not responded to advice about fluid intake, toileting, or an appropriate reward system. Enuresis alarms work best for well-motivated families and children with frequent enuresis (more than twice per week). The alarm is either a sound or a vibratory device that may be clipped to the underwear or kept at the bedside and rings as soon as voiding starts. The child must get out of bed and finish the act of urination or must hold the act until later. It is the most helpful way in training the child to improve bladder capacity and avoid enuresis. It requires long-term use and approximately 70% improve with 5–12 weeks of this therapy. Relapse rates are lower (15–30% in 6 months after treatment) than that with pharmacotherapy.

*Bladder training exercises* Daytime bladder exercises are useful, especially in those with low functional bladder capacity. The following bladder exercises have been found to be helpful; (1) hold urine as long as possible during the day to increase the functional bladder capacity; (2) practice repeated starting and stopping the stream at the toilet bowl; (3) practice getting up from bed and going to the bathroom at bedtime before sleep. Kegel's exercise, i.e., volitional contraction of pelvic floor muscles increases the detrusor contractions.

*Caffeine reduction* Some soft drinks, cocoa and chocolates have significant amount of caffeine which is known to have a diuretic action. Excessive consumption of these items can result in enuresis and should be avoided.

### Pharmacological Measures

Medications are indicated only in children older than 6 years who fail behavioral treatment. Drugs used are (1) imipramine; (2) desmopressin (DDAVP); and (3) oxybutynin.

- *Tablet imipramine (25 mg and 50 mg tablets)* 6–8 years (25 mg), 9–12 years (50 mg), greater than 12 years (75 mg) once a day at bedtime. It is a tricyclic antidepressant which alters the arousal-sleep mechanism. It combines the anticholinergic

effect to increase the bladder capacity with a noradrenergic effect to decrease detrusor contractions. Success rate is 30–60%, whereas relapse rate may be up to 90%. The relapse rate can be decreased if treated for 3–4 months followed by tapering over 3–4 weeks. Common side effects are drowsiness, lethargy, sleep disturbances and cardiotoxic side effects.

- Desmopressin acetate (DDAVP) orally or intranasally (nasal spray, 10 µg per spray) at bedtime. It acts by reducing the nocturnal urine output to a volume less than the functional bladder capacity. Start with 10 µg given at bedtime daily and increase gradually by 10 µg/week to a maximum of 40 µg/day. If effective, it should be used for 3–6 months. Success rate is 40–60%, whereas relapse rate may be up to 90%. It is a costly drug, and has a fast onset of action. It may be used intermittently to allow enuretic children to participate in sleepovers and night camps.
- Oxybutynin is an anticholinergic agent that can be used in those above 6 years of age. It reduces uninhibited bladder contractions and is useful in children manifesting with urgency and urge incontinence during daytime.

Management is summarized in **Box 2**. The various treatment modalities available are not used exclusive of each other and often a combination works best. Failure of one form of therapy should result in substitution or addition of another. The best treatment option, if behavioral therapy fails, is the use of combination therapy with alarms and drugs simultaneously. Evidence is not robust to support the use of hypnosis, psychotherapy, acupuncture, chiropractic, and medicinal herbs for treatment of nocturnal enuresis.

#### BOX 2 Management of enuresis

- Goal of treatment is complete stopping of enuresis
- Initiate treatment after 7–8 years of life
- Coordination between clinician, parent and child required.

##### Nonpharmacological measures

- *Behavior modification*: Includes reassurance and counseling of both parents and child including dietary modification
- *Alarm therapy*: Works best for motivated children and families. Helpful in children with frequent symptoms
- *Bladder exercises*: Useful especially in those with low functional bladder capacity.

##### Pharmacological measures

- *Imipramine*: Combines the anticholinergic effect to increase the bladder capacity with a noradrenergic effect to decrease detrusor contractions
- *Desmopressin*: Acts by reducing the nocturnal urine output to a volume less than the functional bladder capacity
- *Oxybutynin*: Reduces uninhibited bladder contractions and useful in children manifesting with urgency and urge incontinence during the daytime.

**Combination of various treatment modalities often works best.**

Nonresponse to active intervention is defined by less than 50% improvement in symptoms. When motivated children and families do not respond to an adequate trial of treatment with an enuresis alarm (i.e., 3 months) and/or desmopressin (at a dose of 0.4 mg), referral to a health-care professional who specializes in the management of bedwetting that has not responded to initial treatment (e.g., developmental-behavioral pediatrician, pediatric nephrologist or urologist) may be warranted.

## ENCOPRESIS

Defecation is the process of consciously emptying the bowel and continence is the ability to control this act. Fecal continence is regulated by a coordinated action involving the neuromuscular reflex on the anus, rectum, the two anal sphincters and the levator

ani muscles. Conscious bowel control is attained at the age of 28 months on an average. Fecal incontinence is categorized as true incontinence, partial incontinence and overflow incontinence. Impaired neuromuscular function or deficient anorectal muscles as in imperforate anus result in true incontinence. Insufficient anorectal pressure or impaired sensation of peristaltic movement and bowel distension prevents complete evacuation of the bowel resulting in continuing passage of small amounts of feces. Overflow incontinence, results from chronic fecal impaction and leakage of liquid feces through the dilated anorectal ring.

### Definition

*Encopresis* is defined as the involuntary or voluntary passage of formed feces, at inappropriate places (usually into the underwear) in the absence of any physical pathology, after 4 years of age. The act should occur at least once every month for 3 consecutive months. Encopresis is more common in boys with the peak age of affliction being 5–6 years.

### Classification

Encopresis can be *primary* (children who were never continent since infancy) or *secondary* (children with a typical history of clean periods, followed by a relapse of symptoms). Encopresis is also classified as *retentive* and *nonretentive* based on retention of feces for a prolonged time. Approximately two-thirds cases are retentive type and associated with chronic constipation. Nonretentive encopresis is a behavioral or psychological problem.

### Pathophysiology

The course of the rectum is aligned at an approximate angle of 90° to the anal canal. This sharp bend favors rectal continence. The contraction of levator ani muscle which causes the straightening of the anorectal canal results in defecation. The sympathetic nervous system causes rectal filling by relaxing the sigmoid and rectum and contracting the internal anal sphincter. The parasympathetic fibers control bowel emptying by reversing the above. Incontinence occurs when the pressure induced by the peristaltic movement in the distal rectum overcomes the anorectal pressure.

### Etiology

The etiology of encopresis is multifactorial and includes—psychological, anatomical, genetic, physiological and dietary elements. Abnormal gastrointestinal motility and developmental delay also play a part. In most cases, encopresis is thought to develop as a consequence of chronic constipation with resulting overflow incontinence (retentive encopresis). Psychological factors are especially important for secondary incontinence. In many cases encopresis occurs when there is a stressful family situation, such as divorce, birth of a sibling, or a transition such as starting school. When a child actually smears feces, there is a strong indication that there may be a problem in family relationships. The child who is reluctant to openly express anger may express it by soiling. Soiling may also occur in a child who has had a traumatic or frightening experience, such as sexual or physical molestation. Coercive toilet training can also result in encopresis. Other problems to be considered in the diagnosis include the following (especially in cases of primary incontinence): spina bifida, meningomyelocele, spinal-cord injury with dysfunction of the anal sphincter, tethered spinal cord, ultrashort-segment Hirschsprung disease and imperforate anus with fistula.

### Clinical Features

The first and foremost consideration is given to constipation which is often a result of overzealous toilet training by parents, resulting in reactionary fecal retention (often out of anger or retaliation).



Children with nonretentive incontinence are often the products of disturbed homes and with a poor parent-child relationship so that a regular pattern of toilet training was never achieved. Approximately 80–95% of children with encopresis have a history of constipation or painful bowel movements. The remaining 5–20% appears to have nonretentive encopresis and no history of constipation or painful defecation; they generally have no evidence of incomplete evacuation on physical evaluation or radiographic evaluation.

Secondary encopresis is often a result of stress at home or at school and whereas primary is associated with developmental delay and enuresis. This picture is further complicated by behavior and psychological abnormalities in such children. Punitive measures by parents always do more harm than good. Encopresis has adverse implication on school performance and attendance as child is often looked down upon his peers for the foul smell emanating from him.

## Diagnosis

**History** The main aim of the history should be to differentiate between retentive and nonretentive incontinence. It is important to determine whether it is primary or secondary encopresis. The age of onset of incontinence, also frequency of symptoms, stool mass and consistency, any alteration in bowel habits, the time of day it happens and any other related behavioral issues should be noted. Parent-child relation, marital discord or any other family issue should be looked up. Enquiry should be made if the child has sense of fullness, the urge to defecate and the ability to differentiate between the passage of feces and flatus. Urinary abnormality and lower limb weakness should also be assessed when suspecting spinal cord involvement. Details about toilet training should also be elicited as coercive toilet training can lead to fecal retention late. The skin over the spine should be examined for any midline defects. Sphincter tone should be assessed.

**Clinical and laboratory tests** These are undertaken for primary incontinence when anatomical abnormality or neuromuscular dysfunction is suspected. These include proctoscopy and fiberoptic studies of the lower bowel to rule out any structural abnormality. Barium enema and defecography study may be required to monitor the act of defecation in cases where anatomical abnormality is suspected. Specific studies may sometimes include anal sphincter electromyography (in children with suspicion of anal sphincter abnormality), manometric studies, CT of puborectal muscles and external sphincter (for associated anomalies). Sacral ratio (dividing the distance from the lowest point of the sacrum to the line joining the two posterior iliac spines by the distance from that latter line to the line joining the upper limits of the iliac crest) less than 0.52 correlate well with spinal cord anomalies and unfavorable prognosis in children with anorectal malformation.

## Management

The approach to treating a child mainly aims at establishing the normal bowel habit and improving the child to parent relationship. It includes both pharmacological and nonpharmacological measures. There are three main areas of intervention: (1) immediate relief from constipation; (2) long-term relief from constipation through diet and drugs and (3) behavioral therapy and biofeedback training.

Immediate relief of fecal retention in children is achieved by a glycerin suppository or sodium phosphate enema (6 mL/kg). For a slower relief of symptoms over 5–7 days, the available options include oral administration of polyethylene glycol (1.5 g/kg/day × 3

days), lactulose (2–3 mL/kg/day q 12 hours × 7 days), or mineral oil (3 mL/kg/day q 12 hours × 7 days). The dose should be sufficient to produce 1–2 soft stools daily. Long-term laxative use is to be avoided. After removal of impacted stool, plan long-term management of constipation, primarily through dietary modification. A few children may also require long-term maintenance therapy for relief of constipation. Dietary changes are an important management element. Dietary counseling of both parent and child is required to promote the inclusion of fiber in diet. Excessive flatus and soiling may be avoided by preventing certain food types. Dietary recommendations for few children with retentive encopresis are summarized in **Box 3**. In few cases tricyclic antidepressants have been tried but they should be used with caution in young children because of their narrow therapeutic index and potential risk of arrhythmia. They should be avoided in children with retentive incontinence as they may exacerbate constipation.

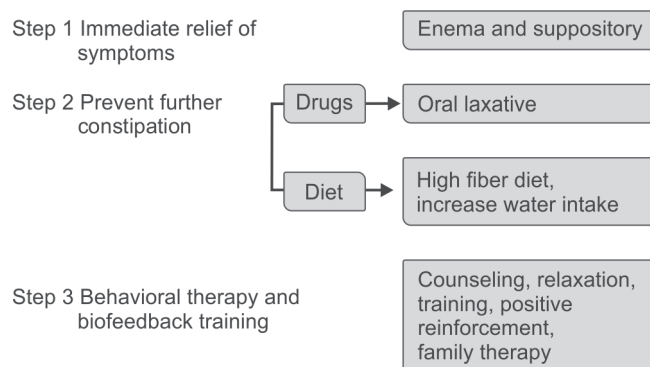
### BOX 3 Dietary recommendations for retentive encopresis

- Reduce the intake of dairy products and bananas (constipating foods)
- Increase intake of high-fiber foods such as bran, whole wheat products, fruit and vegetables
- Increase intake of water and other liquids. Avoid sweetened and high calorie drinks
- Limit drinks with caffeine, such as cola drinks and tea
- Eat well-balanced meals and snacks, and limit fast foods/junk foods that are high in fats and sugars
- Limit whole milk to about 250–300 mL a day for child over 2 years of age.

Concomitant behavioral management is required which lays stress on regular postprandial toilet (sitting on potty seat for 10–15 min after the meal) and adoption of high-fiber diet. Often it may be months before regular bowel habits are acquired. Punitive measures are a strict number. Parents need counseling to be supportive and patient with the child. Compliance may wane with time so reinforcement of behavior therapy along with continued use of high-fiber diet is indicated. Biofeedback training, behavior modification and muscle training coupled with appropriate medication is mostly beneficial. Failure of medical management occasionally requires surgical correction. Long-term studies indicate that encopresis improves irrespective of the method used. **Flow chart 2** summarizes the key strategies in management of encopresis.

Individuals with impaired bowel and bladder control often have low self-esteem with lower perceived quality of life on several domains so an integrated approach involving both the parent and the child along with the treating physician has the most promising outcome.

**Flow chart 2** Management of encopresis





### IN A NUTSHELL

1. Age-appropriate and proper toilet training is essential for preventing incontinence.
2. Overenthusiastic toilet training is as detrimental as incomplete training.
3. A good history and examination of the child are cornerstones for diagnosis.
4. Behavior therapy and dietary modifications often obviate the use of pharmacological measures.
5. Punitive measures do more harm than good whereas parental support can change the outcome in a positive way.

### MORE ON THIS TOPIC

Brazzelli M, Griffiths PV, Cody JD, et al. Behavioural and cognitive interventions with or without other treatments for the management of faecal incontinence in children. *Cochrane Database Syst Rev*. 2011;12:CD002240.

Caldwell PH, Nankivell G, Sureshkumar P. Simple behavioural interventions for nocturnal enuresis in children. *Cochrane Database Syst Rev*. 2013;7:CD003637.

Deshpande AV, Caldwell PH, Sureshkumar P. Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics). *Cochrane Database Syst Rev*. 2012;12:CD002238.

Franco I, von Gontard A, De Gennaro M, et al. Evaluation and treatment of nonmonosymptomatic nocturnal enuresis: a standardization document from the International Children's Continence Society. *J Pediatr Urol*. 2013;9:234-43.

Loening-Baucke V. Encopresis. *Curr Opin Pediatr*. 2002;14:570-5.

Nijman RJ. Diagnosis and management of urinary incontinence and functional fecal incontinence (encopresis) in children. *Gastroenterol Clin North Am*. 2008;37:731-48.

Rajindrajith S, Devanarayana NM, Benninga MA. Review article: faecal incontinence in children: epidemiology, pathophysiology, clinical evaluation and management. *Aliment Pharmacol Ther*. 2013;37:37-48.

van de Walle J, Rittig S, Bauer S, et al. Practical consensus guidelines for the management of enuresis. *Eur J Pediatr*. 2012;171:971-83.

## Chapter 21.5

# Breath-Holding Spells

Sumaira Khalil, Devendra Mishra

Breath-holding spells (BHS) are paroxysmal nonepileptic disorders seen commonly in children belonging to the age group of 6–28 months old, though they may occur even in the first few days of life and up to 6 years. The spells can be either cyanotic or pallid, and the episode frequency may vary from several episodes in a day to as rarely as one or two episodes in a year. First described almost 3 centuries back, BHS are an important differential diagnosis of epileptic seizures among preschoolers. Given that the diagnosis is entirely clinical, with investigations infrequently providing additional diagnostic information, it is not uncommon in practice to find children with BHS being treated with antiepileptic drugs.

### Epidemiology

They constitute 4–18% of all the psychosomatic disorders seen in the pediatric age group. Among otherwise normal children, up to 27% may have BHS with a male to female ratio of 3:1. However, a community survey in India among 0–3-year-old children reported BHS to be the most common psychiatric disorder in this age-group but with a prevalence of only 5.9%. There was no difference in prevalence among rural, urban and slum children. Among an Indian general hospital psychiatry clinic, 11% of the preschoolers had BHS.

### Etiology

A positive family history is present in 23–38% of children with spells suggesting some genetic association. An analysis of family members of children with breath-holding spells showed a 50:50 risk of inheritance from an affected parent. The inheritance pattern based on a regression model for pedigree analysis has suggested autosomal dominant pattern with reduced penetrance. Several times presence of both types of spells is seen in the same family, thereby hinting at a close relationship between cyanotic breath-holding spells and pallid breath-holding spells.

Along-held belief has been voluntary breath-holding as a cause of BHS. However, cinefluoroscopy has shown conclusively that these episodes occur during expiration, and are thus involuntary. Another factor considered to have important etiopathological role has been the presence of behavioral problems in BHS. Children with BHS were described as “neuropathic children of neuropathic parents” almost a century back. Some workers suggested correlation between behavioral problems and BHS, including abnormal behavior like temper tantrums and hyperactivity in 30% of these children. Di Mario et al. reported no significant difference in behavior of children with BHS as compared to their controls suggesting that BHS are nonvolitional and cannot be synonymous to temperamentally difficult children. Another study among Indian children with BHS also reported no apparent difference in parental attitudes or in children’s habits.

A correlation between BHS and syncopal episodes later in life has been shown. Up to 17% children with BHS are reported to develop neurogenic syncope later in childhood or adolescence. The proposed mechanism is the underlying vagal stimulation as a cause for both pallid BHS and neurogenic syncopal episodes.

Some workers have suggested a maturational delay in myelination of brainstem to have a role in the etiology of breath-holding spells in children, whereas others have reported altered

selenium and antioxidant levels in children with BHS. However, the pathophysiologic or therapeutic significance of these findings still remains to be elucidated.

### Pathogenesis

The pathogenesis of BHS is quite unclear and controversial. Both types of spells result from reflex changes that reduce cerebral blood flow, though the exact mechanism may vary from one child to another. Intrapulmonary shunting, disorder of ventilator chemosensitivity and autonomic dysregulation are some of the theories related to the pathophysiology of cyanotic BHS. The loss of consciousness in a BHS is attributed to drop in blood pressure due to increased intrathoracic pressure because of breath holding during expiration. This further causes a greater than normal drop in cerebral blood pressure and due to simultaneous drop in the cerebral vascular resistance the cerebral blood flow is further reduced leading to cerebral hypoxia causing unconsciousness and seizures. Dysregulation of the autonomic nervous system is known to cause vagal mediated cardiac arrest and anoxia.

A relationship between BHS and cardiorespiratory control has also been proposed. Airway obstruction during BHS is mediated by autonomic dysregulation which also controls the patency of the airways. Children with cyanotic BHS have been shown to have a greater increase in pulse rate and greater decrease in diastolic blood pressure without an increase in systolic blood pressure after standing from the supine position. These results support the hypothesis that children with cyanotic BHS have underlying autonomic nervous system dysregulation. The ECG changes before and during BHS spell have also been studied. Sinus arrhythmia and asystole were seen more during pallid breath-holding spells. Moreover, children with iron-deficiency had a lower frequency of respiratory sinus arrhythmia and prolonged asystole time during the spell. This study, thus, demonstrated both the presence of autonomic dysregulation in children with BHS and the effect of iron deficiency on it.

Pallid spells are proposed to be due to parasympathetic system mediated cardiac inhibition leading to bradycardia. The primary mechanism is due to increased vagal tone leading to cerebral hypoperfusion.

Anemia is believed to have a strong association with the disorder. Regardless of the type of the spells, iron-deficiency anemia is known to prolong the duration of asystole during the spell. Low levels of hemoglobin results in decreased oxygen carrying capacity and prolonged cerebral anoxia in an already irritable child secondary to iron-deficiency, which increases the occurrence of a BHS. Complete resolution of spells has been shown in 50% patients on iron therapy, and 50% reduction in another 36.4% of children. Others have suggested a possible relationship between maternal iron-deficiency anemia and children with BHS. The role of iron in BHS is possibly related to it being a cofactor in catecholamine metabolism and neurotransmitter function.

### Clinical Features

Breath-holding spells are commonly seen in developmentally normal children occurring numerous times a day to one episode a year. They start at around 6–18 months of age and usually disappear by 5–6 years of age. By 4 years almost 50% children will be free of spells, and almost all by 7–8 years. BHS typically occur in four phases: (1) provocation, (2) apnea and cyanosis (3) opisthotonic rigidity or abnormal posturing and (4) stupor (**Box 1**). They are classified by the color change of the child during an attack as cyanotic and pallid BHS. In 20% of children, both types of breath holding could be present and are called as mixed episodes. Usually

BHS do not result in serious complications but rare case reports of cause status epilepticus or asystole exist, mostly in those with a complicated medical history, or with severe spells.

#### BOX 1 Characteristic features of breath-holding spells

- Episodes start between the ages of 6 months and 18 months
- Attack frequency varies from many per day to only a few at irregular intervals and may increase during the 2nd year of life
- Characteristic sequence consists of a provocative stimulus, apnea and color-change, limpness, followed by opisthotonic rigidity
- The child regains consciousness within few minutes
- Child may sleep for several hours, especially following a pallid episode
- Family history of breath-holding spells is present in around 30% patients
- The physical examination is normal.

*Cyanotic breath-holding spells* are the most common type, seen in 54–62% of children with BHS. They usually occur in response to anger, leading to a vigorous cry, followed by apnea and rapid onset of cyanosis. This may or may not be followed by loss of consciousness, associated with bradycardia, abnormal posturing or repeated generalized clonic jerks. After regaining consciousness, which is usually within a minute, the child is usually awake and resumes normal activities.

*Pallid breath-holding spells* are seen in about 19–24% of children. They are similar to vasovagal attacks where the child turns pale and can be induced by ocular compression. Pallid spells usually occur in response to fright and pain, or an unexpected event. The child may gasp or cry, stops breathing, becomes hypotonic and loses consciousness; clonic movements may occasionally occur. Sometimes they are associated with prolonged period of asystole and bradycardia. Importantly, after attaining consciousness, pallid spells may occasionally be followed by sleep for several hours.

### Diagnosis

The diagnosis of BHS depends only on a good and detailed clinical history, describing the entire episode as and when it occurred. It should also include presence of any precipitating event like emotional stimuli or trauma. Other important clues from the history that could help in diagnosis include the presence or urinary incontinence, uprolling of eyeballs, and deviation of mouth, which are more commonly seen with seizures, especially if not preceded by a cry. If feasible, parents may be encouraged to make a video recording of a typical episode that could further help in confirming the diagnosis.

A complete physical examination including growth and development is essential, especially cardiovascular examination for any rhythm disturbances or murmurs. No imaging or specific laboratory test is needed to make the diagnosis. An electroencephalogram (EEG) is usually not indicated unless the history is incomplete or unclear, convulsive activity is too prolonged or seizure cannot be ruled out on the basis of history.

An important differential of pallid BHS is long-QT syndrome, a congenital condition characterized by loss of consciousness precipitated by injury, fright or excitement. Thus, an electrocardiogram is an essential investigation in all children with pallid BHS. Hypercyanotic spells in children with cyanotic congenital heart disease are a close differential for cyanotic BHS. In addition to absence of baseline cyanosis, clubbing, and cardiovascular findings in BHS, the time to appearance of cyanosis during the episode also helps in differentiating it from cyanotic heart disease. During a hypercyanotic spell in a child with right to left shunt, there is a baseline cyanosis which increases during the episode even while the child is crying; whereas during a BHS, the cyanosis appears when the child has stopped crying/breathing.

Ocular compression during cardiovascular monitoring or EEG recording has been shown to demonstrate abnormalities (asystole or slowing/voltage attenuation, respectively) in children with pallid BHS. But the clinical utility and safety of this maneuver is controversial and it is best avoided outside of a specialized center.

### Management

Reassurance to the parents regarding the benign nature of BHS is the mainstay of treatment (**Box 2**). The parents must be informed about the low risk of epilepsy and developmental delay in such children. During a spell, the child must be placed in the lateral recumbent position rather than upright on the shoulder, as it shortens the period of cerebral anoxia. Behavioral modification also needs to be directed at reducing the parents' emotional reactions to the episodes.

#### BOX 2 Information to be conveyed to parents of a child with breath-holding spells

- Benign and self-limiting episodes
- During the episode, place the child in lateral/recovery position, away from harm
- Inappropriate attempts for vigorous resuscitation may do more harm than benefit
- Attack frequency may increase during the 2nd year of life
- No increase in risk for developmental delay or epilepsy
- No extra attention to the child with BHS, compared to siblings
- Report back in event of prolonged episodes, life-threatening episodes, very frequent spells, or change in pattern of episodes.

Iron therapy, which has been shown to be beneficial, must be initiated in all children with BHS, with or without iron-deficiency anemia. According to the Cochrane review published in 2010, iron supplementation (at 5 mg/kg/day of elemental iron for 16 weeks) appears to reduce the frequency and severity of the spells, and is of particular benefit in children with iron-deficiency anemia where response correlates with improvement in hemoglobin. This benefits children more who have associated iron-deficiency anemia with data showing a trend towards greater improvement in spells linked to improvements in hemoglobin level. There is paucity of data to prove the role of iron in children who are not anemic or have normal hemoglobin levels. Given the high prevalence of iron-deficiency in children in our country, we feel that the optimum approach would be to provide therapeutic doses to those with iron-deficiency (3–6 mg/kg/day for 4 months) and daily maintenance requirement (2 mg/kg/day) to those without iron-deficiency. The duration can be further tailored on the basis of response.

Atropine has been shown to be effective in pallid BHS (0.01 mg/kg 2–3 times a day) but is rarely required. Piracetam (40 mg/kg/day), although not approved for this indication, is proven to be safe and effective in children with severe and multiple BHS. As the convulsive movements associated with BHS are not epileptic, presently there is no role of anticonvulsants in the management of BHS. Permanent cardiac pacemaker implantation has been tried with success in rare cases of severe BHS not responding to medical management, or those with prolonged asystole following the spells. Other drugs that have been studied in treatment of BHS are glycopyrrolate, theophylline, fluoxetine, and levetiracetam but need further data to confirm their efficacy and safety.

Breath-holding spells are common in preschool children and have excellent prognosis and the crux of diagnosis is a detailed history from an eyewitness. Importance of the condition for the physician is the frequent misdiagnosis of epilepsy and the urge to investigate extensively. For the parents, the correct diagnosis reassures about the benign nature of this apparent life-threatening event and favorable long-term prognosis.

### IN A NUTSHELL

1. Breath-holding spells are common childhood events and are an important differential for childhood seizures.
2. A good history from an eye-witness, especially focusing on the events before the episode, is crucial for an accurate diagnosis.
3. Investigations like EEG or neuroimaging, and treatment with anticonvulsants are not helpful and routine use should be avoided.
4. Iron-deficiency, overt or subclinical, is common and iron therapy is beneficial in reducing the frequency and severity of the episodes.
5. Long-term prognosis for breath-holding spells is good.

### MORE ON THIS TOPIC

- Mishra D, Archana, Pensi T. Health professionals' characteristics associated with requisitioning electroencephalography in breath holding spells. *J Assoc Physicians India*. 2007;55:671-2.
- Olsen AL, Mathiasen R, Rasmussen NH, et al. Long-term prognosis for children with breath-holding spells. *Dan Med Bull*. 2010;57:A4217.
- Sawires H, Botrous O. Double-blind, placebo-controlled trial on the effect of piracetam on breath-holding spells. *Eur J Pediatr*. 2012;171:1063-7.
- Srinath S, Girimaji SC, Gururaj G, et al. Epidemiological study of child and adolescent psychiatric disorders in urban and rural areas of Bangalore, India. *Indian J Med Res*. 2005;122:67-79.
- Zehetner AA, Orr N, Buckmaster A, et al. Iron supplementation for breath-holding attacks in children. *Cochrane Database Syst Rev*. 2010;5:CD008132.



## Chapter 21.6

# Common Speech, Language and Communication Disorders

Prathibha Karanth

It is important to be aware of three important aspects of communication that is speech, language and communication. While *speech* refers to the heard speech that one learns to understand through hearing and produce orally, *language* is the more comprehensive system that governs the rules underlying our speech in both comprehension and production. Speech cannot be understood and produced without the rules of language. Spoken language is referred to as the primary mode of communication while reading and writing, which are mapped on to speech, are the secondary system of language. *Communication* on the other hand refers to all means of exchange of information between individuals including the nonverbal (gestures and signs), the visual (symbols and pictures) and technological (Morse code, telephone, Skype, typing, email, etc.). With the phenomenal increase in the variety of the modes of communication in modern society, their usage in the learning process and day-to-day communication and the fact that these can be selectively affected, speech and language disorders are now viewed/studied within the broader framework of communication disorders.

Proficiency across different modes of communication at different levels of complexity is acquired in different stages of life. However, the most crucial aspects of communication that is the basics of speech and language are learnt in early childhood. Delays and deficiencies in communication skills can affect the child's overall well being by interfering not only in communication, but also affecting the child's social, educational and emotional well being and have a lifelong impact. It is therefore crucial to identify common communication disorders early in childhood and provide the necessary intervention to ameliorate and/or prevent these long-term effects. Communication disorders are generally more common in boys than girls with a ratio of 4:1.

## INCIDENCE AND PREVALENCE

Precise information on incidence and prevalence figures for communication disorders are hard to come by given the range of communication disorders both in terms of types and the wide age range in which they occur. Most studies focus on any one subtype. Overall figures for prevalence of speech, language and communication disorders range from 2% to 25% of the population, with a general consensus centering around 10%. The variance is due to the specific communication disorders being investigated, definition of disorders, mode of identification, age and number of participants.

Reliable reports of incidence and prevalence studies of communication disorders in children in India are even harder to come by. The Indian Census (2011) defining speech disability as *persons who speak in single words and are not able to speak in sentences* arrived at prevalence figures of 683,702 individuals up to the age of 18 years. Given the very broad definition of *speech disability* it is likely that this is an underestimate and the prevalence is in fact considerably higher.

## PATHOGENESIS

The majority of the childhood communication disorders are now known to be caused by congenital/genetic factors. History of communication disorders in other members of the family such as parents and siblings is reported to be between 28% and 60%. The genetic basis of conditions such as a congenital hearing loss have been long known. The genetic links of hitherto poorly understood childhood communication disorders such as specific language impairment (SLI) and autism spectrum disorders (ASD) are now being unraveled, though the exact genetic basis/mechanisms are yet to be understood. A smaller proportion of communication disorders in children are secondary to other conditions such as birth complications and postnatal infections, and injuries, such as hypoxia, otitis media, meningitis and head injuries. An even smaller proportion could be due to environmental factors such as extreme social deprivation and lack of speech stimulation, highly multilingual context and/or constant changes in the linguistic environment due to frequent relocations of the family in early childhood.

## Range of Communication Disorders

Children with communication disorders may not speak at all or their communication skills are not on par with their peers, in any one or more aspect—vocabulary, grammar, clarity of speech, control over voice, smooth flow of speech, specific difficulties in reading, and/or writing and the proper use of language in social situations.

For a child to acquire communication skills it is important that the underlying mechanisms of human communication such as good hearing sensitivity, perception, structural integrity of the brain and body, intelligence, motor control over the voice and speech producing mechanisms and emotional stability should be present. In addition a stimulating environment, which provides adequate language exposure and reinforces the child's attempts at communication, commensurate with age and developmental stage, is also a prerequisite for the smooth development of communication skills.

## CLASSIFICATION

The description and classification of communication disorders in the early and mid part of the twentieth century, was initially influenced by causation, within the medical model. Hence, for instance there were classificatory labels of *mental retardation with speech delay* or *hearing impairment with speech delay* or *cleft palate with speech delay* and so on. However, with the impact of linguistics on the understanding and study of both child language acquisition and its disorders, in the latter part of the twentieth century the characterization and broader classification of speech disorders was extended to include the language disorders. Under the medical model of classifications, communication disorders in children are generally classified with reference to the medical cause that underlies or is comorbid with the disorder. For instance, speech disorders would be classified as *childhood apraxia of speech* or *dysarthria* or *orofacial myofunctional disorders*; language disorders would be *childhood aphasia* or *selective mutism*. In addition, there would be speech-language disorders associated with *autism* or *traumatic brain injury*. The reservation against this type of a classification has been that, while it specifies the cause it does not provide an accurate description of the nature of the communication difficulty per se that is needed for speech-language therapy.

Current classificatory systems used by audiologists and speech language pathologists (ASLPs) are therefore based on the broader framework of the aspect of communication that is impacted such as articulation disorders, voice disorders, fluency disorders and language disorders. Among these four the first three, i.e., impairments of the articulation of speech sounds, fluency and/or voice are considered as speech disorders. Communication disorders in children have also been classified on the basis of the aspect of communication that is affected. This system groups them into four basic subtypes as (1) Articulation disorders; (2) Voice disorders; (3) Fluency disorders and (4) Language disorders. It is to be noted that a given child may have a disorder in one or more of these aspects of communication.

### Articulation Disorders

Articulation disorders are those that affect the clarity of speech sound production. Articulation disorders can be caused by hearing impairment, neurologic problems such as verbal apraxia or dysarthria or structural defects of the articulators such as a tongue-tie, cleft lip or misaligned teeth. Speech sounds in these conditions lack clarity because of distortions, or the omissions and substitutions of 'difficult to produce' sounds. Articulation disorders are at times referred to as phonological disorders. However, the latter denote speech discrimination difficulties and/or speech production issues.

### Voice Disorders

Voice disorders refer to abnormal production of voice. The abnormality is characterized by the use of pitch, loudness, resonance or duration that are not appropriate for the child's age and sex. For example in *puberphonia* the typical changes in voice that occur, more noticeably in males at puberty, do not take place, leaving the young male with a high pitched voice that is inappropriate to his sex. Or the oro pharyngeal cavity in a child with an unrepaired cleft palate would result in distorted resonance with speech, acquiring a hyper nasal quality. Hoarseness of voice is also a common condition and if untreated could lead to lifelong voice disorders.

### Fluency Disorders

Fluency disorders are characterized by difficulties in the continuity, rhythm and smooth flow of speech with repetitions of syllables, words or phrases along with tension in the speech mechanisms. Commonly known as stammering or stuttering, fluency disorders tend to occur in 4–5% of children between the ages of 2 years and 4 years. As with the other communication disorders they are more common among boys than girls (3:1) and may co-occur with other speech disorders, especially in articulation.

### Language Disorders

Language disorders are delays or disorders in acquisition of language affecting one or more aspects of language including phonology, semantics, syntax, and pragmatics as well as higher order language skills such as discourse. Children with language disorders may exhibit impaired comprehension and/or use of any one or more of the communication modes such as the spoken, written, and/or other symbol systems such as gestures and signs. Children with language disorders have issues in any one or more aspects of communication such as the form, content, and/or function of language in communication.

Language acquisition is affected in all of the congenital developmental disabilities such as hearing impairment, cerebral palsy and mental retardation. They may also be the consequence of degenerative neurologic disorders, infection, head injury or

neglect. Moderate to severe language disorders in these children persist along with impairments in developmental skills such as motor and functional skills as well as cognitive and social development, in the preschool years. With estimated prevalence rates of 2–19% they tend to have long-term difficulties in schooling along with behavioral issues.

A major subcategory of language disorders in children, that has emerged in the last decade or two include the developmental language disorders with no clear understanding as yet of the underlying pathology. Specific language impairment (SLI) which is representative of this group, is diagnosed when children present with language maturation which is at least 12 months behind their chronological age, in the absence of sensory or intellectual defects, pervasive developmental disorders, evident cerebral damage, and adequate social and emotional conditions. SLI is considered one of the most common childhood disorders, affecting 7% of children. As with other children with language disorders there are often associated impairments in other developmental skills such as motor skills, but to a much milder and nonapparent degree. A genetic basis is strongly suspected given the higher incidence in families with a similar history. Many of these children are later found to have difficulties in learning to read.

Auditory processing issues in children whose peripheral hearing is essentially within normal limits is also being increasingly documented under the label of Auditory processing disorders (APD), earlier referred to as Central auditory processing disorders (CAPD). Whether APD and SLI are essentially two faces of the same coin remains debatable.

Apart from these established traditional categories of children with developmental disorders, SLPs are increasingly contributing to populations of children with developmental disorders which until recently were not seen as being communication disorders. For instance, it is only during the last couple of decades that it is acknowledged that children with learning disabilities (LD) often have subtle underlying or associated speech and language disorders, which went unrecognized until the advances in speech language assessment that took place in the latter half of the twentieth century. Similarly, the loss or abnormal use of language seen in children with Autism Spectrum Disorders (ASD) were seen as secondary to the core disability in ASD, but are now increasingly being seen as a part of the core disability with implications for the individual's psychological, sociological, and educational growth. The contribution of speech language therapy, for amelioration of these issues, is also now being documented.

### Learning Disabilities

Learning disabilities is defined by the US National Joint Committee on Learning Disabilities (LD) as a *general term to refer to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical skills*. Developmental language disorders such as SLI is now documented as being the most common developmental disability of childhood, occurring in 5–10% of children. The difficulties in language learning and use, put these children at risk for learning disabilities, given that learning occurs largely through language and can persist through out the school years impacting reading and writing skills too. Similarly, the regression and lack of communication on the part of children with ASD, initially seen as being a part of the unwillingness of the child to communicate or a lack of desire to communicate, is now recognized as being due to difficulties in communication, more particularly in social communication.

The change in the classificatory systems used in the Diagnostic and Statistical Manual of Mental Disorders that is commonly used by clinicians such as psychiatrists and psychologists

reflects these changes in perspective on communication issues in these *psychological/mental disorders* in its fifth edition. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), communication disorders were classified as (1) Expressive language disorder; (2) Mixed receptive-expressive language disorder; (3) Phonological disorder; (4) Stuttering and (5) Communication disorder not otherwise specified (NOS). While the first two are language disorders highlighting both receptive and expressive aspects, the *phonological disorders* are equivalent to the *articulation disorders* though it has the broader connotation of speech sound processing difficulty too. Stuttering is the most common of the fluency disorders. The last category *Not otherwise specified* encompasses all other communication disorders that do not fit into any of the preceding categories.

In the DSM-5, the most recent edition, communication disorders have been defined more broadly as *deficits in language, speech, or in any behaviors affecting verbal and nonverbal communications*. In this most recent classification the language disorders (receptive and expressive) have been clubbed in one category, the phonological disorders are now termed *speech sound disorder*, stuttering has been renamed as *childhood onset-fluency disorder* and the last category of NOS is now labeled as *unspecified communication disorder*. A new subgroup labeled as *social (pragmatic) communication disorder* has been added in recognition of the increasing numbers of children who are found to have specific difficulties in communication in social situations in the absence of specific language deficits.

## IDENTIFICATION

Children learn to communicate from early infancy to adulthood beginning with the first cries right up to adulthood when they master complex rules that govern social communication. The identification of communication disorders that are comorbid with congenital birth anomalies such as cleft palate and lip or cerebral palsy is relatively straightforward. Communication disorders caused by other *hidden* congenital defects such as a hearing impairment or a mental retardation are more difficult to identify, particularly if they are mild to moderate in degree. The most difficult communication disorders to identify in early childhood are the developmental language disorders seen in conditions such as developmental verbal dyspraxia (DVD), specific language impairment (SLI), autism spectrum disorders (ASD) or social pragmatic disorders (SPD) largely, because the child appears to have normal development otherwise. Identification of communication disorders in children is further compounded by the fact that there is a fairly wide range with respect to the acquisition of early speech-language milestones, even in typically growing children.

In some children, while speech-language acquisition occurs in typical fashion in early childhood, they may lose these skills consequent to other illnesses such as encephalitis or meningitis or due to a head injury or an acquired hearing loss.

Broad guidelines in terms of *red flags* for speech-language acquisition are given in **Table 1** that may be used for an initial identification of a child who might be at risk for a communication disorder. It is important that children must be observed/screened for skills in understanding (receptive) and producing (expressive) speech.

A child who fails the above, either in terms of receptive or expressive language, should be considered at risk and screened for any possible underlying cause. While the delay in speech-language acquisition in children with cerebral palsy or Down syndrome are easily identified, many other developmental language disorders with more subtle communication disorders manifest as inattentiveness, deliberate disregard, specific issues with following

directions, usage of incomplete sentences with frequent pauses and clumsiness in organizing and expressing their thoughts.

## CLINICAL FEATURES

The distinguishing clinical features of the major subtypes of communication disorders in children, along with possible causes are listed in **Table 2** for an overview of the clinical features of these different disorders.

## Assessment

The first step in assessments for identifying a communication disorder is a complete medical check up by the pediatrician to be followed up by an audiologist and/or speech language pathologist (ASLP), who will document a case history covering medical and developmental milestones as well as family and language exposure history, to identify significant contributory factors, if any. Some common assessment procedures and tests used for children with different communication disorders are presented in **Table 3**. The list is by no means exhaustive and is provided for a general overview of the diagnostic process.

## MANAGEMENT

Procedures for management of communication disorders are generally initiated subsequent to medical/surgical intervention, where needed and feasible. Management is generally initiated with a counseling session in which the parents are counseled regarding the outcome of the assessments and the possible options for intervention, along with their pros and cons. The decision for a particular line of intervention say, oral language training versus sign language, or cochlear implant versus hearing aid, remains with the family and should be dependent on the merits and demerits of either option. While the management of the speech disorders are generally possible within a time frame of a few weeks, management of the language disorders is generally much more time consuming and can extend over months and years, given the nature of typical language acquisition and families need to be sensitized to these issues.

A ready reference for the key aspects of treatment along with examples of some well established approaches are provided for each category of communication disorder in **Table 3**. These are some of the more common lines of treatment and should not be taken as being a comprehensive statement.

Traditionally, speech language therapy services are provided on a one on one basis in outpatient clinics. These sessions are generally of 45 minutes duration with a frequency of 3-5 times a week and at times even fewer. As mentioned above outcomes for management of speech disorders can be seen and measured in shorter periods of time ranging from 4 weeks to 12 weeks. Management of language disorders and more complex communication disorders can extend over several months and years and the measurable impact is harder to document. Nevertheless, there is an emphasis on evidence-based studies for the wider acceptance of specific therapeutic approaches.

Access to speech language therapy services in India and in the Asia Pacific region as a whole is limited largely to urban middle and upper classes of society as of date. Attempts to expand services to the rural populations through community-based programs have been initiated sporadically, but have not met with much success. New initiatives such as the *Rashtriya Bal Swasthya Karyakram* (RBSK) are on the anvil, but need to be tried out.

## OUTCOME AND PROGNOSTIC FACTORS

Outcomes for children with communication disorders can be varied depending on the age of identification, consistency and



**Table 1** Red flags for identification of a child with delay in acquisition of communication skills

Age range (in months)	Understanding	Expression
0–6 months	Looks at you with interest when you talk to him	Uses vocal expression of pleasure when played with
6–12 months	Appears to listen to conversation between others	Babbles series of sounds that 'sound' like speech
12–18 months	Follows simple one step command	Asks for something by pointing/using a word
18–24 months	Recognizes names of familiar people and objects	Names 3 pictures
24–30 months	Can name objects when told their use for e.g. "Something that you cut with"	Uses two word combinations
30–36 months	Shows interest in 'how' and 'why' of things	Answers 'who' questions
36–42 months	Understands three step directions	Requests permission (verbally)
42–48 months	Understand words that relate one idea to another – if, why, when	Appropriately answers 'what- if' questions
48–54 months	Hears and understands most of what is said at home and in school	Likes to tell others about family and experience
54–60 months	Understands sequencing of events	Responds appropriately to 'how often' and 'how long' questions
60–66 months	Understands some jokes, surprises and make believe	Uses all speech sounds of his language correctly
66–72 months	Has an awareness of socially appropriate uses of communication	Remembers lines of simple poems, repeats full sentences, and expressions from others

Source: Karanth P. Communication DEALL Developmental Checklists. 2008.

duration of intervention, family involvement and school support. In general the earlier the identification and intervention, the better the long-term impact. While speech disorders such as articulation and voice disorders can generally be corrected within a few weeks to months, children with language disorders would need language therapy for a considerable length of time depending on severity and the age at which intervention is initiated. Family involvement and school support are crucial for generalization and sustenance of skills.

## PREVENTION

Specific measures to prevent communication disorders are few, given that many of these disorders are consequent to or coexistent with genetic conditions. The preventive measures are related to general maternal and infant health and risks at birth, as well as those that relate to the early language stimulation and environment. However, early identification of and intervention for communication disorders are of paramount importance in order to prevent the snowballing effect of a communication disorder

on a child's overall development including his education and emotional status.

To conclude, communication disorders in children is a major health issue that can and needs to be addressed. When provided consistently on a systematic basis and monitored regularly, the impact of speech language therapy services can be considerable, often making the difference in the inclusion or otherwise of the child in mainstream society. However, these services in countries like India are limited to urban areas and grossly inadequate to meet actual needs. Listed below are a few websites that may be accessed for more information on the availability of clinical services across the country (Indian Speech & Hearing Association, and National Trust) as well as the training programs (Rehabilitation Council of India).

- RCI-Registered professionals—<http://rehabcouncil.nic.in/forms/Sublink1.aspx?lid=814>
- ISHA-Colleges that train in ASLP—<http://www.ishaindia.org/in/index.php>
- National Trust—Registered organizations [http://www.thenationaltrust.co.in/nt/index.php?option=com\\_frontpage&Itemid=1](http://www.thenationaltrust.co.in/nt/index.php?option=com_frontpage&Itemid=1)

## IN A NUTSHELL

1. About 10% of children have communication disorders.
2. Many communication disorders in children have a genetic basis.
3. Communication disorders have a wide-ranging impact on the educational, social and emotional well being of the child.
4. In the context of the increasingly important role of communication in current society, intervention is crucial.
5. Early identification and intervention have the best long-term impact for children with communication disorders, even the more severe ones.
6. Many school going children have mild undetected communication disorders that interfere in their learning.
7. Communication deficits are emerging as core underlying deficits in childhood disorders such as *learning disabilities* and *autism spectrum disorders* which were formerly not considered as *communication disorders*.
8. Many speech disorders can be corrected with speech therapy.
9. When provided with early, consistent speech—language therapy, many children with even the more severe communication disorders can be mainstreamed in regular schools.
10. Training and clinical services in speech-language therapy are now available across the country.

## MORE ON THIS TOPIC

- Gore M. Cochlear Implants: An Overview. Mysore: Indian Speech & Hearing Association; 2014.
- Hegde MN. Hegde's Pocket Guide to Communication Disorders. USA: Thomson Delmar Learning; 2007.
- Johnson AF, Jacobson BH. Medical speech-language pathology: A Practitioner's Guide. New York: Thieme Medical Publisher's Inc; 1998.
- Karanth P, Rozario J (Ed). Learning Disability in India: Willing the Mind to Learn. New Delhi: Sage; 2003.
- Karanth P. Children with Communication Disorders. New Delhi: Orient Blackman; 2010.



**Table 2** Classification of communication disorders

Possible causes	Characteristics
<b>I. Articulation disorders</b> <b>Organic causes</b> <ul style="list-style-type: none"> <li>• Orofacial abnormalities</li> <li>• Cleft palate/lip</li> <li>• Tongue tie</li> <li>• Malocclusion</li> <li>• Neurological conditions</li> <li>• Apraxia, dysarthria, cerebral palsy</li> <li>• Communication disorders like hearing loss, mental retardation</li> </ul> <b>Functional causes</b> <ul style="list-style-type: none"> <li>• Encouragement of baby talk</li> <li>• Exposure to two or more language</li> </ul>	Substitution, omission, distortion and addition of speech sounds.
<b>II. Voice disorders</b> <ul style="list-style-type: none"> <li>• Vocal abuse/misuse</li> <li>• Acute or chronic laryngitis</li> <li>• Vocal fold web/inflammation due to reflux disorder</li> <li>• Vocal fold paralysis</li> <li>• Cleft palate</li> </ul>	Change in the quality of voice, voice break, pitch changes, change in loudness and resonance, and dysphonia/aphonia.
<b>III. Fluency disorders</b> <ul style="list-style-type: none"> <li>• Psychological factors</li> <li>• Genetic factors</li> <li>• Developmental delays</li> <li>• Neurophysiologic immaturity</li> <li>• Family dynamics</li> <li>• Environmental and behavioral factors</li> </ul>	Repetition of small speech units, filled and unfilled pauses in speech, rate, rhythm and continuity of speech is affected, prolongation of speech sounds, effortful speech, and secondary behaviors.
<b>IV. Language disorders</b> <b>Specific language impairment</b> <ul style="list-style-type: none"> <li>• Neurological factors</li> <li>• Genetic factors</li> <li>• Environmental factors</li> <li>• As yet unknown causes</li> </ul> <b>Semantic pragmatic disorder or pragmatic language impairment</b> <ul style="list-style-type: none"> <li>• Exact cause unknown</li> <li>• Genetic basis</li> </ul>	Vocabulary deficits and grammatical inadequacy, auditory processing deficit, clumsiness, slow rate of phonological acquisition, difficulty with morphological inflection, less communicatively interactive, and poor short term memory for speech sounds.  Slow in acquiring verbs, difficulty in understanding meanings of words, difficulty in rapid retrieval of words, difficulty in understanding word play, idioms puns and slang, poor conversation skills, use either a flat/exaggerated intonation pattern, poor narrative skills, and poor topic initiation, maintenance and termination.
<b>Language learning disability</b> <ul style="list-style-type: none"> <li>• Genetic factors</li> <li>• Neurological</li> <li>• Subtle deficits in visual and auditory processing</li> <li>• Exact cause unknown</li> </ul>	Poor auditory processing, poor speech discrimination, difficulty in following directions and word games, poor short term memory for verbal materials, difficulty in retrieving words, poor auditory, visual integration and perceptual-motor skills, poor eye-hand coordination, poor social skills, and poor at meta phonological and metalinguistic skills.
<b>V. Communication disorders in other developmental disabilities</b> <b>Hearing impairment</b> <ul style="list-style-type: none"> <li>• Genetic</li> <li>• Congenital</li> <li>• Ototoxins</li> <li>• Noise trauma</li> <li>• Auditory processing</li> <li>• Psychological</li> </ul> <b>Cerebral palsy</b> <ul style="list-style-type: none"> <li>• Pre-, peri-, post-natal damage to the brain</li> <li>• Infection</li> <li>• Seizure</li> <li>• Thyroid issues</li> <li>• Rh-incompatibility</li> <li>• Birth trauma</li> <li>• Asphyxia</li> <li>• Low birthweight</li> </ul>	Delayed onset of speech and language, asking for repetition, inconsistent response to verbal task, appears inattentive, and unclear speech.  Spasticity, flaccidity, akinesia, involuntary movements, seizures, abnormal sensational perceptions, impairments of hearing or speech, mental retardation, and speech qualities—slow, jerky, labored, effortful irregular, in general unintelligible, breathiness.

Contd..

Contd...

**Mental retardation***Biological*

- Genetic
- Fragile X syndrome
- Phenylketonuria
- Down syndrome
- Prenatal illness/complication
- Meningitis/encephalitis
- Head trauma

*Environmental or psychological factors*

- Lack of stimulation
- Inadequate nutrition
- Exposure to toxins such as lead

**Autism spectrum disorders**

- Genetic
- Environmental factors

Slow developmental milestones, impairment in intellectual development and adaptive functioning, and misarticulations.

Lack of social interest, skills and participation, regression/difficulty in communication, and repetitive/rigidity in behavior.

**Table 3** Management procedures for communication disorders

<i>Types</i>	<i>Management procedures</i>
<b>I. Articulation disorders</b>	<ul style="list-style-type: none"> <li>• Phonetic placement</li> <li>• Minimal pair approach</li> <li>• Motokinesthetic approach</li> <li>• Progressive approximation</li> </ul>
<b>II. Voice disorders</b>	<ul style="list-style-type: none"> <li>• Vocal hygiene/prevention methods</li> <li>• Speech therapy               <ul style="list-style-type: none"> <li>• Digital manipulation</li> <li>• Inhalation phonation</li> <li>• Glottal fry</li> <li>• Yawn sigh</li> </ul> </li> <li>• Surgery</li> </ul>
<b>III. Fluency disorders</b>	<ul style="list-style-type: none"> <li>• Indirect and direct methods of intervention</li> <li>• Some stages—Enhancing fluency, generalization and self-monitoring</li> <li>• Motivation identification desensitization Variation stabilization (MIDVAS)</li> <li>• Shadowing</li> <li>• Masking</li> <li>• Delayed auditory feedback (DAF)</li> <li>• Analogies</li> <li>• Airflow and modified airflow technique</li> </ul>
<b>IV. Language disorders</b>	
Specific language impairment	<ul style="list-style-type: none"> <li>• Intensive speech stimulation</li> <li>• Role play</li> <li>• Intensive language stimulation</li> <li>• Parallel talk</li> </ul>

Contd...

Semantic pragmatic deficits or pragmatic language impairment	<ul style="list-style-type: none"> <li>• Role play</li> <li>• Role reversal</li> </ul>
Language learning disability	<ul style="list-style-type: none"> <li>• Milieu teaching</li> <li>• Strategy to improve receptive and expressive skills</li> </ul>
<b>V. Other communication disorders</b>	
Hearing impairment	<ul style="list-style-type: none"> <li>• Medical procedures</li> <li>• Surgical procedures</li> <li>• Amplification device fitment—Hearing aid/Cochlear implant</li> <li>• Teaching communication skills               <ul style="list-style-type: none"> <li>– Auditory skill therapy/Auditory verbal therapy</li> <li>– Speech reading/Lip reading</li> <li>– Sign language</li> </ul> </li> </ul>
Cerebral palsy	<ul style="list-style-type: none"> <li>• Alternative augmentative communication (AAC)</li> <li>• Speech stimulation</li> </ul>
<i>Types</i>	<i>Management procedures</i>
Mental retardation	<ul style="list-style-type: none"> <li>• Tea-party technique</li> <li>• Speech stimulation</li> </ul>
Autism spectrum disorders	<ul style="list-style-type: none"> <li>• Teaching and Educating Children with Autism and Other Communication Handicap (TEACCH)</li> <li>• Applied Behavior Analysis (ABA)</li> <li>• Communication DEALL</li> </ul>

Contd...

## Chapter 21.7

# Autism Spectrum Disorder

Monica Juneja, Rahul Jain

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and interaction, and presence of repetitive, restricted pattern of behaviors, interests and activities. It typically manifests in early developmental period, usually before 3 years of age and significantly affects the functioning of child. ASD is a lifelong disorder, though the impact can range from mild to severe and may improve or change across the person's life.

The nomenclature, diagnostic criteria and classification of this condition have been changing with time. The criteria laid down in various editions of Diagnostic and Statistical Manual (DSM) for psychiatric disorders are the most widely accepted and were last revised in May 2013 in DSM-5. In DSM-IV (1994), an umbrella term *Pervasive Developmental Disorders* was used for these disorders and included five diagnostic categories: (1) autistic disorder, (2) Asperger's disorder, (3) Rett's disorder, (4) childhood disintegrative disorder, and (5) pervasive developmental disorder-not otherwise specified (PDD-NOS). Autistic disorder was diagnosed in the presence of qualitative impairment in social interaction and communication, along with presence of restrictive, repetitive patterns of behaviors, interests or activities. The term high functioning autism was often used for children with autistic disorder who have normal intelligence. Asperger's disorder was said to be present when there is qualitative impairment in social interaction with presence of restrictive, repetitive patterns of behaviors, interests or activities, but grossly normal speech. Childhood disintegrative disorder was characterized by normal development till 2–10 years of age followed by marked regression in multiple areas of functioning.

One of the main concerns with the use of DSM-IV was the significant variation in the diagnostic labels being given amongst autistic disorder/high functioning autism, Asperger's disorder and PDD-NOS because of the overlap in symptoms and change in them over time. In DSM-5, the term *autism spectrum disorder* has replaced *pervasive developmental disorders* and there are no diagnostic categories within this disorder.

## EPIDEMIOLOGY

The currently available epidemiological data is based on diagnostic categories in DSM-IV. The estimated global prevalence of all pervasive developmental disorders is 62/10,000 with the range of 1–189/10,000. The same for autistic disorder is 17/10,000 with the range of 2.8–94/10,000. The male preponderance of autistic disorder is well known with the male to female ratio of 4:1.

There have been concerns about the rising prevalence of autism spectrum disorders. Though, some vaccines and environmental toxicants have been implicated, it is more likely to be due to expanded diagnostic criteria, increasing awareness of this condition and improved facilities for diagnosis.

## NEUROPATHOLOGY

During 1st year of life, a significant proportion of children with autism may show increased rate of head growth. However, only small percentage of children with ASD actually becomes macrocephalic. On neuroimaging, the brain overgrowth is most prominent in the frontal lobes, anterior temporal regions and may involve interconnected parietal areas, key areas responsible for language and social cognition.

Functional magnetic resonance imaging (fMRI) studies have found reduced size of the corpus callosum and reduced functional and structural connectivity between frontal and temporal regions as well as between cerebellum and other brain regions. An emerging theory is that short-range connections may be overgrown, whereas longer-range connections between different brain regions are reduced.

## ETIOLOGY

Autism spectrum disorder is considered to be a genetic disorder. Monozygotic twin concordance rate of autistic disorder is as high as 73–95%, with the sibling recurrence rate of 5–6% (much higher than the risk in general population). An association has been found between increasing parental age and increased risk, especially of *ASD with intellectual disability* and in females with nonfamilial ASD. This could be because of de novo mutations or epigenetic alterations in the germ cells, with increasing age. Fetal exposure to valproate is another important risk factor of ASD.

Around 10% cases of ASD are due to known genetic syndrome (*syndromic* autism) and are typically associated with dysmorphic features and/or congenital anomalies. The well-known syndrome in this group include fragile X syndrome, tuberous sclerosis, neurofibromatosis, untreated phenylketonuria, Angelman syndrome, Cornelia de Lange syndrome and Down syndrome. Syndromic autism shows equal male:female ratio.

New techniques like array comparative genomic hybridization (CGH), whole exome and whole genome sequencing have significantly contributed to our understanding of genetics of ASD; however genetic aberrations are identified in up to 10% of nonsyndromic cases. Array CGH studies have shown increased frequency of copy number variants (CNV) in ASD population as compared to controls (6–10% vs. 1–3%, respectively). However, the location of CNV and its functional relevance is more important than their mean number and size. Mutations in certain genes have also been linked to ASD including synaptic genes (neuroligins, *SHANK* and *neurexins*), morphogenetic and growth-regulating genes (*HOXA1*, *PTEN*, *EIF4E*), and calcium-related genes (*CACNA1C*, *CACNA1F*, *KCNMA1* and *SCN2A*).

## CLINICAL FEATURES

There is a wide heterogeneity in clinical expression of ASD and goes with the saying that “if you know one person with autism, you know only one person with autism.” The DSM-5 has described the core clinical features of ASD under two domains: deficits in social communication and social interaction; and presence of restricted, repetitive patterns of behavior, interests, or activities.

### Deficits in Social Communication and Social Interaction

Deficits in social communication and social interaction would manifest with the following symptoms:

- Deficits in social-emotional reciprocity
- Deficits in nonverbal communication used for social interaction
- Deficits in developing, maintaining and understanding relationships.

### Deficits in Social-Emotional Reciprocity

These can manifest as impaired sharing of interests, emotions and affect. This is one of the earliest deficits noted in ASD. Normal infants develop a behavior known as *joint attention*, by which they enjoy and share an event or object with other person by looking back and forth between the object and the person. This is impaired in ASD. There is also reduced or lack of imitation of other's behavior. Children with ASD often do not look or focus,

when shown an interesting object or event. They may lack or have delayed development of *protodeclarative pointing*. This refers to pointing at objects/events for the purpose of sharing interest like showing a flying kite, bird, dog, etc. This should be differentiated from *protoimperative pointing* that refers to pointing of objects for the purpose of getting the objects. Protoimperative pointing is part of nonverbal communication and is often also lacking in children with ASD. Similarly, these children may not show newly acquired toy/clothes to their family members or show a reward that he/she has received in school. Though, these behaviors may be exhibited later in life because of training or insistence by the family members. *Inability to share emotions and affect* manifests as decreased awareness or complete insensitivity to other people's emotions (sadness, happiness, etc.). They may also not like themselves to be calmed or comforted when in pain/distress. These children may laugh or cry without any apparent reason.

These children also have abnormality in social approach and may fail to initiate or respond to social interactions of other people. Abnormal social approach may manifest as going and talking to absolute strangers or pushing/pinching other people for interaction. The child may straightaway sit in the lap of a stranger or ask for things. On the other hand, some children with ASD are very clingy to their parent. Also, these children do not use social gestures like *namaste*, *salam*, *bye-bye*, etc. appropriately, though they may use them on prodding by the parent. They may also not initiate or respond to social smiles.

There is also failure of normal back and forth conversation. The child may not respond to his name when called or when directly spoken to. Verbal children with ASD may not initiate conversation on their own and it may be limited to answering the questions being asked. Those with good conversational skills may frequently deviate from the topic or may only talk about a particular topic of their interest.

### Deficits in Nonverbal Communication for Social Interaction

There is poor integration of verbal and nonverbal communication. Thus they may be saying something but their facial expressions and body language may imply something else. There is abnormality in eye contact, which may be inappropriate for the social situation. Some children may even show *gaze avoidance*, i.e., when a person tries to look in to their eyes, they will look the other way. Poor eye contact is considered to be cardinal feature of ASD, however many children with ASD have good eye contact or may even stare at people. Facial expressions are often limited. They may have expressionless face or may have same expression for example *smiling all the time*. Expressions of sadness, shyness, fear, etc. may be reduced or lacking.

Deficits in nonverbal communication may also manifest as deficits in understanding and use of gestures. They often do not point for objects with their index finger, a milestone that usually develops by end of first year. Understanding and use of other gestures like that for *yes*, *no*, *come*, *go*, *give*, etc. are also delayed or absent. Some children may show abnormal forms of nonverbal communications like pointing with the whole hand, or pointing using hand of an adult (hand over hand pointing).

Besides problems in nonverbal communication, speech is also often delayed in children with ASD, in fact, many may not acquire any speech at all. Delay in speech is often the presenting symptom in preschool children with ASD, though it is not a diagnostic feature in DSM-5.

### Deficits in Developing, Maintaining and Understanding Relationships

These manifest as difficulties in sharing imaginative play or making friends. Typically growing children of about 2 years of age develop pretend or imaginative plays like feeding a doll, making her sleep, combing her hair, copying her mother or pretending to talk on

phone. There is subtle sharing of this play with people around by looking at them to see if they are watching them and exchanging smiles with them. They may also bring over the toys to other people and ask them to join in. In next 1 year this play becomes more complex like going on a picnic, animal party, tea party, etc. which would usually have other people as partners in the game. Children with ASD often do not develop these behaviors. Some may have one or two types of imaginative play, but lack variety and there is also not much sharing. They often have difficulty in making friends, when they do, they often lack concept of friendship. They may become friends with much older kids, whom they keep following or very young kids, when they become the leaders. Some children with ASD may not show any interest in peers at all.

These children also have difficulties adjusting the behaviors to suit social contexts. Thus a child may not modify his behavior in classroom, library, other people's house or doctor's clinic vis-à-vis their home. They may not understand social cues from others and may suddenly butt in others conversation, not really knowing when to join in.

### Restricted, Repetitive Patterns of Behavior, Interests, or Activities

These may manifest as following:

- Stereotyped or repetitive motor movements, use of objects, or speech
- Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal/nonverbal behavior
- Highly restricted, fixated interests that are abnormal in intensity or focus
- Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment.

#### Stereotyped or Repetitive Motor Movements

Children with autism can have stereotyped or repetitive motor movements, use of objects or speech. They may have motor stereotypies in form of hand flapping, head banging, going in circles, spinning or walking on toes. There may be excessive stereotypic use of objects in form of lining of objects or toys, spinning of wheels of cars or stacking of utensils. Children may have stereotypic or repetitive speech in form of echolalia, pronoun reversal or idiosyncratic phrases. Echolalia refers to repetition of words or phrases. This repetition may be immediately on hearing something or may be delayed. In some children, the whole speech may consist of only echolalia, with the child repeating everything that he has heard before or seen on television. There may be pronoun reversal with child refereeing to himself as *you* or by his name instead of *I* or *me*.

#### Insistence on Sameness

There may be insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal/nonverbal behavior. The child may always insist on wearing a particular cloth or a particular color of cloth or particular pattern of clothes. This may also manifest as feeding problems. He may always insist on taking a particular way to the school. The child may get upset with the minor changes in the house or even in the way his/her mother is dressed. They may become very rigid about their daily routines and may throw tantrums or point blank refuse any change in the routine. Ritualized patterns may manifest as food being always served in a particular sequence. An older child may enter his house in a particular sequence of *steps followed by jumping*, etc. Ritualized nonverbal behavior can manifest as a particular sequence of *high-five followed by hand shaking* on meeting anybody while ritualized verbal behaviors may manifest as repetitive questioning about same thing.



### *Highly Restricted, Fixated Interests*

They may have highly restricted, fixated interests that are abnormal in intensity or focus. They may spend whole day playing with a piece of paper or pens, or collecting coins or stones or toffee wrappers. Older children with ASD may be preoccupied with a puzzle or cartoon character or may show fascination with certain letters, characters, logos, signages or train schedules. ASD children with good cognition may spend weeks studying narrow topics like robots, fishes, etc.

### *Hyper- or Hyporeactivity to Sensory Inputs*

They may have hyper- or hyporeactivity to sensory inputs or unusual interests in sensory aspect of the environment. Pain and temperature insensitivity is quite common in children with ASD. They may not show any response to a truly painful stimulus like a burn or laceration. On contrary, some children may cry incessantly after minor pain. They are often hypersensitive to certain loud sounds like that of pressure cooker, horns, but may not respond to human sounds. Some children with ASD will have excessive smelling and may smell unusual objects like books or toys. Few will even smell people around them. Some may not even tolerate usual environmental smells. They may also show visual fascination with mirrors, flashing lights, shadows or moving objects like pendulum. Some may show repeated visually scanning of their hands.

### **Other Associated Symptoms**

Beside the core symptoms described earlier, a number of other symptoms and comorbidities are present in children with ASD.

Behavior problems are quite common in children with ASD. Hyperactivity is a common presenting symptom and often a diagnosis of only attention deficit hyperactivity disorder is made, without symptoms of ASD being recognized. On contrary, some children with ASD are lethargic and may not move around much. Other common behavior problems are temper tantrums, self-injurious behaviors, aggression and irritability. Temper tantrums are often the result of unmet needs due to their inability to communicate. Self-injurious behaviors can be in form of hand biting, skin picking, head banging, or eye poking. Few children are also aggressive towards the family members or peers. Persistent irritability/crying is another common behavior problem, especially in low functioning children with ASD. These behavioral problems often lead to stress among the caregivers and also interfere with the intervention programs.

Children with ASD show a spectrum of intellectual functioning ranging from profound intellectual disability to superior intelligence. About three-fourths of children with Autism have global developmental delay or intellectual disability.

Epilepsy is another common comorbidity of ASD. Around 25% children with ASD have epilepsy. The onset of epilepsy in autism has two peaks: first before 5 years of age and another in adolescence. The type of seizures and the response to treatment are almost same as in general population. On electroencephalography (EEG), epileptiform discharges are commonly seen in those without clinical seizures, however their significance is not well understood and they do not require any treatment.

Sleep problems are present in more than 50% children with ASD. They often have frequent awakenings at night, delayed sleep time, prolonged sleep latency and early wake up time. Overall, the total sleep time is reduced in these children, however some children with ASD may sleep excessively also.

Often children with ASD show unawareness of dangers like that of height, fire or stray animals. Others demonstrate excessive fear to certain harmless objects or stimuli like soft toys, some particular people or images.

Older children with ASD may show psychiatric comorbidities like depression, low self esteem, anxiety, etc.

Occasionally children with ASD have some extraordinary skills, referred to as savant skills. They may be exceptionally good at arts, spellings, calculations or music. This is often related to their restricted interests.

### **Patterns of Onset and Early Symptoms**

There are three patterns of onset of ASD. Most of the children with ASD have symptoms from early infancy with impairments in typically seen social behaviors and communicative intent. Some children with ASD develop normally till 9–12 months of age after which the social and communication development ceases and typical features of ASD manifest. Others (around 15–25%) develop normally till about 15–18 months of age after which they show gradual regression of social and communicative milestones. These children may have started speaking few words with meanings, enjoying social play like peek-a-boo and started pointing. Subsequently regression occurs with gradual loss of speech and development of poor eye contact, social aloofness, and motor stereotypes. Many of these children with apparently normal development prior to regression actually have mild delay in social milestones from the beginning.

The symptoms of ASD seen in infancy include poor social smile and vocalization, decreased interest in people, poor eye contact, decreased response to their names, absence of stranger anxiety and poor imitation. In second and third year of life, most of the children present with delayed speech, hyperactivity or severe tantrums. They may also have poor eye contact, preference for aloofness, decreased interest in peers, poor response to being called and motor stereotypes.

### **DIFFERENTIAL DIAGNOSIS**

#### **Global Developmental Delay/Intellectual Disability**

As this is a common comorbidity in ASD, it is often difficult to differentiate it from global developmental delay (GDD)/intellectual disability without ASD, especially when the GDD/intellectual disability is in severe range. The diagnosis of ASD is considered in these circumstances when the delay in social and language domains is more than other domains and features typical of ASD are present like poor eye contact/gaze avoidance, poor listening response, social aloofness, poor use of gestures or presence of atypical gestures like *hand over hand pointing*.

#### **Attention Deficit Hyperactivity Disorder**

This is an important differential diagnosis of ASD because hyperactivity and attention problems are seen in both the conditions. Children with attention deficit hyperactivity disorder (ADHD) may manifest fleeting eye contact, because of problems in attention and poor relationship with family members and peers because of impulsivity or frequent fights but not due to lack of social interest. During assessment in one-is-to-one setting, hyperactivity and the attention problems are usually not manifest in children with ADHD. However, children with ASD are hyperactive even in the doctor's office because of impaired awareness of social context. They also show other characteristic features of ASD.

#### **Expressive Language Disorder**

This condition is quite common and presents with speech delay. However, their receptive speech, nonverbal communication and social skills are normal.

#### **Hearing Impairment**

Children with hearing impairment also present with speech delay, however their nonverbal communication and social skills are appropriate for age.

## Vision Impairment

Visual impairment results in poor eye contact. These children may also have impaired peer interaction, self-stimulatory behaviors and impaired gesture use.

## Social (Pragmatic) Communication Disorder

This is a new disorder described in DSM-5. Children with impairment in only social communication and social interaction, in the absence of repetitive or restricted pattern of behaviors or interests are given this diagnosis. As per DSM-IV, children with this symptomatology were diagnosed as PDD-NOS.

## Rett Syndrome

Rett syndrome was included in pervasive developmental disorders in DSM-IV, however this has been excluded in DSM-5, as it is now considered a neurodegenerative disorder. Females with Rett syndrome often fulfill the diagnostic criteria for ASD till preschool age group. Subsequently most of the children show improvement in their social skills and may no longer meet the criteria for ASD.

## Schizophrenia

Childhood schizophrenia is quite a rare entity, usually manifesting after 10 years of age. It can also present with impaired social interaction, problems in speech and some atypical interests and may be confused with ASD. However, there is always a period of normal development before the onset of symptoms and hallucinations and delusions are characteristically present.

## Selective Mutism

These children have normal speech but do not speak in particular situations or contexts.

## SCREENING AND EARLY DIAGNOSIS

Early diagnosis and early intervention in ASD provides the best outcome. There are certain clinical clues that can raise a suspicion in a young child. These red flag signs are:

- No big smiles or other warm, joyful expressions by 6 months or thereafter
- No back-and-forth sharing of sounds, smiles, or other facial expressions by nine months or thereafter
- No babbling by 12 months
- No back-and-forth gestures, such as pointing, showing, reaching, or waving by 12 months
- No words by 16 months
- No two-word meaningful phrases (without imitating or repeating) by 24 months
- Any loss of speech or babbling or social skills at any age.

Screening for ASD using a tool is more objective way of assessment. The American Academy of Pediatrics recommends routine use of ASD specific screening tool at 18 and 24 months of age. Various ASD specific screening tools have been developed and are used widely. A child who fails on a screening tool needs detailed diagnostic evaluation. Like all screening tools, these tools also have false negatives and false positives results.

Modified checklist for autism in toddlers (MCHAT) is the most widely used screening tool. It is designed for toddlers in the age group of 18–30 months; however it can be used as early as 15 months of age. It is modification of checklist for autism in toddlers (CHAT) and consists of 23 yes/no questions, to be completed by the parents. A child who fails on any 3 items or 2 critical items (out of the 6 critical items) needs further evaluation. MCHAT includes a follow up parental interview that increases the positive predictive value of the instrument. MCHAT has been translated in various languages including some Indian languages and is available freely.

Other screening tools that can be used in toddlers includes the Screening Tool for Autism in Two-Year-Old (STAT), Infant Toddler Checklist, The Developmental Behavior Checklist-Early Screen

(DBS-ES), Checklist for Early Signs of Developmental Disorders (CESDD) and Early Screening of Autistic Traits (ESAT).

Social communication questionnaire (SCQ), previously known as the Autism Screening Questionnaire is a good tool for children above 4 years of age. It is a parent report tool comprising of 40 yes/no questions derived from Autism Diagnostic Interview-Revised (ADI-R). There are two forms; one for less than 6-year-old and other for those above 6 years. It takes less than 10 minutes to complete and less than 5 minutes to score. The Autism Spectrum Screening Questionnaire (ASSQ) and Social Responsiveness Scale (SRS) are other tools that can be used in older age group.

## DIAGNOSTIC ASSESSMENTS

As there is no biological test for ASD, the diagnosis is based on the constellation of clinical features. The most recent diagnostic criteria have been laid down in DSM-5 by American Psychiatric Association (Available at <http://www.psych.org/practice/dsm>).

While evaluating a child with suspected ASD, a detailed history is elicited from the caregivers including their current concerns and also that of other manifestations present in ASD. Emphasis is laid on the early development of social behaviors and communication skills. Other important histories include that of associated problems or comorbidities, birth history, family history and developmental history pertaining to all developmental domains.

A general physical and neurological examination is performed. A detailed observation of the child is performed for his behavior and interaction with parents, peers, strangers and the examiners. The play of the child with various toys/objects, eye contact, speech and gesture use is also observed.

The DSM criteria does not give cut-offs for any of the behaviors, thus various objective tests have been developed to facilitate the diagnostic process. Amongst these tools, Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) are considered as gold standard for research purposes. ADI-R is standard semistructured interview that is administered to the caregiver by a trained administrator. It consists of 93 questions and is suitable for children above the mental age of 18 months. ADI-R has a sensitivity of around 77% and specificity of around 63% in diagnosing Autism.

Autism Diagnostic Observation Schedule (ADOS) is a semi-structured, direct observational assessment. ADOS consist of four separate modules. An individual is evaluated on any one module based on his age, language and developmental level. In each module, a protocol of activities or social presses is administered in approximately 45 minutes and each item is scored on 4-point scale. Wide range of ASD specific characteristics like joint attention, nonverbal communication and conversational skills are assessed. ADOS has a sensitivity of around 91% and specificity of around 65% in diagnosing Autism.

Childhood Autism Rating Scale (CARS) is another tool that can be used for screening or diagnosis. The current edition (CARS-2) consists of two 15-item behavior rating scales and a questionnaire for parents or caregivers. The second 15-item rating scale was introduced later in CARS-2 and has to be administered only if high functioning ASD is suspected. CARS can be used for children of 2 years of age or above and involves parental interview and direct observation of the child. The 14 items incorporated in CARS are rated on Likert scale of 1–4. A score between 30 and 36.5 is considered indicative of a mild to moderate autistic disorder and a score of 37 or higher is indicative of severe autistic behavior. CARS has a sensitivity of around 70% and specificity of 75% in diagnosing Autism. A score of 25.5 or above has been found to have good sensitivity and specificity for diagnosing ASD.

## COMPLIMENTARY ASSESSMENTS

Assessment for cognitive functioning, adaptive functioning, maladaptive behaviors, and developmental level of speech is an integral part of assessment and helps in designing the intervention program for these children. Assessment of cognition is quite difficult

in children with ASD as there are deficits in verbal and nonverbal communication, often accompanied by behavior problems. Nonverbal intelligence scales like Mullen's scale and Leiter's scale are often useful. Vineland adaptive behavior scale (VABS) or Vineland social maturity scale (VSMS) is used to assess adaptive functioning. VABS can also assess for maladaptive behaviors. Evaluation by a speech therapist is required for assessment of receptive and expressive level of speech, nonverbal communication and presence of stereotypic or idiosyncratic use of language. Audiological evaluation should also be done in all children.

## ETIOLOGICAL EVALUATION

Diagnostic testing can identify an etiology in less than one-fourth of cases. The testing can be in form of genetic testing, neuroimaging, EEG and metabolic testing. American Academy of Pediatrics have given recommendations for testing, however the degree of evaluation depends on the available resources. Comparative genomic hybridization (CGH) or high resolution karyotyping can be offered to children with ASD, especially those with intellectual disability. These children should also be tested for fragile-X syndrome. Genetic testing for Rett syndrome (*MECP2* gene mutation) should be done based on clinical suspicion. Magnetic resonance imaging should be considered in children with regression, microcephaly, midline facial defect, neurocutaneous stigmata or abnormalities on neurological examination. EEG should be considered in presence of clinical seizures, unexplained behavior change, and presence of regression. Metabolic testing should only be considered in children with features suggestive of inborn errors of metabolism.

## MANAGEMENT

Educational intervention therapy is the mainstay of treatment for children with ASD. Over the years, many different techniques of educational intervention therapies have evolved. Out of these, programs based on Applied Behavior Analysis (ABA) are the most evidence based and practiced. Other widely known techniques are Treatment and Education of Autistic and Related Communication-Handicapped Children (TEACCH), and Pivotal response treatment (PRT). The intervention program should have some essential components as shown in **Box 1**.

### BOX 1 Essential components of an intervention program

- Start the intervention program as soon as the diagnosis is made
- It should be comprehensive addressing communication, socialization, and adaptive behaviors
- It should be individualized and be intensive, to be delivered on a daily basis (American Academy of Pediatrics recommends at least 25 hours of therapy per week)
- It should be either in one-to-one setting or involving small groups
- Parental training and involvement should also be an integral component of the program.

Applied Behavior Analysis (ABA) is based on the principle of *functional behavior analysis*. Thus, all the behaviors (actions) of the child are analyzed in detail regarding their antecedents and the consequences, for determining the function of each behavior. After this analysis, the intervention program is designed to increase or decrease any particular behavior by modifying the antecedents or consequences. The program is delivered at high intensity by a teacher in one-to-one setting.

PRT is treatment based on ABA but the treatment is delivered in natural setting of the child and the teaching/learning process is initiated by the child, with the teachers following the cues of the child.

TEACCH is a classroom based program, with essential component of structuring the environment and physical activities. Structuring environment involves organization of physical space

and predictable sequence of activities. Classroom teaching is done using visual schedules to guide the child for doing activities, which are determined by the likes of the child.

Early Start Denver Model (ESDM) is a recently launched eclectic behavior program that tries to follow the normal development of a child to deliver interventions in a naturalistic play based setting, using principles of ABA. It is designed for young children with ASD till 60 months of age. This model has shown substantial benefits in well designed research.

## Pharmacological Management

Presently, there is no drug that addresses the core deficits of social interaction and communication in children with ASD, however pharmacotherapy has a definite role in management of associated symptoms like maladaptive behaviors, repetitive movements and sleep problems. These comorbid symptoms often limit the functional abilities of the child and interfere with implementation of the early behavioral intervention program.

Maladaptive behaviors like aggression including self directed aggression, irritability, temper tantrums and hyperactivity are common targets of pharmacotherapy. Psychotropic drugs like haloperidol, risperidone, olanzapine and aripiprazole have shown moderate to large short-term benefits in controlling these behaviors. Risperidone, an atypical antipsychotic drug has been most widely studied in children with ASD. The drug is usually started in dose of 0.5 mg at night time with addition of morning dose subsequently. Increments are usually done every 3rd day by 0.5 mg/day, till the desirable effect is achieved to a maximum dose of 3.5 mg/day or significant side effects occur. Drowsiness and weight gain are the most commonly reported side effects. Other side effects are QTc prolongation, dyslipidemia, hyperprolactinemia, extrapyramidal symptoms, etc. Haloperidol, although as effective as risperidone, is less often used because of the extrapyramidal side effects. Aripiprazole is another atypical antipsychotic for treating irritability in children aged 6–17 years with ASD. It is associated with lesser weight gain and decreased risk of hyperprolactinemia. It is generally used when risperidone is not effective or not tolerated. The therapeutic dose ranges from 5 mg/day to 15 mg/day.

Methylphenidate and atomoxetine can also be used for management of inattention, impulsivity and hyperactivity symptoms in children with ASD, though the benefits are moderate. Selective serotonin reuptake inhibitors like Fluoxetine has been used in management of anxiety and depression in adolescents and adults with ASD. Sleep problems is another comorbidity that can be managed using Melatonin, however it has moderate effect in reducing sleep latency and night-time awakenings and increasing total sleep duration. It is used in dosages of 1–10 mg/day, 30 minutes before the bedtime. Other drugs used in management of sleep problems include Risperidone, Mirtazapine and Clonidine.

## LONG-TERM OUTCOME

Although there is a great heterogeneity in the gains in children with ASD, with early intensive therapy there is significant improvement in socialization and communication domains till 6 years of age, when almost 10% of children may outgrow their condition. Subsequently, there is relative flattening in gains though repetitive and maladaptive behaviors continue to improve even in adolescents and adults. Despite this improvement, very few persons with ASD achieve high level of independence. The important prognostic factors are good cognition (intelligence quotient above 50), early language development, early diagnosis, early intensive behavior therapy and management using ABA. Socioeconomic factors also impact the prognosis.

The average life expectancy of persons with ASD is only about 3 years less than the general population, the mortality is mainly related to seizure disorder and intellectual disability. Adults with ASD also suffer from wide range of psychiatric comorbidities like anxiety, depression and obsessive compulsive disorders.

### IN A NUTSHELL

1. Autism spectrum disorder is characterized by persistent deficits in social communication and social interaction, and the presence of repetitive, restricted pattern of behaviors, interests and activities.
2. ASD has very high concordance rate amongst monozygotic twins and is considered to be a genetic disorder; however the genetic determinants are mostly unknown.
3. Common clinical features seen in children with ASD are speech delay, poor eye contact, poor use of gestures, social aloofness, impaired peer interaction and stereotypic body movements.
4. Children with ASD often have associated problems like intellectual disability, behavior problems, epilepsy, and sleep problems.
5. Early diagnosis and early intensive educational interventions is recommended for all children with ASD.
6. Modified checklist for autism in toddlers (MCHAT) is the most widely used screening tool in early age. Social communication questionnaire (SCQ) can be used for screening in older age groups.
7. Diagnosis is based on the criteria laid down in DSM-5 by American Psychiatry Association. Alternatively, tools like Autism Diagnostic Interview–Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS) and Childhood Autism Rating Scale can be used for diagnosis.
8. Pharmacological agents, mainly atypical antipsychotics are used to control maladaptive behaviors.

### MORE ON THIS TOPIC

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> edn. Arlington, VA: American Psychiatric Association; 2013.
- Geschwind DH. Advances in autism. *Annu Rev Med*. 2009;60:367-80.
- Johnson CP, Myers SM. American Academy of Pediatrics council on children with disabilities. Identification and evaluation of children with autism spectrum disorders. *Pediatrics*. 2007;120:1183-215.
- Myers SM, Johnson CP. American Academy of Pediatrics council on children with disabilities. Management of children with autism spectrum disorders. *Pediatrics*. 2007;120:1162-82.
- Ozonoff S, Heung K, Byrd R, Hansen R, Hertz-Picciotto I. The onset of autism: patterns of symptom emergence in the first years of life. *Autism Res*. 2008;1:320-8.
- Rosti RO, Sadek AA, Vaux KK, Gleeson JG. The genetic landscape of autism spectrum disorders. *Dev Med Child Neurol*. 2014;56:12-8.
- Volkmar FR, Paul R, Klin A, Cohen D. *Handbook of Autism and Pervasive Developmental Disorders*, 3<sup>rd</sup> ed. New York: John Wiley & Sons; 2005.
- Zwaigenbaum L, Bryson S, Lord C, et al. Clinical assessment and management of toddlers with suspected autism spectrum disorder: insights from studies of high-risk infants. *Pediatrics*. 2009;123:1383-91.



## Chapter 21.8

# Rett Syndrome

Monica Juneja, Rajni Khajuria

Rett syndrome (RTT) is a neurodevelopmental disorder primarily affecting females, but recently has also been found in few male patients. It is the second most common genetic cause of intellectual disability in girls, accounting for up to 10% of all cases, but is commonly misdiagnosed as autism, cerebral Palsy or Angelman syndrome due to the overlap of clinical features.

## EPIDEMIOLOGY

Rett syndrome is a pan ethnic disorder with worldwide incidence of approximately 1 in 10,000 to 1 in 15,000 live female births. It generally starts in children aged 6–18 months with neurodevelopmental arrest, but characteristic clinical features become evident by the age of 2–4 years. They usually survive into adulthood, but the incidence of sudden, unexplained death is significantly higher.

## ETIOPATHOGENESIS

Rett syndrome is a genetic disorder caused by mutations in methyl-CpG binding protein-2 (*MECP2*) gene, present on X chromosome. The *MECP2* gene has four exons and codes for the *MECP2* protein, which contains four significant domains including a *methyl binding domain* and a *transcription repression domain*. Functioning as a global transcriptional repressor, mutations in this gene produce loss of function of this protein and unregulated expression of the other genes that it normally represses. *MECP2* expression is ubiquitous throughout the body, but its expression in mature postmigratory neurons is of particular importance.

*MECP2* mutations, which are mostly sporadic, account for majority of mutations in classically affected females, suggesting that these mutations are the major cause of classical RTT. There are eight most common mutations (R106W, R133C, T158M, R168X, R255X, R270X, R294X and R306C) of *MECP2* gene that account for almost 70% of all mutations. The symptoms and severity of RTT may depend on both the percentage of activated defective genes and the type of mutation. In atypical RTT, the rate of *MECP2* mutation detection is lower, but a proportion of atypical RTT cases result from mutations in a different genes such as *CDKL5*, *NTNG1* and *FOXG1*.

In families with a child with RTT, the risk of having a second child with the RTT is reportedly less than 1%. However, recurrence in families can occur through mechanisms such as germline mosaicism.

## CLINICAL FEATURES

Rett syndrome can have a classical presentation or an atypical one. Girls with classical presentation have an uneventful pre-perinatal period with a normal head circumference at birth and no dysmorphic facies. First few months are grossly normal, with development of some speech and hand functions. Though decrease in head size may start from 4 months onward and there may be some subtle features, none are severe enough to raise concerns by the family or the pediatrician. This apparently normal period is followed after 6–18 months of age with *early onset stagnation phase* (stage 1) with delay in development of milestones, most obvious as delay in independent sitting, crawling or walking. It may last for few months or a year and is followed by stage 2.

The most characteristic period of *rapid destructive stage* (stage 2) is at age 1–4 years. The onset is usually heralded by sudden onset irritability marked by episodes of excessive crying, self injurious

behaviors, aggression toward others and decreased sleep. The girls develop autistic features with poor eye contact, solitary play and characteristic midline hand stereotypies (washing, clapping, tapping, wringing, hand mouthing, hair pulling, pin rolling, clenching, clapping), preceded by loss of purposeful fine motor skills. There is gait apraxia with ataxia and evolving spasticity of limbs, breathing abnormalities in the form of episodic hyperventilation, apnea, aerophagy and valsalva maneuver and development of seizures. Breathing abnormalities usually occur only during awake state.

This phase may last for few weeks to months and is followed by 3rd phase, *Pseudostationary stage*, starting from 2 years to 10 years of age. This stage is characterized by improvement in socialization, eye contact, nonverbal communication skills and some gain in gross motor milestones with achievement of locomotion. In fact, this improvement of skills or stabilization of symptoms helps in differentiating RTT from other neurodegenerative disorders. Sleep problems, GIT problems, compulsive hand stereotypies, breathing abnormalities and seizures however continue. Seizures may appear for the first time during this phase but stereotypies may decrease later. During this stage, RTT girls characteristically have a mask like facies but are very alert, smiling and communicate with their eyes.

Many girls may continue in this stage throughout their lives, but others progress to *fourth stage of late motor deterioration*, which is characterized by development of increased rigidity/parkinsonian features, dystonia, ataxia-tremors, scoliosis and worsening of mobility. Progressive scoliosis usually appears after 10 years of age, is believed to be neurogenic and is more marked in those with more severe developmental impairment.

Although most girls with RTT would survive till adulthood but there is increased risk of sudden death. The cause is unclear but may be related to seizures, autonomic dysfunction, or cardiac conduction abnormalities, e.g. long QT intervals and cardiac arrhythmias. The clinical features of atypical RTT are given in **Table 1**.

## DIAGNOSIS

The diagnosis of RTT is clinical as typical features of RTT may be seen in the absence of *MECP2* mutations and also because these mutations may be identifiable in other conditions as well. The diagnostic criteria of RTT have evolved over time and were revised recently in 2010 (**Table 2**). Although initially recognized only in girls, boys (most commonly males with X-chromosome aneuploidy), who meet the criteria for typical RTT have also been identified and are considered to have typical RTT. Acquired microcephaly is a distinctive clinical feature of RTT, but is not included as essential criteria in the revised criteria as it is not found in all individuals with typical RTT. However, because it can alert a clinician to this diagnosis, it has been included as a feature that should raise suspicion of RTT.

It is important to remember that regression is essential feature in all types of RTT (classical and atypical) and because many patients would regain skills later on, it is essential to very carefully take history of regression of speech and hand functions in suspected cases. Some RTT cases may not show regression till 5 years of age and in otherwise typical cases without regression prior to this age, a diagnosis of probable RTT may be made.

Genetic testing should be offered to all those patients who meet the clinical diagnostic criteria for RTT.

## Differential Diagnosis

### Stage I (Early Onset Stagnation)

Benign congenital hypotonia, cerebral palsy, Prader-Willi syndrome, Angelman syndrome and other metabolic disorders are important conditions to be considered during this phase.

**Table 1** Variants of Rett syndrome

<i>Preserved speech variant (Zappella variant)</i>	<i>Early seizure variant (Hanefeld variant)</i>	<i>Congenital variant (Rolando variant)</i>
<b>Clinical features</b> <ul style="list-style-type: none"> <li>Regression at 1–3 years, prolonged plateau phase</li> <li>Milder reduction of hand skills               <ul style="list-style-type: none"> <li>Better retained hand use</li> </ul> </li> <li>Recovery of language after regression               <ul style="list-style-type: none"> <li>Mean age of recovery is 5 years</li> </ul> </li> <li>Single words or phrases</li> <li>Milder intellectual disability (IQ up to 50)</li> <li>Autistic behaviors common</li> <li>Decreased frequency of typical RTT features               <ul style="list-style-type: none"> <li>Rare epilepsy</li> <li>Rare autonomic dysfunction</li> <li>Milder scoliosis and kyphosis</li> </ul> </li> <li>Normal head circumference</li> <li>Normal height and weight in most</li> </ul> <b>Molecular genetics</b> <ul style="list-style-type: none"> <li>Mutations in <i>MECP2</i> found in the majority of cases</li> </ul>	<b>Clinical features</b> <ul style="list-style-type: none"> <li>Early onset of seizures</li> <li>Before 5 months of life               <ul style="list-style-type: none"> <li>Infantile spasms</li> <li>Refractory myoclonic epilepsy seizure onset before regression</li> </ul> </li> <li>Decreased frequency of typical RTT features</li> </ul> <b>Molecular genetics</b> <ul style="list-style-type: none"> <li>Mutations in <i>MECP2</i> rarely found</li> <li>Analysis for mutations in <i>CDKL5</i> should be performed</li> </ul>	<b>Clinical features</b> <ul style="list-style-type: none"> <li>Grossly abnormal initial development               <ul style="list-style-type: none"> <li>Severe psychomotor delay</li> <li>Inability to walk</li> </ul> </li> <li>Severe postnatal microcephaly before 4 months</li> <li>Regression in the first 5 months</li> <li>Lack of typical intense RTT eye gaze</li> <li>Typical RTT autonomic abnormalities present               <ul style="list-style-type: none"> <li>Small cold hands and feet</li> <li>Peripheral-vasomotor disturbances</li> <li>Breathing abnormalities while awake</li> </ul> </li> <li>Specific movement abnormalities               <ul style="list-style-type: none"> <li>Tongue stereotypies</li> <li>Jerky movements of limbs</li> </ul> </li> </ul> <b>Molecular genetics</b> <ul style="list-style-type: none"> <li>Mutations in <i>MECP2</i> rarely found</li> <li>Analysis for mutations in <i>FOXG1</i> should be performed</li> </ul>

**Table 2** Revised diagnostic criteria for Rett syndrome (RTT)

<b>RTT diagnostic criteria 2010</b>
Consider diagnosis when postnatal deceleration of head growth observed
<b>Required for typical or classic RTT</b>
<ul style="list-style-type: none"> <li>A period of regression followed by recovery or stabilization</li> <li>All main criteria and all exclusion criteria</li> <li>Supportive criteria are not required, although often present in typical RTT</li> </ul>
<b>Required for atypical or variant RTT</b>
<ul style="list-style-type: none"> <li>A period of regression followed by recovery or stabilization</li> <li>At least 2 of the 4 main criteria</li> <li>5 out of 11 supportive criteria</li> </ul>
<b>Main criteria</b>
<ul style="list-style-type: none"> <li>Partial or complete loss of acquired purposeful hand skills</li> <li>Partial or complete loss of acquired spoken language</li> <li><i>Gait abnormalities</i>: Impaired (dyspraxia) or absence of ability</li> <li>Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms</li> </ul>
<b>Exclusion criteria for typical RTT</b>
<ul style="list-style-type: none"> <li>Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems</li> <li>Grossly abnormal psychomotor development in first 6 months of life</li> </ul>
<b>Supportive criteria for atypical RTT</b>
<ul style="list-style-type: none"> <li>Breathing disturbances when awake</li> <li>Bruxism when awake</li> <li>Impaired sleep pattern</li> <li>Abnormal muscle tone</li> <li>Peripheral vasomotor disturbances</li> <li>Scoliosis/kyphosis</li> <li>Growth retardation</li> <li>Small cold hands and feet</li> <li>Inappropriate laughing/screaming spells</li> <li>Diminished response to pain</li> <li>Intense eye communication—<i>eye pointing</i></li> </ul>

**Stage II (Rapid Destructive Stage)**

At this stage, RTT must be differentiated from autism spectrum disorders, tuberous sclerosis, metabolic disorders (e.g., phenylketonuria, ornithine transcarbamylase deficiency), infantile neuronal ceroid lipofuscinosis, Angelman syndrome,

or an infectious encephalopathy. Even though, ASD occurs predominantly in males and is much more common, RTT should be considered in girls with autism spectrum disorder (ASD), especially if there is history of regression. Girls with RTT not only have loss of communication and social skills but also lose motor skills, unlike girls with ASD in whom motor skills are usually preserved. Similarly, acquired microcephaly is common in RTT, whereas children with ASD usually have increased head growth in early infancy. Even though eye contact and socialization is poor in stage II, they both significantly improve later, in fact, eye gaze is commonly used for communication in RTT. Apart from this, presence of typical hand stereotypies, gait apraxia and breathing abnormalities are usually not seen in ASD.

**Stage III (Pseudostationary Stage)**

In stage III, RTT must be differentiated from ataxic cerebral palsy, spinocerebellar degeneration, leukodystrophies, neuroaxonal dystrophy, Lennox-Gastaut syndrome and Angelman syndrome as these share some similar features with RTT.

**Stage IV (Late Motor Deterioration)**

Degenerative disorders must be kept as differential diagnosis.

**MANAGEMENT**

There is no specific medical treatment for patients of RTT except symptomatic and supportive treatment. It is very important to do an EKG as soon as diagnosis of RTT is made. Apart from medications to treat seizures, hyperactivity, sleep problems and digestion or gastric problems, it is important to avoid drugs which will depress ventilation or prolong QT interval. Comprehensive management also includes physical rehabilitation, educational as well as psychosocial support and is best provided by a team. Physiotherapy, occupational therapy and adaptive technologies have been found effective in facilitating communication, maintaining hand function and locomotion. Progression of scoliosis and the ability to walk can be managed by intensive physical therapies. Adaptive equipments like braces and arm splints have also been found very effective.

Psychosocial support for families is an integral part of the holistic approach to management, and parent support groups offer immense practical day-to-day support to families.

### IN A NUTSHELL

1. Rett syndrome is a neurodevelopmental disorder usually seen in females but has also been diagnosed in some males. It is second commonest cause of intellectual disability in females.
2. Though mutations in *MECP2* gene have been identified as etiology of RTT, the diagnosis is clinical. Some atypical cases may have mutations in *CDKL5*, *NTNG1* and *FOXP1* genes. The common atypical variants are: (i) preserved speech variant, (ii) congenital variant and (iii) an early seizure variant.
3. Classical RTT follows a typical course with stage 1 of *early onset stagnation* from 6–18 months of age followed by the *rapid destructive stage* (stage 2), the *pseudostationary stage* and *late motor deterioration stage*.
4. The rapid destructive stage is the most characteristic period and is characterized by loss of purposeful hand movements followed by distinctive midline, compulsive hand stereotypies. There is also loss of motor, communication and social skills with poor eye contact and decreased interaction, gait ataxia, seizures, breathing problems and sleep problems. Bruxism is another stereotypy which is present in more than 80% of girls with RTT.
5. The improvement of social and motor skills during pseudo stationery stage helps in differentiating RTT from other neurodegenerative disorders.
6. Many girls with RTT reach adulthood but there is increased risk of sudden death, which may be due to seizure, cardiac arrhythmias or autonomic disturbances.
7. Treatment is symptomatic. It is essential to avoid drugs that depress respiration or prolong QT interval.

### MORE ON THIS TOPIC

- Ben Zeev Ghidoni B. Rett syndrome. *Child Adolesc Psychiatr Clin N Am*. 2007;16:723-43.
- Chapleau CA, Lane J, Pozzo-Miller L, Percy AK. Evaluation of current pharmacological treatment options in the management of Rett syndrome: from the present to future therapeutic alternatives. *Curr Clin Pharmacol*. 2013;8:358-69.
- Chahrour M, Zoghbi HY. The story of Rett syndrome: from clinic to neurobiology. *Neuron*. 2007;56:422-37.
- Hagberg B. Rett syndrome: long-term clinical follow-up experiences over four decades. *J Child Neurol*. 2005;20:722-7.
- Huppke P, Gartner J. Molecular diagnosis of Rett syndrome. *J Child Neurol*. 2005;20:732-6.
- Khajuria R, Gupta N, Sapra S et al. A novel *MECP2* change in an Indian boy with variant Rett phenotype and congenital blindness: implications for genetic counseling and prenatal diagnosis. *J Child Neurol*. 2011;26:209-13.
- Lotan M, Ben-Zeev B. Rett syndrome. A review with emphasis on clinical characteristics and intervention. *Scientific World Journal*. 2006;6:1517-41.
- Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol*. 2010;68:944-50.
- Percy AK. Rett Syndrome: from recognition to diagnosis to intervention. *Expert Rev Endocrinol Metab*. 2008;3:327-36.
- Weaving LS, Ellaway CJ, Gecz J, et al. Rett syndrome: clinical review and genetic update. *J Med Genet*. 2005;42:1-7.

## Chapter 21.9

# Attention Deficit Hyperactivity Disorder

Rajesh Sagar, Rohit Verma

Attention-deficit hyperactivity disorder (ADHD) is characterized by developmentally inappropriate motor hyperactivity, inattention and impulsiveness leading to impairment at home and school. Impairment in academic and social functioning along with skill deficits render such children to academic failures and social isolation leading to demoralization, poor self-esteem, delinquency and substance use.

Its inheritance is complex and is modulated by environmental factors with genetics playing a major role. Several gene variations involved with the regulation of dopamine, norepinephrine, and serotonin neurotransmission have been linked with ADHD. Cognitive and functional studies frequently indicate altered processing in ADHD with dysfunction of frontosubcortical networks of the brain.

The lack of an objective test makes the behavioral features and the resulting dysfunction as an important tool to diagnose the condition, which is complicated by the frequent presence of coexisting psychiatric disorders. Pharmacological treatment needs to be appended with psychosocial interventions, such as parent training and cognitive behavior therapy, for management.

## EPIDEMIOLOGY

Worldwide studies report prevalence of ADHD in children to be between 3% and 9%. The most common subtype is combined subtype with features of inattention and hyperactivity/impulsivity comprising 50–70% of all ADHD individuals. ADHD affects both genders with male to female ratio of up to 10:1 in clinics to 2–3:1 in epidemiological samples. Prevalence rates of ADHD in the Indian subcontinent vary from 5% to 15.5% with the male to female ratio ranging from 3 to 6.4:1. The Indian Council of Medical Research reported prevalence rate of hyperkinetic disorders to be 1.6% among children aged 4–16 years with higher rates in urban middle class (3.7%), than slum (1.2%) and rural areas (0.5%).

## ETIOLOGY

Attention-deficit hyperactivity disorder is highly heterogeneous and multifactorial in its etiology; proposed to be mediated by a combination of environmental and genetic factors. The genetic cause linking to dopamine deficit is considered to be the primary cause for ADHD and various acquired factors to be secondary.

## Environmental Factors

There have been numerous risk factors (Table 1) associated with ADHD but it is difficult to prove any casual association with any, many associations are linked retrospectively by reverse causation. Some of these risk factors may modify each other by gene-environment interactions.

## Genetic Factors

The mean heritability of ADHD is about 80% which suggests the role of nonheritable factors also in the etiology. Family studies have found two- to eight-fold higher rates of ADHD in affected families in comparison to their healthy unaffected relatives. Twin studies have observed higher concordance rates in monozygotic compared to dizygotic twins. Adoption studies report increased rates of ADHD in biological parents of ADHD adoptees in comparison to adoptive parents of the affected child and the parents of children without ADHD. Several genes regulating multiple neurotransmitters have been associated with ADHD (Table 2).

## PATHOGENESIS

### Neuropsychological Studies

An alteration in the corticostriatal circuitry has been implicated in ADHD. This circuit includes the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), the dorsal striatum (especially the caudate nucleus) and the thalamus, linking to the cerebellum. The DLPFC has role in response inhibition, working memory, planning and organizing behavior. The ACC apart from its role in cognition and motor control, govern the arousal/drive state. Dorsal striatum modulates responses and the cerebellum coordinates motor activities and attention.

Deficits have been shown in areas of vigilance-attention and executive functioning (EF) which mainly includes: response inhibition, nonverbal and verbal working memory, self-regulation of emotion and motivation, and reconstitution (Barkley model). Response inhibition delays and interrupts responses and controls interference for controlling verbal and motor impulses. The nonverbal and verbal working memories govern the capacity for reading comprehension and moral conduct. Working memories also provide the ability to control emotions along with the motivation and persistence necessary to meet goals. Analysis of experiences in order to synthesize new responses for achieving goal is undertaken by reconstitution. Deficit in executive functioning is not a universal finding in ADHD which have led to emergence of other hypothesis involving impairments in state regulation and delay aversion contributing to the neurobiological heterogeneity.

Delay aversion is based on reinforcement and extinction processes proposing that goal directed behavior requires recurrent and effective proximal reinforcers, lack of which can

**Table 1** Environmental determinants causing attention-deficit hyperactivity disorder (ADHD)

Maternal	Prenatal factors	Smoking, alcohol intake, drug use (e.g., cocaine)
	Perinatal factors	Stress in pregnancy, maternal health (obesity, anemia, and exanthema)
	Natal and postnatal factors	Bleeding in pregnancy, protracted/complicated delivery, breech delivery, prematurity/low birthweight/ intrauterine growth restriction, low Apgar score, hypoxic-ischemic encephalopathy, small head circumference
External	Childhood illnesses	Viral infections, meningitis, encephalitis, otitis media, anemia, cardiac disease, thyroid disease, epilepsy, autoimmune disorders and metabolic disorders
	Head injury	Particularly involving the frontal lobes
	Toxins and drugs	Organic pollutants, e.g., pesticides, polychlorinated biphenyls (PCBs), lead, arsenic, aluminum, mercury and cadmium
	Nutritional disorders	Food additives, food allergies, sucrose, gluten sensitivity, and fatty acid and iron deficiencies
	Psychosocial adversities	Low socioeconomic status, low parental education, excessive criticism, bullying and family discords



**Table 2** Genes implicated in attention-deficit hyperactivity disorder (ADHD)

Candidate genes	Catecholaminergic genes	7-repeat allele of dopamine D4 receptor gene ( <i>DRD4</i> ) variant, <i>DRD4*7</i> (most robust association), <i>DRD5</i> gene, dopamine transporter gene ( <i>DAT1</i> ; <i>SLC6A3</i> ) and genes encoding dopamine beta hydroxylase enzyme, monoamine oxidase A (MAO A), <i>DRD2/3</i> receptors, and catechol-O-methyl transferase (COMT) enzyme
	Nonadrenergic genes	Alpha-2A, 2C and 1C adrenergic receptors and norepinephrine transporter ( <i>SLC6A2</i> ) genes
	Serotonergic genes	Serotonergic receptors <i>HTR1B</i> and <i>HTR2A</i> , serotonin transporter (HTT, <i>SLC6A4</i> ) and tryptophan hydroxylase genes
	Other genes	Gene associated with synaptosomal-associated protein of 25kDa ( <i>SNAP25</i> ), cholinergic genes encoding $\alpha 4$ and $\alpha 7$ subunits of nicotinic acetylcholine receptors ( <i>CHRNA4</i> and <i>CHNRA7</i> ), genes encoding glutamate receptors and brain-derived neurotrophic factor
Single nucleotide polymorphism arrays	Genes concerned in cell division, cell adhesion, neuronal migration and neuronal plasticity	
Chromosomal anomalies	Chromosomal regions containing ADHD predisposing loci-5p, 6q, 7p, 11q, 12q, and 17p	
Genetic syndromes	Fragile X syndrome, tuberous sclerosis and microdeletion syndromes such as Smith, Magenis, and Velocardiofacial (VCFS; 22q11 microdeletion) syndromes (commonly seen in inattentive subtype)	
Copy number variants	Preliminary findings have associated these chromosomal structural variants with ADHD. Their overlap has been seen with autism and schizophrenia, further supporting the neurodevelopmental theory for ADHD	

lead to inattention and impulsivity. The dual pathway model (Sonuga-Barke model) suggests simultaneous involvement of both EF and delay aversion such that the children with ADHD demonstrate aversion to delay, preferring smaller, immediate rewards in comparison to larger, delayed rewards. The cognitive energetic model proposes that deficit in attention and EF is not due to impaired cognitive resources per se but rather ascribed to deficiencies in activation, arousal, and effort controlling the allocation of cognitive resources.

### Neurochemistry of ADHD

Dopaminergic neural circuits are suggested to play a major role in altered reward processing mechanism endorsed by ADHD. Other factors implicating dopamine hypothesis are: drugs (like methylphenidate) utilized in managing ADHD act on dopaminergic synapses; linkage of various dopamine transporter and receptor genes to ADHD; and changes in brain regions activated by dopamine in imaging studies.

### Neurophysiological Studies

Few electroencephalograph (EEG) studies report increased slow wave activity (predominantly theta) in frontal region whereas others have shown decreased delta and increased beta percent power over the left hemisphere, indicating both under-arousal and over-arousal in ADHD. Event related potential (ERP) showed smaller amplitude of P300 along with a longer latency in ADHD, a finding which lacks specificity. Stimulus processing research has showed deficits in early as well as later processing.

### Structural Neuroimaging

Decrease in overall total brain size is the most consistent finding being reported. Magnetic resonance imaging (MRI) studies report of decreased right prefrontal cortex volume, reversal or loss of asymmetry of caudate nucleus volume (usually right caudate nucleus is larger than the left), lack of age-related decrease in caudate volume (usually caudate nucleus volume decreases with age in males), smaller size of globus pallidus, and decreased volume of corpus callosum. Cerebellar volume differences have also been observed.

### Functional Neuroimaging

There is evidence of decreased striatal blood flow and hypofrontality, which annul on initiating methylphenidate (MPH)

in some studies. Positron emission tomography (PET) scans associate ADHD with an abnormality in frontostriatal circuitry. Functional MRI (fMRI) studies suggest a primary dysfunction of dorsal anterior cingulate cortex (dACC), which is associated with perigenual anterior cingulate cortex (pACC) hyperactivity. Magnetic resonance spectroscopy (MRS) studies reported depletion of N-acetyl aspartate (NAA), a marker of neuronal integrity, in left DLPFC and also decreased striatal glutamate and lower NAA/creatine ratio in globus pallidus.

Both the functional and structural studies are consistent with each other in attributing frontosubcortical system in the pathophysiology of ADHD.

### NOSOLOGY AND DIAGNOSIS

Earliest description of behavioral abnormalities similar to ADHD was reported as squeal to head injury and postinfluenza encephalitis. Since then the disorder has traversed changes in its conceptualization reflected in the changing terminology, from “minimal brain dysfunction” to “hyperkinetic reaction of childhood” to “ADHD” in Diagnostic and Statistical Manual (DSM) editions and “hyperactive disorder” in International Classification of Diseases (ICD) (Table 3).

The DSM-5 suggests three presentations of ADHD: (1) combined, (2) predominantly inattentive, (3) predominantly hyperactive-impulsive; while ICD-10 hyperkinetic disorder requires both inattentive and hyperactive-impulsive behavior to formulate a diagnosis, thereby suggesting only the combined type of DSM-5 ADHD. Thus, DSM-5 identifies a broader group of children than ICD-10. DSM-5 suggests that several symptoms must be present prior to age 12 years, in comparison to 7 years as the age of onset in previous versions of DSM and ICD-10.

DSM-5 specifies the severity of disorder as mild, moderate or severe. There is also provision in DSM-5 for a diagnosis of ADHD in partial remission for grown up individuals with functional impairment, even when the required symptoms may not be all present.

### CLINICAL FEATURES

The core symptoms of ADHD are hyperactivity, impulsivity and inattention. While teachers usually complain of creating nuisance in the classrooms and deterioration of academic performance, parents report a lack of interest in activities requiring sustained

**Table 3** Tenth revised edition of International Classification of Diseases (ICD-10) criteria for hyperkinetic disorders

The research diagnosis of hyperkinetic disorder requires the definite presence of abnormal levels of inattention, hyperactivity, and restlessness that are pervasive across situations and persistent over time and that are not caused by other disorders such as autism or affective disorders.

**G1. Inattention.** At least six of the following symptoms of inattention have persisted for at least 6 months, to a degree that is maladaptive and inconsistent with the developmental level of the child:

- Often fails to give close attention to details, or makes careless errors in schoolwork, work, or other activities
- Often fails to sustain attention in tasks or play activities
- Often appears not to listen to what is being said to him or her
- Often fails to follow through on instructions or to finish schoolwork, chores, or duties in the workplace (not because of oppositional behavior or failure to understand instructions)
- Is often impaired in organizing tasks and activities
- Often avoids or strongly dislikes tasks, such as homework, that require sustained mental effort
- Often loses things necessary for certain tasks or activities, such as school assignments, pencils, books, toys, or tools
- Is often easily distracted by external stimuli
- Is often forgetful in the course of daily activities.

**G2. Hyperactivity.** At least three of the following symptoms of hyperactivity have persisted for at least 6 months, to a degree that is maladaptive and inconsistent with the developmental level of the child:

- Often fidgets with hands or feet or squirms on seat
- Leaves seat in classroom or in other situations in which remaining seated is expected
- Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, only feelings of restlessness may be present)
- Is often unduly noisy in playing or has difficulty in engaging quietly in leisure activities
- Exhibits a persistent pattern of excessive motor activity that is not substantially modified by social context or demands.

**G3. Impulsivity.** At least one of the following symptoms of impulsivity has persisted for at least 6 months, to a degree that is maladaptive and inconsistent with the developmental level of the child:

- Often blurts out answers before questions have been completed
- Often fails to wait in lines or await turns in games or group situations
- Often interrupts or intrudes on others (e.g., butts into others' conversations or games)
- Often talks excessively without appropriate response to social constraints.

**G4.** Onset of the disorder is no later than the age of 7 years.

**G5. Pervasiveness.** The criteria should be met for more than a single situation, e.g., the combination of inattention and hyperactivity should be present both at home and at school, or at both school and another setting where children are observed, such as a clinic.

**G6.** The symptoms in G1–G3 cause clinically significant distress or impairment in social, academic, or occupational functioning.

**G7.** The disorder does not meet the criteria for pervasive developmental disorder, mania, depressive, or anxiety disorder.

Specify if:

**Disturbance of activity and attention:** The general criteria for hyperkinetic disorder must be met, but not those for conduct disorders.

**Hyperkinetic conduct disorder:** Both the general criteria for hyperkinetic disorder and conduct disorder must be met.

**Other hyperkinetic disorders**

*Hyperkinetic disorder, unspecified:* This residual category is not recommended and should be used only when there is a lack of differentiation between disturbance of activity and attention and hyperkinetic conduct disorder but the overall criteria for hyperkinetic disorders are fulfilled.

Source: World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. World Health Organization, Geneva, 1993.

effort or child being constantly “out of control”. The symptoms suggestive of the disorder need to be present in two or more setting (at home, at school, during play, in social gatherings, etc.); present for at least 6 months; and must be severe enough to interfere with functioning in various settings.

### Symptoms of Hyperactivity

- Excessive fidgetiness (e.g., tapping hands or feet, squirming in seat)
- Difficulty remaining still when sitting is expected (e.g., at dinner, school, etc.)
- Excessive talking, difficulty playing quietly
- Run around a lot, always “on the go”.

### Symptoms of Impulsivity

- Impatient, difficulty waiting turns, interrupt conversations or others' activities
- Blur out inappropriate statements/answers too quickly
- Express emotions without restraint
- Act without considering consequences.

### Symptoms of Inattention

- Easily distractible, frequently switch from one task to another, forgetfulness in routine activities (e.g., homework, chores, etc.)
- Difficulty in focusing on organizing and completing an activity or learning something new in play, school, or home activities
- Avoids tasks that require consistent mental effort
- Gets easily bored, unless doing some enjoyable activity
- Misses details, makes careless mistakes, often loses belongings (e.g., pencils, toys, books)
- Seems not to listen when spoken to
- Have difficulty in following instructions as quickly and accurately as others.

These core behaviors must lead to a disturbance in functioning related to academic, social, or occupational activities for reaching a diagnosis of ADHD. The symptoms may secondarily dispose a child towards difficulty in forming friendships, peer rejection, poor self-esteem, and increased risk for depression and anxiety. The symptoms should also not be part of another psychotic disorder.

## DIFFERENTIAL DIAGNOSIS

Multiple conditions (**Table 4**) exhibiting some or the other symptoms of ADHD should be differentiated with a thorough history, observation and/or the use of a behavior rating scale. It is essential to differentiate from subtle aberrant behavior which may usually be present in normally developing children not having any impairment like short attention span in a preschool child or occasional impulsivity in a school going child.

### Approach to Diagnosis

Every child visiting the clinic should be assessed for ADHD. The evaluation comprises of medical, developmental, behavioral, educational and psychosocial perspectives. The assessment should include careful and detailed medical, social, and family history taking; clinical interviews and observation of the child with and without the parent; gathering information about functioning in child care center or school (from teachers) and at home (from parents/caregivers); and assessment for coexisting emotional or behavioral disorders. Thorough assessment generally requires multiple visits.

**Table 4** Differential diagnosis of attention-deficit hyperactivity disorder (ADHD)

Condition	Type
Developmental variations	Intellectual disability
	Giftedness
Neurologic or developmental conditions	Normal behavior of children
	Learning disabilities
	Language or communication disorders
	Autism spectrum disorders
	Neurodevelopmental syndromes (e.g., fragile X, fetal alcohol syndrome, Klinefelter syndrome)
	Seizure disorder
	Sequelae of central nervous system infection or trauma
	Metabolic disorders (e.g., adrenoleukodystrophy, mucopolysaccharidosis III)
	Motor coordination disorders
	Emotional and behavioral conditions
Emotional and behavioral conditions	Anxiety disorder
	Mood disorders
	Oppositional defiant disorder
	Conduct disorder
	Obsessive compulsive disorder
	Post-traumatic stress disorder
	Adjustment disorder
Psychosocial and environmental factors	Stressful home environment or an inappropriate educational setting
Medical conditions	Hearing or visual impairment
	Lead poisoning
	Thyroid abnormalities
	Sleep disorders (e.g., obstructive sleep apnea, restless leg/periodic limb movement disorder)
	Drug induced effects (e.g., albuterol)
	Substance abuse disorders

### Medical Evaluation

An evaluation of child and family cardiac history, dietary history and daily sleep pattern should be undertaken before initiating medications. The physical examination including a complete neurological examination should be undertaken. Regular monitoring of vital signs, height, weight and head circumference aids in assessment of medication effects.

### Developmental and Behavioral Evaluation

A thorough assessment should be conducted regarding:

- Developmental history, particularly language milestones
- Onset, duration, course, and degree of functional impact of ADHD symptoms
- Behavior at home and school—explore the behavioral excessiveness, pervasiveness, sustenance, comparison with other children, and temporal distribution.

The difficulty in collecting information may arise in situations of parental denial, minimization, manipulation, rationalization or contradictory views. Open-ended questions or questionnaires may be utilized to acquire historical information regarding symptoms. This should be compounded by direct observation of child's behavior and parent-child interactions.

**Behavior rating scales** Scales are useful for acquiring structured information of behavior, estimating symptom severity, measure treatment response and may add to the validity of the diagnosis. However, none of the global rating scales can provide a definitive diagnosis. *Narrow band scales* focus on the core symptoms of ADHD and have a high sensitivity and specificity. They have parent, teacher and patient versions. These include Vanderbilt assessment scales: can be used in children more than or equal to 4 years; Conners Comprehensive Behavior Rating Scales: validated in preschool children; and ADHD Rating Scale IV: validated in preschool children. *Broadband scales* assess a broad variety of behavioral symptoms, e.g., Child Behavior Checklist. They can help to recognize comorbid conditions and make the differential diagnosis narrow.

**Educational evaluation** Assessment of the functional impact of ADHD symptoms in academic setting should be conducted utilizing information regarding grades, absences, learning pattern, report cards, samples of schoolwork, etc. Details of parent-teacher meetings should also be sought.

**Psychosocial evaluation** It is prudent to assess the impact of symptoms on the psychosocial environment and vice versa which may provide an alternative explanation for the symptoms.

- Social responses at home and school—play activities, peer relationship, etc.
- Psychosocial stressors (death, divorce, or economical constraints in family).

**Neuropsychological testing** It may be valuable in assessing coexisting conditions (like learning disabilities), excluding other disorders, planning interventions, and charting treatment progress. It can also help to identify specific problem areas in EF like abstract reasoning, cognitive flexibility, planning and working memory. Various tests may be applied like Wechsler Intelligence Scale for Children, Wide Range Achievement Test-Revised, Differential Abilities Scale, or Wechsler Individual Achievement Test.

**Electrophysiological testing and imaging** Recently, US Food and Drug Administration (FDA) approved the first medical device based on brain function to help assess ADHD in children. This neuropsychiatric EEG-based assessment aid (NEBA) system device is a noninvasive test based on EEG technology recording different types and frequencies of brain electrical impulses (waves) given off by neurons and calculates the theta/beta ratio which has been reported to be high in ADHD. Quantitative EEG (qEEG) may also be employed for assessing prognosis. Variable resolution

electromagnetic tomography (VARETA) is a useful test to localize abnormal brain activity.

**Adjuvant evaluation** These are not routinely indicated but may aid in estimation of differential diagnosis and comorbid conditions, such as:

- Psychological development and occupational therapy evaluation (speech, language, specific scholastic skills and motor coordination developmental disorder)
- Mental health evaluation (behavioral and emotional disorders of childhood onset like anxiety, oppositional defiant disorder, conduct disorder (CD), adjustment disorder; mood disorder and post-traumatic stress disorder)
- Blood investigations for lead level (lead poisoning) and thyroid hormone levels (thyroid disorder)
- Genetic testing (fragile X syndrome, tuberous sclerosis, microdeletions)
- Polysomnography (obstructive sleep apnea or restless legs syndrome).

**Comorbid evaluation** Multiple conditions may mimic or coexist with ADHD such as CD, oppositional defiant disorder (ODD), major depressive disorder, bipolar disorder, anxiety disorders, substance-related disorders, tic disorders and learning disabilities. Common coexisting conditions reported in Indian literature are developmental delays, temper-tantrums, enuresis, tics, parental discord and parental psychiatric illness.

After the complete evaluation, a thorough discussion of the clinician with the parents is recommended regarding the child problematic behavior with its appropriate management measures which may entail implementing a *daily report card* procedure prior to initiating a medication trial or other psychosocial intervention.

## MANAGEMENT

An effective treatment strategy includes pharmacological and psychosocial approach, intervening in the personal, social, educational and occupational spheres. Before initiating treatment, clinician should discuss the myths regarding ADHD, precise information about ADHD, available treatment options, along with medication optimization and adverse effects with the primary caregiver/parent of the child. Regular follow-ups should be ensured to increase treatment adherence.

### Pharmacological Intervention

Pharmacological treatment relies on agents targeting dopamine and/or norepinephrine receptors. Stimulants imply the most extensively available first-line treatment option for ADHD. Stimulant medications should be used as supervised treatment in patients 6 years or older with no medical contraindications meeting the diagnostic criteria for ADHD. As being an activating drug, they should be given in daytime. The general rule of “start low and go slow” approach is followed during drug titration.

The most commonly used stimulants are methylphenidate (MPH), dextroamphetamine, and combination of amphetamine (AMP) and dextroamphetamine. Lisdexamfetamine dimesylate, a pro drug of AMP, remains inactive until metabolized therefore have less abuse potential and is also resistant to pH variation in gastrointestinal tract. Among the stimulants, only MPH is available in India for prescription under supervision. Stimulants are listed as Schedule II drugs, i.e., they provide desirable medicinal effects but at the same time are prone to be abused.

Other drugs approved by FDA having less abuse potential than stimulants are atomoxetine and extended release formulations of clonidine and guanfacine, which recently were approved as an adjunctive treatment to stimulant therapy for treating pediatric ADHD.

Second-line agents (off label drugs) include antidepressants such as bupropion, venlafaxine and tricyclic antidepressants particularly desipramine, nortriptyline and imipramine. Other useful agents include cholinesterase inhibitors, noradrenergic/dopaminergic agonists, and alpha-2a-adrenoreceptor agonists such as guanfacine. The role of atypical antipsychotics and antiepileptics like carbamazepine is still underway. Favorable effect of nicotinic modulators has also been observed.

Modafinil is a wake promoting agent which selectively activates the cortex without generalized effects on the central nervous system. It was declined FDA approval due to concerns over the possible development of Stevens-Johnson syndrome. It is generally prescribed in dose range of 200–340 mg once daily with children less than 30 kg and 300–425 mg in children weighing more than 30 kg.

Drug treatment is summarized in **Table 5**.

### Psychosocial Intervention

Psychosocial treatment is beneficial in cases where pharmacological treatment, despite its effectiveness, may lead to intolerable side effects. It enhances self-observation and coping skills in ADHD patients. Psychosocial treatments include psychoeducation, parent training, academic organization skill teaching and remediation, behavior modification, cognitive behavioral therapy (CBT), social skills training and individual therapy. These therapies focus on reducing ADHD-related behaviors, reinforcing desired behaviors, and developing positive habits which in turn helps to improve social relationships and overall functioning. This modality is preferred in children with age less than 6 years, mild symptomatology, uncertain diagnosis and when preferred by parents.

Behavioral parent training has been the most widespread and effective intervention being advised to preschool and school age children with oppositional and socially aggressive behavior. It utilizes principles of social learning theory teaching parents regarding positive reinforcement which include direct instruction, modeling and role playing.

CBT has been especially beneficial with coexisting anxiety, depression, and disruptive disorders but not for the core ADHD symptoms. It gives emphasis to problem solving approaches as well as emphasizes anticipation and consequences of behavior. Social skill training is one of the types of CBT.

Adolescents generally respond well to behavior techniques, academic interventions and family therapy whereas adults response better with CBT which includes psychoeducation and environmental modification strategies (problem solving, organization, activity scheduling, and replacement of dysfunctional thoughts).

Though nonpharmacological treatment plays important role in management of ADHD, the effect is modest. The most favorable treatment in general is individually tailored psychosocial treatment plus pharmacotherapy.

### Alternative Therapy

Agreeable evidence is lacking to support the beneficial effect of alternative therapies. These unproven remedies include elimination diet, herbal treatments, specific nutritional supplements, sensory integrative training, chiropractic medicine, body and craniosacral manipulation, electroencephalography biofeedback and optometric vision training.

### OUTCOME

With a family history of ADHD there are 50% increase chances of developing the disorder if either parent has ADHD or 35% chances if one of the siblings have ADHD. Symptom onset can occur at



**Table 5** Recommended pharmacological options for children/adolescents with attention-deficit hyperactivity disorder (ADHD)

<i>Medications</i>	<i>Duration of behavioral effects</i>	<i>Initial dose</i>	<i>Titration schedule</i>	<i>Maximum daily dose</i>
<i>Stimulants: Immediate release preparations</i>				
Methylphenidate	3–4 hours	0.3–1 mg/kg/day, 2.5–5 mg, 1–3 times daily	Increase by 2.5–5 mg daily at weekly intervals, split dose three times daily	60 mg
Dextroamphetamine	4–5 hours	0.15–0.5 mg/kg/day, 2.5–5 mg, 1–2 times daily	Increase by 2.5–5 mg daily at weekly intervals, split dose twice daily	40 mg
Amphetamine/ Dextroamphetamine mixed salts	4–6 hours	2.5–5 mg, 1–2 times daily	Increase by 2.5–5 mg daily at weekly intervals, split dose twice daily	40 mg
<i>Stimulants: Sustained release preparations</i>				
Methylphenidate	10–12 hours	18 mg	Increase by 18 mg daily at weekly intervals	Ages 6–12: 54 mg Ages 13–18: 72 mg
Methylphenidate ER	6–8 hours	10 mg	Increase by 10 mg daily at weekly intervals	60 mg
Dextroamphetamine SR	6 hours	5 mg	Increase by 5 mg daily at weekly intervals	40 mg
Amphetamine/ Dextroamphetamine mixed salts	8–12 hours	5 mg	Increase by 5 mg daily at weekly intervals	30 mg
<i>Nonstimulants: Second-line agents</i>				
Atomoxetine	8–24 hours	Weight ≤ 70 kg: 0.5 mg/kg/day × 3 days, then 1.2 mg/kg/day Weight > 70 kg: 40 mg daily × 3 days, then 80 mg daily All patients: Single dose after dinner or split dose twice daily with food		1.4 mg/kg daily or 100 mg, whichever is less
Guanfacine extended release	16–24 hours	1 mg/day, once daily	1 mg/day at weekly intervals	4 mg daily
Clonidine extended release	10–16 hours	single 0.1 mg tablet at bedtime	0.1 mg/day at weekly intervals	0.4 mg/day

3–4 years age, though only half the cases develop the disorder by 7 years of age and more than 90% develop by 12 years of age.

With the child reaching 4 years of age, hyperactive and impulsive symptoms starts appearing which continue to increase over next 3–4 years peaking at 7–8 years of age with emergence of inattentive symptoms. Hyperactive symptoms start declining after 7–8 years of age with almost negligible symptoms (in form of restlessness or inability to settle down) by the adolescence. On the other hand, impulsive symptoms persist throughout life.

Persistence of behavior is seen among the preschoolers who are difficult to control, have persistent inattentive and hyperactive behavior, display greater child defiant behavior or have greater parenting stress such as parent-child conflict or greater maternal directedness and negativity. Oppositional and socially aggressive behavior may appear between 6 years and 12 years of age in at least 40–70% of ADHD children which may further progress to ODD or CD symptoms in 25–45%. In middle childhood, they may develop learning disability, social skills deficits, low self-esteem and depression.

By late childhood, adaptive functioning is hampered due to deficit in executive functioning which is significantly below their intellectual ability. Preschoolers and childhood group are also more prone to recurring upper respiratory infections, asthma and allergies. In adolescence, there is greater alcohol and drug use. Overall, hyperactive individuals are also more prone to accidents.

ADHD symptoms can persist up to adulthood in 60% of children. The prevalence rate of adult ADHD is 4%. It may manifest in form of personality trait disorders, drug and alcohol misuse and antisocial behavior.

Despite their poor overall performance in comparison to non-ADHD counterparts, children with ADHD are capable of attaining high educational and vocational objectives. Many children have negligible emotional or behavioral problems by the time they reach mid-twenties.

## PREVENTION

Numerous factors have been linked as a casual factor for ADHD, so it is not possible to avoid all the factors but addressing them may reduce the risk.

*Primary prevention* includes promotion of maternal health during pregnancy, such as caution against use of alcohol and cigarette. Initiative should be taken to reduce environmental toxins like lead, mercury, and polychlorinated biphenyls. Though not accepted worldwide, an elimination diet has been proposed to lessen hyperactivity which targets artificial colorings, flavorings and preservatives. Hyperactivity has also been associated with sugary sodas and candy. Free fatty acids have some role in reducing ADHD symptoms. Children should be given clear cut age appropriate expectations with development of structured daily routine since early childhood. Though still needs approval, but preventing the child to watch television or video games may prevent ADHD. Regular physical exercise should be promoted. Couples with family history should be counseled regarding the risk of genetic loading of ADHD.

*Secondary prevention* includes early intervention of at risk children such as children with a family background of ADHD,

premature children, low birthweight babies, mothers with intake of toxic substances during pregnancy and children with serious craniocerebral traumas. Making teacher and parents to work together to identify ADHD at early stage should be a priority. Behavior management may be put forth through techniques such as focusing attention, disciplinary classroom promulgation and anger management. Monitoring of academic performance via multiple measures such as class participation and homework completion should also be incorporated. Regulation of social behavior and adequate organizational skills need to be provided.

*Tertiary prevention* is applied actively in symptomatic children with provision of pharmacological management and individual based therapy.

### MORE ON THIS TOPIC

- Aguiar A, Eubig PA, Schantz SL. Attention deficit/hyperactivity disorder: a focused overview for children's environmental health researchers. *Environ Health Perspect.* 2010;118:1646-53.
- Feldman HM, Reiff ML. Clinical practice. Attention deficit-hyperactivity disorder in children and adolescents. *N Engl J Med.* 2014;370:838-46.
- Li Z, Chang SH, Zhang LY, et al. Molecular genetic studies of ADHD and its candidate genes: a review. *Psychiatry Res.* 2014;219(1):10-24.
- Reinhardt MC, Reinhardt CA. Attention deficit-hyperactivity disorder, comorbidities, and risk situations. *J Pediatr (Rio J).* 2013;89:124-30.
- Verma R, Balhara YPS, Mathur S. Management of attention deficit hyperactive disorder. *J Pediatr Neurosci.* 2011;6:13-8.
- Weyandt L, Swentosky A, Gudmundsdottir BG. Neuroimaging and ADHD: fMRI, PET, DTI findings, and methodological limitations. *Dev Neuropsychol.* 2013;38:211-25.

### IN A NUTSHELL

1. ADHD, a neuropsychologically heterogeneous condition, is among the most common disorders of childhood.
2. It is highly prevalent worldwide with a long-term course and pervasive effects.
3. Multiple factors may be responsible for its varied manifestations such as symptom dimensions, illness severity, family history of the disorder, shifting impairment between home and school setting, executive functioning deficits, comorbidity and developmental stage.
4. Recent studies provide more insight into the genetic, environmental, and neurobiological causes of this disorder, thereby, further enhancing our understanding of pathophysiologic processes, which, in turn, will bring about novel prevention and intervention strategies.
5. Although debatable, current classificatory system approaches provide reliable and valid cross cultural diagnostic criteria's for the disorder.
6. Promising pharmacotherapeutic options in form of stimulant as well as nonstimulant medications offers new options for managing ADHD.
7. Utmost treatment outcome may be achieved using a multimodal management approach employing appropriate pharmacotherapy with psychosocial intervention.
8. A pragmatic, multifaceted management based around the establishment of good working relationships with family and school should be incorporated.
9. The disorder requires a long-term therapeutic alliance among clinician and the patient along with their families improving their quality of life.

## Chapter 21.10

# Oppositional Defiant and Conduct Disorders

Rajesh Sagar, Rajeev Ranjan

Aggression, oppositionality and impulsivity are some of the most frequent behavioral problems seen at children and adolescents clinic. Our diagnostic system terms, such condition as oppositional defiant disorder (ODD) and conduct disorder (CD). These two conditions differ in terms of intensity as ODD refers to repetitive pattern of defiant, disobedient and hostile behavior toward authority figures, whereas CD is characterized by a persistent pattern of aggressive and nonaggressive rule breaking antisocial behaviors leading to considerable burden for the patients, their family and society. These conditions can also lead to impaired functioning in multiple domains in adult life. Both of these disorders are important clinical conditions because they repeatedly cause physical harm and property loss of others and also patients themselves are at risk for depressive symptoms, suicidal tendency and substance use. **Flow chart 1** depicts the developmental course and subtypes of ODD and CD.

## EPIDEMIOLOGY

The prevalence of ODD and CD is estimated to range between 2% and 16% in community settings, but is likely to be much greater in clinical settings. Prevalence estimates also vary by age and sex. ODD usually will present before 8 years of age, rarely later than early adolescence. Onset of CD occurs as early as 5 or 6 years, but usually occurs at late childhood or early adolescence. In Indian studies, reported prevalence of CD ranges from 0.2% to 11%, and that of ODD has been reported as 1.3%.

## ETIOLOGY

### Oppositional Defiant Disorder

Oppositional defiant disorder is reportedly more common in families with at least one parent with a positive psychiatric history and particularly those with ODD, CD, attention deficit hyperactivity

disorder (ADHD), antisocial personality disorder, mood disorders, and substance use disorders.

### Conduct Disorder

No single or combination of etiologies can be described as definitive. Both genetics and environmental factors can contribute. Neuro-transmitter system abnormalities, noradrenergic and dopaminergic activities, and serotonin may play a role. It is perhaps more useful and accurate to view CD etiology in terms of risk factors.

### Temperamental Factors/Child Factors

Male gender, difficult temperament, early behavioral problems, low IQ and school failure, impulsivity, emotional dysregulation, and hyperactivity.

### Familial Factors

Poor family functioning, marital discord, child abuse and neglect, poor parenting (harsh, inconsistent, lack of supervision), parental rejection, large family size, frequent changes in caretakers and psychiatric diagnosis in parents.

### Environmental Factors

Poor quality of schooling, socioeconomic disadvantage, peer rejection, association with delinquent peer groups, exposure to violence.

## DIAGNOSIS

### Oppositional Defiant Disorder

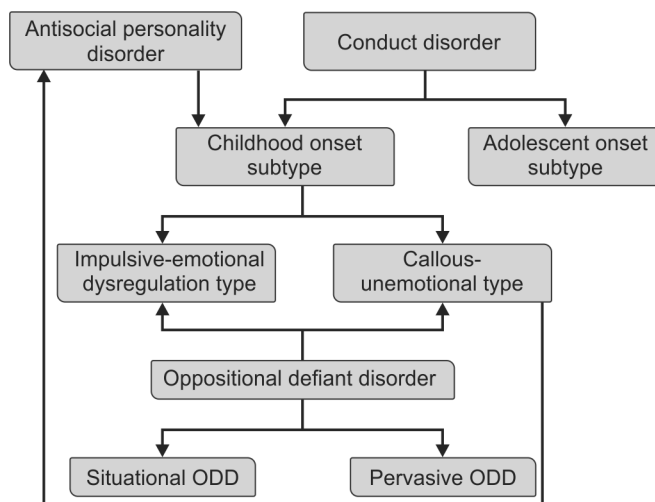
To diagnose children with ODD, there are eight possible symptoms in Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV), from which four or more must be present during the past 6 months with suitable frequencies. These symptoms include loss of temper; argument with adults; actively defying an elder's requests; deliberately irritating others; blaming others for own mistakes; being moody or easily upset; being angry and offended and being mean or hurtful to others. ODD must not be diagnosed if the youth meets diagnostic criteria for CD or antisocial personality disorder (APD).

ODD and conduct disorder is placed in separate new section called disruptive, impulse control and conduct disorder in DSM 5. Four changes have been made to the criteria for ODD. First, symptoms are now grouped into three subtypes: (1) irritable mood, (2) argumentative or defiant behavior and (3) vindictiveness. Second, the exclusion criterion for conduct disorder has been deleted. Third, frequency typically needed for a behavior to be considered symptomatic of the disorder is provided, because many behaviors associated with symptoms of ODD occur commonly in normally developing children. Fourth, a severity rating has been added to the criteria. ODD is included in subtypes of conduct disorder in International Classification of Diseases (ICD 10).

### Conduct Disorder

DSM-IV lists 15 criteria or symptoms grouped into 4 major categories: (1) aggression to people or animals, (2) destruction of property, (3) deceitfulness or treachery, (4) serious violations of rules. Aggression to people or animals includes bullying, threatening and often indulging in physical fights with others; using any blunt or sharp object as a weapon that can cause serious physical harm to others; being physically cruel to people or animals; stealing with actual confrontation of victim and forced sexual activity (eight symptoms). Destruction of property comprises deliberate fire setting with intention of causing serious damage to others and deliberate destruction of someone's property, other than fire setting (two symptoms). Deceitfulness or

**Flow chart 1** Developmental course and subtypes of oppositional defiant disorder and conduct disorder



treachery involves breaking into a house, building or car; lying to obtain goods or favors and stealing nontrivial value items without breaking or shoplifting (three symptoms). Serious violations of rules symptom list consist of staying out at night (running away overnight is defined as running away at least two times from home while living in parental or surrogate parental home or only once, but for a lengthy amount of time) and skipping school despite parental prohibitions and it should begin before age 13 (two symptoms). Three (or more) of the criteria or symptoms should have been present for the last 12 months, with at least one criterion or symptom must be present in the past 6 months for diagnosis of CD. Conduct disorder is classified as mild, moderate and severe according to severity of symptoms.

The symptoms in ICD-10 are uniform across the subtypes of CD (**Table 2**) that also includes ODD. Criteria for diagnosis require presence of more than three symptoms from the listed symptoms (**Table 1**), of which at least three must be from items 9–24, and at least one of the symptoms from items 9–24, must have been present for at least 6 months. Difference lies in subtypes of conduct disorder, in (a) whether normal peer relationships are maintained (socialized vs. unsocialized conduct disorder) and (b) whether conduct disturbance is limited to the family context.

Oppositional defiant disorder requires presence of four or more symptoms from the listed symptoms (**Table 1**), of which no more than two are from items 9–24 (**Table 1**). The symptoms must be maladaptive and inconsistent with the developmental level. At least four of the symptoms must have been present for at least six months.

**Table 1** Item/symptom lists in ICD 10 for diagnosis of ODD and CD

Item number	Items/symptom lists
1–8	<ul style="list-style-type: none"> <li>• Unusually frequent or severe temper tantrums for the child's developmental level</li> <li>• Often argues with adults</li> <li>• Often actively defies or refuses adults' requests or rules</li> <li>• Often, apparently deliberately, does things that annoy other people</li> <li>• Often blame others for one's own mistakes or misbehavior</li> <li>• Often touchy or easily annoyed by others</li> <li>• Often angry or resentful</li> <li>• Often spiteful or vindictive</li> </ul>
9–24	<p>Frequent and marked lying (except to avoid abusive treatment), excessive fighting with other children, with frequent initiation of fights (not including fights with siblings), uses a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun), often stays out after dark without permission (beginning before 13 years of age), physical cruelty to other people (e.g., ties up, cuts or burns a victim), physical cruelty to animals, deliberate destruction of others' property (other than by fire-setting), deliberate fire-setting with a risk or intention of causing serious damage, at least two episodes of stealing of objects of value (e.g., money) from home (excluding taking of food), at least two episodes of stealing outside the home without confrontation with the victim (e.g., shoplifting, burglary or forgery), frequent truancy from school beginning before 13 years of age, running away from home (unless this was to avoid physical or sexual abuse), any episode of crime involving confrontation with a victim (including purse snatching, extortion, mugging), forcing another person into sexual activity against their wishes, frequent bullying of others (i.e., deliberate infliction of pain or hurt including persistent intimidation, tormenting, or molestation), breaks into someone else's house, building or car</p>

Comorbid diagnostic categories are hyperkinetic CD (Individual meets the diagnostic criteria for attention-deficit hyperactivity disorder and CD), depressive CD (individual meets the diagnostic criteria for CD and one of the mood disorders) and mixed disorders of conduct and emotions (individual meets the criteria for CD and additional neurotic, stress-related or somatoform disorder according to the ICD-10 criteria).

## Comorbidity

The prevalence rate of ADHD in youth with severe conduct problems (CPs) in clinic setting is about 90%, whereas this rate is 36% in community samples. CD and ODD are also associated with internalizing problems, such as anxiety and depression. One-third of children in community setting and three quarters of clinic referred children with CD have comorbid depressive disorder. However, internalizing problems has been primarily linked to ODD. Suicidal ideation and attempts are greater in CD. Studies have shown that CD comorbidity with learning disorders may be as high as 50% to 70%. Even in the absence of a learning disorder, those with CD often experience academic and other school-related difficulties. Other psychological characteristics may include decreased self-esteem, irritability, low frustration tolerance and anger outbursts. Excessive risk-taking and increased accident rates are also found in CD.

## MANAGEMENT

### Assessment

Active probing for each of the DSM 5 or ICD 10 symptoms of CD is required, when interviewing the patient and other informants. Assessment should further address important issues regarding the presence of comorbid disorders including ADHD, anxiety and mood disorders, learning difficulties and substance use disorders in adolescence. All structured psychiatric interview schedules (i.e. K-SADS, [Kiddie-Schedule for Affective Disorders and Schizophrenia] CAPA, DISC) have well-organized sections for the assessment of CD. Several specific scales are also available for assessment of symptoms of CD and ODD. Their discussion is beyond the scope of this chapter.

### DIFFERENTIAL DIAGNOSIS

Although CD can present with any or all of the features of ODD, it can be differentiated from ODD by the presence of its clearly defined more serious forms of violation of rights of others, age appropriate norms and societal rules and regulations. When both diagnoses are met, CD preempts an additional diagnosis of ODD. If ADHD is the only disorder present, it will not cause nor will its symptoms violate norms and rules in the manner of CD. In some instances, one must determine whether a behavior exhibited occurs as a result of the impulsive and inattentive symptoms of ADHD. CD symptoms may also occur along with a mood disorder. Isolated events of conduct, not meeting criteria for CD diagnosis, should be given a diagnosis of child or adolescent antisocial behavior. Disruptive behavior disorders may also be present in some cases. Differential diagnosis of ODD and CD is summarized in **Table 2**.

### Treatment

#### General Approach

To be effective, treatment must be multimodal, involve a family-based and social systems-based approach, to address multiple locus and to continue for substantial periods of time. Treatment should start with informing the patient and his parents/caretakers about the disorder and its potential complications and long-term



**Table 2** Differential diagnosis of oppositional defiant disorder and conduct disorder

<i>Oppositional defiant disorder</i>	<i>Conduct disorder</i>
Conduct disorder (by DSM-IV criteria; cannot be diagnosed both, but DSM 5 allows both diagnosis)	Oppositional defiant disorder
Attention-deficit/hyperactivity disorder	Attention-deficit/hyperactivity disorder
Impaired language comprehension (e.g., hearing loss, mixed receptive-expressive language disorder)	Mood disorders
Mental retardation	Child or adolescent antisocial behavior (V code; isolated events of conduct, not meeting criteria for CD diagnosis)
Mood disorders (including bipolar disorder)	Antisocial personality disorder
Normal individualization (in adolescence)	Pervasive developmental disorders and mental retardation
Psychotic disorders	Neurotic stress related and somatoform disorder (Mixed disorder of conduct and emotion)

sequelae. Treatment strategies should be targeted to identify comorbid disorders, such as ADHD. Pharmacological management is usually not the first choice, but should be considered in those patients who have previously failed to respond to other interventions and show escalating levels of dangerous aggression and violent behavior. Additionally, pharmacotherapy is more effective when administered in combination with psychosocial/behavioral treatments.

### Psychological Interventions

Treatment outcome studies have recognized three effective treatments for CD. These include various behavioral management strategies, parenting interventions, and cognitive-behavior skills building programs.

*Behavioral or contingency management programs* has four basic mechanism: (1) To define a clear behavioral target that figure a child behavior in specific area of concern; (2) To monitor the child progress toward achieving these target; (3) To strengthen suitable steps toward achieving these target; and (4) To identify and to grant consequences for inapt behavior. These programs have been found to be effective for altering inappropriate behaviors in different settings (e.g. home, school).

*Parent management training (PMT)* Parent management training teaches consistent parenting, positive and less harsh discipline practices, monitoring of the child and positive feedback for the child. Parent management training programs focus on structured contingency management programs at home, improving the quality of parent-child interactions and to use more effective discipline strategies, to increase positive prosocial behaviors, to strengthen parents supervising. Among all psychological intervention for children with conduct disorder, the efficacy of parent training has been the most consistently reported.

*Cognitive-behavioral skills building approach* Social-cognitive and social problem-solving deficits in children and adolescents with conduct problem are targeted by this intervention. In these deficits, children with CPs tend to think their violent behavior will

lead to positive results and this cognitive error makes them more likely to select belligerent choices when solving peer conflict. These programs inhibit impulsivity or recklessness, by training them to internalize a sequence of problem-solving steps and to adapt alternative responses and overcome deficits in the way they process social information.

### Multisystemic Therapy

It focuses on child's strength and difficulties in relation to wider social environment than intrinsic deficit. Thus, the intervention focuses on using various systemic strengths (e.g. support of grandmother or prosocial peers, etc.) for promoting responsible behavior which requires a balanced effort from both child as well as family members.

Multisystemic therapy, functional family therapy and multidimensional treatment foster care are programs developed for the treatment of aggression in older children and adolescents with juvenile justice involvement. These programs have shown effectiveness in the treatment of aggressive and violent adolescents, resulting in decreased arrest rates. In juvenile justice system, replacement home may be indicated. In India, observational home are available for these children (Juvenile in conflict with law) in bigger cities running with help of NGO.

All these psychosocial treatment approaches; however, have serious limitations. The effectiveness of PMT (parent management training) declines with increasing age with strong evidence for efficacy limited to younger children (up to around 8 years of age). Further, after therapy has been completed, the generalization of treatment benefits is low. Dropout rates are high, and parental psychopathology and lack of motivation of parents are serious obstacles in administering these interventions. Finally, these psychosocial treatments appear to bring greater benefits to children with high levels of impulsive aggression, whereas children with high levels of callous unemotional (CU) traits tend to be rather unresponsive to these interventions.

### Medical Interventions

Psychostimulants such as methylphenidate, atomoxetine, amphetamine are used to treat aggression/oppositional defiant symptom in the context of CD and ODD as a comorbid condition with ADHD. Apart from psychostimulants, risperidone amongst the second generation antipsychotics is the most widely studied medication for the treatment of aggression and conduct symptoms in children and adolescents. Lithium and carbamazepine are found to be effective in reducing aggression associated with CD. Treatment algorithm for single diagnosis of ODD/CD and comorbid diagnosis with ADHD is provided in

**Table 3.**

### Prevention

Interventions that have proven effective in treating early emerging CPs in young children target early during preschool years in growing up phase. Researched programs which are effective named triple P (positive parenting program) and incredible year parenting series. These programs are most suitable for those parents whose children are at greater risk of developing emotional or behavioral problems because of number of risk factors and identifiable symptom check list. School-based programs are also effective to identify antisocial behavior or delinquent peer groups at school and provide adequate support. Family physicians have also greater role in identifying early cases of ODD when parents report an excessively quarrelsome, disobedient, aggressive and hostile child. Other programs named intensive home visiting support services and child centered preschool stimulation program are effective in preventing early emerging conduct problems.

**Table 3** Treatment algorithm for oppositional defiant disorders (ODD) and conduct disorders (CD)

<b>Step 1</b>	Clinical evaluation to rule out psychiatric comorbidity and if required, use a general psychopathology screening and rating scale or a structured interview.
<b>Step 2</b>	In the absence of psychiatric comorbidity, psychosocial interventions should be first treatment option for ODD/CD.
<b>Step 3</b>	<ul style="list-style-type: none"> <li>• If no response from psychosocial interventions within first 3 months, either psychostimulants or atomoxetine can be tried.</li> <li>• If no response to the first medication, a second medication from a different class can be tried.</li> <li>• If the first two trials were with psychostimulants and an adequate response is not achieved, then a trial with atomoxetine is indicated.</li> </ul> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>• If aggression is the primary symptom, the first two trials should be either a methylphenidate or amphetamine.</li> <li>• If compliance is the issue, long-acting medications are recommended, to be supervised by family members.</li> </ul>
<b>Step 4</b>	Children and adolescents with serious behavioral problem like aggression, not responded to either psychosocial interventions or psychostimulants/atomoxetine, can be considered for a trial with risperidone.
<b>ODD/CD + ADHD</b>	Children and adolescents with ODD/CD and comorbid ADHD, if aggression is primary clinical symptom; either methylphenidate or amphetamine should be tried first, followed by risperidone.

Source: Turgay A. Psychopharmacological treatment of oppositional defiant disorder, 2009.

## MORE ON THIS TOPIC

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4<sup>th</sup> ed, text revised (DSM-IV-TR). Washington (DC): American Psychiatric Association. 2000.
- Barrickman L. Disruptive behavioral disorders. *Pediatr Clin North Am*. 2003;50:1005-17.
- Buitelaar JK, Smeets KC, Herpers P, et al. Conduct disorders. *Eur Child Adolesc Psychiatry*. 2013;22(Suppl 1):S49-54.
- Frick PJ. Developmental pathways to conduct disorder. *Child Adolesc Psychiatr Clin N Am*. 2006;15:311-31.
- Frick PJ, Dickens C. Current perspectives on conduct disorder. *Curr Psychiatry Rep*. 2006. pp. 59-72.
- Hamilton SS, Armando J. Oppositional defiant disorder. *Am Fam Physician*. 2008;78:861-6.

- Kimonis ER, Frick PJ. Oppositional defiant disorder and conduct disorder grown-up. *J Dev Behav Pediatr*. 2010;31:244-54.
- Loeber R, Burke JD, Lahey BB, et al. Oppositional defiant and conduct disorder: a review of the past 10 years, part I. *J Am Acad Child Adolesc Psychiatry*. 2000;39:1468-84.
- Malhotra S. Incidence of childhood psychiatric disorders in India. *Indian J Psychiatry*. 2009;51:101-7.
- Pardini D, Frick PJ. Multiple Developmental Pathways to Conduct Disorder: Current Conceptualizations and Clinical Implications. *J Can Acad Child Adolesc Psychiatry*. 2013;22:20-5.
- Shastri PC, Shastri JP, Shastri D. Research in child and adolescent psychiatry in India. *Indian J Psychiatry*. 2010;52(Suppl 1):S219-23.
- Srinath S, Girimaji SC, Gururaj G, et al. Epidemiological study of child and adolescent psychiatric disorders in urban and rural areas of Bangalore, India. *Indian J Med Res*. 2005;122:67-79.
- Tcheremissine OV, Lieving LM. Pharmacological aspects of the treatment of conduct disorder in children and adolescents. *CNS Drugs*. 2006;20:549-65.
- The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). Geneva: World Health Organization, 1992.
- Turgay A. Psychopharmacological treatment of oppositional defiant disorder. *CNS Drugs*. 2009;23:1-17.

## IN A NUTSHELL

1. Conduct disorder is strongly associated with significant dysfunction in the scholastic, social and work related domains leading to imperative burden for the patient, family and immediate environment.
2. Oppositional defiant disorder and CD as an individual diagnosis are placed in separate new section called disruptive, impulse control and conduct disorder in DSM 5, while in ICD 10, ODD is a subtype of CD.
3. Childhood-onset CD and high levels of CU traits are associated with severe and stable antisocial behavior associated with APD in adulthood.
4. Nonmedical psychosocial interventions are recommended as the first option for the treatment of CD.
5. There is a role for medication in the treatment of comorbid syndromes or in case of insufficient response to psychosocial interventions and severe aggressive behaviors.
6. Research on temperamental risk factors early in life can determine protective factors that help in reducing antisocial behavior later in development.

## Chapter 21.11

# Learning Disabilities

Nandini Mundkur, Chitra Sankar

A learning disability (LD) is a neurobiological disorder that presents as a serious difficulty with reading, arithmetic, and/or written expression that is unexpected for the individual's intellectual ability. These disorders can have significant impact on the child's academic and emotional development.

The learning problems significantly interfere with academic achievement or activities of daily living that require reading, mathematical or writing skills. Besides the integral difficulty in learning, it is seen that the family, school, sociocultural milieu and education play a significant influence in the ultimate outcome of learning in children. Therefore, LD is diagnosed when the individual's achievement on individually administered, standardized tests in reading, mathematics or written expression is substantially below that expected for age, schooling and level of intelligence.

### DEFINITION

Specific LDs can be defined as *a category of developmental disabilities characterized by difficulty learning in one or more areas despite otherwise typical neurological, physical, and emotional development, and adequate experiential and educational opportunities*. Another widely accepted definition is: LD is a generic term that refers to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning or mathematical abilities. These disorders are intrinsic to the individual and are presumed to be due to a dysfunction of the central nervous system (CNS). Even though a LD may occur concomitantly with other disabling conditions (e.g., sensory impairment, mental retardation, social-emotional disturbance) or environmental influences (e.g., cultural differences, insufficient/inappropriate instruction), it is not the direct result of those conditions or influences.

### Terminology

*Dyslexia* refers to disorder of reading, *dysgraphia* means disorder of writing and *dyscalculia* is a disorder in mathematics. Frequently a child may have a combination of one or more difficulties. Rarely do they occur in isolation.

*Dyslexia* is a specific language-based disorder characterized by difficulties in accurate or fluent word reading, usually reflecting insufficient phonological processing abilities. These difficulties in single word decoding are often unexpected in relation to age and other cognitive and academic abilities; they are not the result of generalized developmental disability or sensory impairment. *Dyslexia* is manifest by variable difficulty with different forms of language, often including, in addition to problems reading, a conspicuous problem with acquiring proficiency in writing and spelling.

*Dysgraphia* is a writing disability in which a person has difficulty expressing thoughts on paper and is associated with unreadable penmanship and problems in gripping and manipulating a pencil.

*Dyscalculia* refers to a mathematical disability in which a person has unusual difficulty solving arithmetic problems and grasping math concepts manifesting as difficulty in mathematical operations such as addition, subtraction, multiplication, division, with poor retention and retrieval of mathematical concepts.

Diagnostic and Statistical Manual of Mental Disorders-5th edition (DSM-5) labels this group of disorders as *specific learning*

*disorder* with impairment in reading, or with impairment in written expression, or with impairment in mathematics.

### PREVALENCE

The prevalence of LD depends upon the definition and varies from study to study. Dyslexia is perhaps the most common neurobehavioral disorder affecting children, with prevalence 5–17.5%. Previously, it was believed that dyslexia affected boys primarily; however, more recent data indicate similar numbers of affected boys and girls. Prevalence rates for reading disorder are estimated at 4% of school-age children, with a range of 2–10. International epidemiological studies report a prevalence of 4–17% for dyslexia, 2–8% for dysorthography and 1–5% for dyscalculia.

### NEUROBIOLOGICAL BASIS OF LEARNING DISABILITIES

Several chromosomal, genetic, inherited, teratogenic and intrauterine factors like maternal malnutrition, exposure to irradiation, TORCH infections (Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus and Herpes infections) and substance abuse have been associated with varying degrees of learning and cognitive impairments. Disorders of cerebral dysgenesis and inborn errors of metabolism; perinatal causes like placental insufficiency, prematurity, complications of labor and delivery; postnatal causes like CNS damage due to trauma, infections, malnutrition, resistance to thyroid hormones, abuse, neglect, toxin exposure, uncontrolled seizures and neurodegenerative disorders are other causes.

Advances in imaging and electrophysiological studies have made it possible to study differences in the brains of reading impaired and reading nonimpaired individuals. In the left hemisphere of the brain, an anterior system in the region of inferior frontal gyrus believed to serve articulation and word analysis and two posterior systems—one in the parietotemporal region for word analysis and a second region in the occipitotemporal region for automatic and fluent reading of words—have been identified as neural systems for reading. In children with dyslexia, the posterior systems are found to be less activated during reading. Compensatory systems have been found to develop in right and left inferior frontal gyrus. This pattern of underactivation in left posterior reading systems is referred to as neural signature for dyslexia.

### GENETICS OF LEARNING DISABILITIES

Twin studies, sibling analysis and family pedigree analysis have shown a genetic basis for LDs. For example, twin studies have shown that if one twin has reading disability, the probability of its occurrence in the other twin is 68% for monozygotic twins and 40% for dizygotic twins. Familial transmission is known to occur. For example, if there is family history of reading disabilities, the probability of its occurrence is significantly increased. The relatives of children with learning disorders have a relatively high incidence of expressive language disorder. Linkage studies implicate loci on chromosomes 6 and 15 in reading disability. Additional findings of the strong heritability of phonologic awareness suggest that it may be the main proximal cause of most genetically based deficits in word recognition, and thus it may be the most appropriate focus for diagnosis and remediation.

### SIGNS OF LEARNING DISABILITY

Children with learning difficulties may present with poor school performance but more commonly present with school phobia or school absenteeism and somatic complaints. The earliest pointer

to a child with LD may be language delay. Other signs in preschool children are delay in learning the alphabets, difficulty in learning nursery rhymes, learning numbers, mispronunciations and difficulty in letter-sound associations. They may also have delay in fine motor skills which would later have implications for writing skills. In the primary school, there may be delay in learning to read common one syllable words such as *cat* or *bat* or difficulty in reading common irregularly spelled words, e.g., *two* or *know*; slow and hesitant reading characterized by word substitutions, omissions, guessing of words and poor comprehension. In later classes, they may read simple words easily but would skip parts of long syllable words, e.g., *aminal* for *animal* or *pictures* or *comfortable*. Children in middle grades may also have poor comprehension even when they can read fast and accurately. Problems in reading may be accompanied by writing difficulties. Handwriting may be illegible, messy with reversals and inconsistencies in the formation, sizing and spacing of letters. It is usually slow and laborious with spelling errors.

This may be accompanied by poor performance in arithmetic, computations and difficulty in solving word problems. One of the hallmarks of dyscalculia is the persistent use of effortful calculation strategies (such as using finger counting) when typically developing peers have shifted towards retrieving the solutions to calculation problems from memory. More recently, studies have shown that children with dyscalculia may also have difficulties with number sense, the ability to quickly understand, approximate and manipulate numerical quantities. It has been found that dyscalculia is associated with difficulty estimating the number of objects in a group, and comparing quantities, particularly when represented in a symbolic format (e.g., Arabic numerals).

Other signs may be fine motor incoordination, visuospatial difficulties and behavior, memory and attention dysfunctions varying from mild to severe. During adolescence, the presenting features may be behavioral problems such as aggression, truancy, school refusal, psychosomatic complaints and symptoms of stress and anxiety accompanied by poor scholastic achievement.

There is a high incidence of language impairment among those identified as dyslexic (19–63%) and vice versa there is also reading impairment among those identified with specific language impairment (SLI) (12.5–85%). In two twin studies, rates of reading impairment were significantly higher than matched control groups in children with SLI. Generally high rates of comorbidity have been reported for dyslexia and dyscalculia ranging from 17% to approximately 60%.

## ASSESSMENT OF LEARNING DISABILITY

When LD is suspected, the child is referred for complete physical, neurological and neuropsychological assessments. In general, most children do not show any neurological impairment except some may exhibit soft neurological signs. There is no single examination for eliciting subtle signs, but a number of overlapping examinations are performed such as lateral preferences, stressed gaits, gait/steadiness, sustentation postures/stations, finger to nose, tongue protrusion, maintaining eye closure, balance, hopping, and timed coordination. Assessments should be made for visual and hearing impairments.

Neuropsychological assessments include a variety of tests of abilities and functions in the domains of cognitive/intellectual, language, visual-perceptual, academic, motor, sensory, and emotional/behavioral. A correlation is then drawn between a profile of strengths and weaknesses and known brain functions.

### Neuropsychological Testing

Standardized tests are administered by a clinical psychologist. Intellectual functioning can be measured yielding an intelligence

quotient (IQ). Commonly used tests are Wechsler Scale of Intelligence-Revised (in India, the Wechsler test is adapted as Malin's Intelligence test for Indian children), Binet-Kamat Intelligence Scale. Copying geometric figures, Goodenough Draw-a-Person Test, Kohs Block Design and geometric puzzles may be used as screening tests for visual-motor coordination. Assessments of adaptive functioning can be done with Vineland Adaptive Behavior Scales.

One of the commonly used criteria for diagnosis of LD is ability-achievement discrepancy and for assessing the achievements in academic skills various tests are available, e.g., Woodcock-Johnson-III, *Wide Range Achievement Test-4* (WRAT4) and some curriculum-based Indian tests like National Institute of Mental Health and Neurosciences (NIMHANS) specific LD Index, *Grade Level Assessment Device* (GLAD) and the test by Sholapurwala. The test by Sholapurwala is available for children till 10th standard. Though Woodcock-Johnson-III, WRAT4 are validated tests, they have not been standardized for Indian population. Although the DSM-5 has specified a cut-off of at least 1.5 standard deviations (SDs) below the population mean for age on one or more standardized test, it has allowed a more lenient threshold of 1.0–2.5 SDs. Below mean, based on clinical judgment, when LD is suspected from academic history, school reports or test reports.

### Woodcock-Johnson-III Tests of Achievement

Woodcock-Johnson-III Tests of Achievement is an individually administered, comprehensive test of academic achievement and scholastic aptitude for individuals between age 2 years and 90 years. It provides age-based norms by month from ages 24 months to 90+ years and grade-based norms for kindergarten through 12<sup>th</sup> grade, 2-year college and 4-year college including graduate school. It measures academic achievement in broad curricular areas of reading, mathematics, written language, oral language and knowledge. The Standard Battery (form A or B) consists of tests 1 through 12 and test-letter-word identification, reading fluency, passage comprehension, story recall, understanding directions, calculations, math fluency, applied problems, spellings, writing fluency, writing samples, story recall delayed, handwriting legibility scale. After calculating the raw score, estimated age and grade equivalent scores are obtained by using the scoring tables.

### Grade Level Assessment Device

Grade Level Assessment Device was developed by Jayanthi Narayan for the National Institute for the Mentally Handicapped (NIMH) in 1997. It was standardized on 1,197 children from four schools from Andhra Pradesh and one school from Delhi. It assesses for english, hindi and mathematics for grade level 1–4. Oral reading, silent reading, reading comprehension, writing, arithmetic computation and arithmetic reasoning are tested. After calculating the percentage marks obtained by the child, he/she is finally classified as independent (> 70%), instructional (40–70%) and frustational (< 40%).

### Wide Range Achievement Test-4

The WRAT4 is a norm-referenced test that measures the basic academic skills of word reading, sentence comprehension, spelling and math computation. It is used for a quick, simple, psychometrically sound assessment of important fundamental academic skills. It is more valuable in the initial evaluation of children referred for learning, behavioral or vocational difficulties. The results of this test by themselves are not intended to provide formal identification of learning or cognitive disorders. Although the WRAT4 is administered individually, some of the subtests or sections of subtests may be administered to small groups of up to 5. The interpretation of WRAT4 scores has been enhanced by the



addition of grade-based norms, thereby increasing the usefulness of the test. The age-based norms are applicable from 5 years to 94 years so that the basic literacy skills of older adults could be assessed.

### Neuropsychological Assessment

A neuropsychological evaluation is important to evaluate the specific functions that are often involved in LDs such as auditory-linguistic abilities, visual abilities, memory, processing speed, cognitive efficiency and reasoning apart from assessing attention and motor and sensory abilities. This assessment is very important determining the critical areas for intervention. NEPSY-II is one such comprehensive instrument designed to assess neuropsychological development in preschool and school-age children.

### Neuropsychiatric Comorbidities

Difficulties in psychosocial adjustment appear to be the major social-emotional manifestations of LDs. Children with LD experience less acceptance, lower popularity, more peer rejection and increased neglect by peers than do normally achieving children or low-achieving peers.

It has been estimated that 30–70% of children with LD will experience ongoing comorbid symptoms of attention-deficit/hyperactivity disorder (ADHD) as they enter into adulthood. Both LD and ADHD have a high degree of comorbidity with other neuropsychiatric disorders like depression, conduct disorder, anxiety disorder, substance abuse, Tourette syndrome, tic disorders and other stereotypic movement disorders, and sleep disorders. These facts stress the need for screening, early detection, recognition, comprehensive assessments and early intervention or even incorporate prevention strategies and thus improve the quality of life of the affected individuals.

### MANAGEMENT

All the available facts and diagnostic studies are assembled and reviewed in the management of a child with LDs. A set of diagnoses and diagnostic formulations are generated. It is important to take into account the child's areas of strengths and areas of weaknesses. The strengths have to be capitalized on and the weaknesses have to be supported or strengthened. An individualized treatment plan is developed. Treatment should be multimodal and judiciously utilize medical intervention, psychopharmacological treatment, behavioral management, and educational and remedial teaching. Parent support groups and advocacy organizations also have a very important role to play. A multidisciplinary approach has to be taken to provide the most effective and efficient therapeutic care. The team would ideally comprise of developmental pediatrician, neuropsychiatrist, psychologist, remedial teachers, physiotherapist, occupational therapist, speech and language therapist, and the school. Other professionals may need to be consulted depending on the nature of the problem.

### Remedial Education

Remedial education is the focus of management. This has to be individualized and tailored to each child keeping in mind the child's various strengths and weaknesses. Reading proficiency depends on phonological processing and awareness and understanding of the alphabetical principle. A large body of evidence has been reviewed by the National Reading Panel commissioned by the National Institute of Child Health and Human Development (NICHD), USA that concluded that, direct and systematic phonologic awareness and phonics instruction produced significant effects in dyslexic children as well as children in kindergarten or first grade who are found to be at risk for reading disability.

Children identified as dyslexic receive systematic and highly structured instructions in basic phonologic skills required for decoding and reading. Instructions are provided either individually or in small groups of 2:1 or 3:1. Along with knowledge of phonics, a rapid sight word vocabulary is also focused on, for development of efficient reading. Difficulties in handwriting and mathematics are tackled simultaneously with instructions in phonology. Drills, rehearsals, practice and repetitions are required to consolidate the learning.

### Role of School and Parents

The role of the school and parents is very crucial in the successful remediation of a child with learning difficulties. The school has to be actively involved in the entire process of identification, assessment and remediation. For individual phonics instruction, children may have to be pulled out of the regular classroom for part of the school hour. Children with milder problems may be taught in the regular classroom itself but a high degree of awareness, commitment and motivation not to mention specific training is required from the teacher. Children may also need to attend after school programs.

The management of dyslexia in students in secondary school is based on accommodation rather than remediation. Accommodations are alterations in the way tasks are presented that allow children with LDs to complete the same assignments as other students. Common accommodations are preferential seating of the child, providing extra time for completion of tests, tape-recorded lessons and allowing verbal responses and frequent breaks. Individual tutoring or small-group instruction may be required in mathematics and/or written language if these disorders are also present. LD students in higher classes also need specific tutoring in study skills, organization of notes, time and material, and specific memory strategies. Use of assistive technology such as calculators, spell checkers, word processors and computers helps in making the task easier and makes it possible for learning disabled students to achieve success.

Parent counseling, education and support is essential to develop a supportive home environment and a consistent home/school program. Support and understanding of the parents and the school of the child's problem is vital for successful remediation. Affected children may also need other interventions such as pharmacological treatment if there is an associated ADHD or other comorbid conditions, social skills training for deficits in social cognition and behavioral management.

Periodic monitoring and review is essential to make sure that interventions are taking place. Review of pharmacological treatment, side effects is also necessary in children on medications.

### Facilities Available for Children with Learning Disability

Children evaluated fully and diagnosed as learning disabled by a registered psychologist can avail of many facilities. The psychologist has to make the recommendations suitable for the child and these recommendations are then forwarded to the relevant board of education through the school. Many educational boards recognize the difficulties faced by these children and are sympathetic to their plight.

- Second language exemptions are provided for children with dyslexia
- Extra time for board examinations is available
- Provision of scribes for children with dysgraphia
- Use of calculators in the examinations for children with dyscalculia.

National Institute of Open Schooling (NIOS) formerly known as the National Open School (NOS) is an autonomous educational board established by the Ministry of Human Resource Development, Government of India. NIOS offers a wide selection

of vocational and nonvocational subjects, as per students' choice regarding combination of subjects, up to the predegree levels. Students registered with NOS are free to select their subjects of choice in any combination and are free to pursue their education at their own pace. Several schools in major cities offer this facility. This is one option for education that pediatricians have to be aware of to guide their patients and parents (*www.nos.org*).

### MORE ON THIS TOPIC

- Bernstein S, Atkinson AR, Martimianakis MA. Diagnosing the learner in difficulty. *Pediatrics*. 2013;132:210-2.
- Chacko A, Uderman J, Feisen N, et al. Learning and cognitive disorders: multidiscipline treatment approaches. *Child Adolesc Psychiatr Clin N Am*. 2013;22:457-77.
- DuPaul GJ, Gormley MJ, Laracy SD. Comorbidity of LD and ADHD: implications of DSM-5 for assessment and treatment. *J Learn Disabil*. 2013;46:43-51.
- Kaufmann L, von Aster M. The diagnosis and management of dyscalculia. *Dtsch Arztebl Int*. 2012;109:767-77.
- Scanlon D. Specific learning disability and its newest definition: which is comprehensive? And which is insufficient? *J Learn Disabil*. 2013;46:26-33.
- Vedi K, Bernard S. The mental health needs of children and adolescents with learning disabilities. *Curr Opin Psychiatry*. 2012;25:353-8.

### IN A NUTSHELL

1. Learning disabilities are lifelong disorders. The diagnosis of affected children should be before second grade for better outcome.
2. Children with consistent poor school performance should be evaluated for learning disorders. Behavioral problems related to the educational setting should also lead to a suspicion of learning disorders.
3. Inclusive education with personalized attention in a supportive school and home environment is the cornerstone of management of specific learning disability (SLD).
4. Milder cases can be managed in the regular classrooms with slight modifications and accommodations. The moderate and severe cases need smaller group instruction.
5. Awareness of the facilities available for such children is not very well known and should be propagated by schools, pediatricians and other professionals.
6. Problems related to vision and hearing need to be ruled out before a structured evaluation for LD is done.
7. Phonetic-based management is important during preschool and primary classes.

## Chapter 21.12

# Anorexia Nervosa and Bulimia

Koushik Sinha Deb, Rajesh Sagar

Eating disorders (EDs) are a group of behavioral conditions characterized by insufficient, excessive or peculiar patterns of food intake which leads to health impairment and psychological distress in sufferers. Anorexia nervosa (AN) and bulimia nervosa (BN) are the most important EDs that have received wide attention from clinicians and researchers. However, it was increasingly realized that most patients with EDs did not meet the full criteria of either AN or BN, but rather fell somewhere in between, with some features of both. Currently *eating disorder not otherwise specified (EDNOS)* remains the most common diagnosis of ED reported worldwide. The recently published Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) and the upcoming International Classification of Diseases (ICD-11 to be released by 2017) therefore have made significant changes in the conceptualization of EDs, along with introduction of several new categories.

Eating disorders were previously often considered as a *Western disorder* of the affluent, driven by the social and cultural pressure for thinness and perception of beauty, and were labeled as a form of *culture-bound syndrome*. Over the last few decades, multiple reports of ED have been documented from eastern countries, most notable from Japan, Hong Kong and China reflecting the undeniable march of globalization and changing value systems in Asia. In India too, these disorders are being reported with increasing regularity from metropolitan cities, in tune with the changing definition of Indian beauty from buxom to petite.

The Composite International Diagnostic Interview (CIDI) and the Eating Disorder Examination-Questionnaire (EDE-Q) are most commonly used tools to generate ED diagnoses. The EDE-Q (Fairburn and Beglin, 1994) provides extensive information on multiple eating problems is often considered the method of choice for ED diagnosis and assessment. The Eating Attitudes Test (EAT: Garner and Garfinkel, 1979) is the most commonly used screening instrument for EDs.

## ANOREXIA NERVOSA

Anorexia nervosa is an ED where sufferers drastically reduce their total food intake or partake in severe physical exercise and other purging behaviors in their inexorable quest for progressive thinness. The term anorexia nervosa is derived from the Greek word *anorexia*, meaning loss of appetite, and the Latin word *nervosa*, implying of nervous origin; although true loss of appetite rarely occurs in AN. The syndrome is characterized by a morbid fear of fatness, resulting in significant self-induced starvation, despite the presence of a normal appetite. A disturbance of body image, characterized by the perception that one is distressingly large or of an abnormal body shape is also present.

## Epidemiology

Anorexia commonly affects young females between the ages of 10 years and 30 years. The lifetime prevalence of AN in young females is around 0.9%, although it varies widely (0.1–5.7%) between individual studies. AN is 10–20 times more common in females than in males and is even more frequent in specific risk groups like fashion models, ballet dancers, gymnasts and those involved in wrestling sports. The prevalence of EDs in India is unknown although there has been a recent increase in case reports from Delhi and Bengaluru. A case finding survey in 2012 among 66 qualified psychiatrists in Bengaluru however found a surprising 74 cases of ED in the previous 1 year, including 32 cases of AN, 30 cases of EDNOS and 12 cases of BN.

## Etiology

Dysfunction in the neurotransmitters involved in regulating eating behavior; namely: serotonin, dopamine and norepinephrine are commonly reported in studies. Endogenous opioids may play a role in denial of hunger by anorexic patients and opiate antagonists like naltrexone have been shown to cause dramatic weight gains in some AN patients. The dopamine receptor D4 (DRD4) gene abnormalities were associated with the binge/purge subtype of AN. Starvation induced biochemical changes, such as hypercortisolemia, hypothyroidism, and positive dexamethasone suppression test are also seen, although they reverse on alimentation. Positron emission tomography (PET) studies report an increase in caudate nucleus metabolism. Family studies report a concordance rate of 55% in monozygotic twins as compared to only 5% in dizygotic twins, suggesting strong genetic loading. AN occurs in 4–5% of first degree relatives of probands, while occurring in less than 1% of controls. About 88% of the AN vulnerability can be attributed to additive genetic effects and 12% explain for individual environmental effects.

Psychological factors implicated in etiology of AN include having a lifetime of generalized anxiety and obsessive-compulsive traits, a lack of the sense of autonomy and selfhood, poor self-esteem and low optimism. Such temperamental traits when combined with precipitating factors such as teasing, stressful events, social comparison lead to precipitation of the disorder. The society's emphasis on thinness and exercise also reinforces anorexic belief systems in both gender. A gay orientation in men is proven risk factors as the need for muscular slimness are very strong in such groups. In contrast, a lesbian orientation may be protective in females, as female partners may be more tolerant and less demanding regarding weight and body shape.

## Clinical Features and Diagnosis

Anorexia nervosa patients eat significantly less, although they harbor a normal appetite and indeed are often excessively preoccupied with food. Various food fads like cutting food on plate in multiple small pieces rather than eating it, arranging food obsessively, and hiding food in bags or at home are often present in sufferers. Inability to maintain the anorexic control results in *binging*, characterized by sudden bouts of excessive eating, which is then followed by *purging*, commonly by self-induced vomiting. Other compensatory behaviors of AN include abuse of laxatives, diuretics, insulin, thyroid hormones or excessive jogging and strenuous exercising.

Due to the persistent and severe energy restriction, individuals with AN fail to maintain a body weight that is appropriate for age, sex and developmental trajectory. In severe cases, features of starvation like abnormal reproductive hormone functioning, amenorrhea, hypothermia, bradycardia, orthostasis, dependent edema, hypotension and lanugo hair appear. Adolescents with AN might suffer from delayed puberty, and adults generally also show an aversion to sex while anorexic. The diagnostic criteria for AN as per ICD-10 are described in **Box 1**.

Patients of AN often report additional obsessive-compulsive behavior, depression or anxiety symptoms. Major depressive disorder or dysthymia is the commonest comorbid diagnosis and may be present in up to 50% of patients with AN. About half of AN patients develop symptoms of bulimia sometimes during the illness.

## Differential Diagnosis

Medical illness that can account for the weight loss [e.g., a brain tumor, cancer cachexia, hyperthyroidism, human immunodeficiency virus (HIV), tuberculosis (TB) or other chronic wasting disorders] need to be ruled out in all cases. Of psychiatric disorders, depression may mimic AN, with loss of appetite and weight

**BOX 1 ICD-10 criteria for anorexia nervosa**

- Body weight is maintained at least 15% below that expected (either lost or never achieved), or Quetelet's body mass index is 17.5 or less. Prepubertal patients may show failure to make the expected weight gain during the period of growth
- A self-perception of being too fat, with an intrusive dread of fatness, which leads to a self-imposed low weight threshold
- The weight loss is self-induced by avoidance of *fattening foods*. One or more of the following may also be present: self-induced vomiting; self-induced purging; excessive exercise; use of appetite suppressants and/or diuretics
- A widespread endocrine disorder involving the hypothalamic-pituitary-gonadal axis is manifest in the female as amenorrhea and in the male as a loss of sexual interest and potency.

loss. Depressive patients however are lethargic and complain of tiredness, whereas AN patients often are overly active. Schizophrenic patients when aversive to food generally claim their food to be poisoned, rather than having calorific concern. Anxiety patients too may have decreased food intake and suffer from rapid weight loss, although they do not suffer from body image misperceptions. Multiple gastrointestinal and eating-related problems may occur in somatoform disorder but the focus on symptoms and recurrent treatment seeking differentiates them from AN patients who are generally secretive and try to avoid treatment.

### Management

These patients are generally brought to clinical attention unwillingly by their family members, often resist treatment, or are openly hostile to treating team. Therefore, involving family members into the treatment plan is necessary for success. Hospitalization, at least at the beginning of the therapy, may be needed for severe cases and in patients where compliance to outpatient treatment fails. The primary consideration during hospitalization is to correct patients' dehydration, electrolyte imbalances and nutritional state; as these can seriously compromise health or lead to death. Constipation often occurs in AN due to the minimal food intake and is usually relieved when patients begin to eat normally. Stool softeners may occasionally be given, but never laxatives. Realimentation should be started slowly because of the rare complication of stomach dilation and the possibility of circulatory overload when patients immediately start consuming large calories. Multiple small feeds (about six) throughout the day or liquid food supplement may be better accepted by patients.

Psychotherapy is preferred over pharmacotherapy. Cognitive and behavioral approaches have the most evidence base and include teaching patients to monitor their food intake, their bingeing and purging behaviors, and their problems in interpersonal relationships. Cognitive restructuring to identify automatic thoughts about body image and to challenge them are useful. Family therapy, stressing on family relationships may also help. In pharmacotherapy, selective serotonin reuptake inhibitors (SSRIs) have had some success in causing weight gain and in reducing symptoms anxiety or depression, and fluoxetine at dosage at or above 20 mg/day has shown some promise in preventing relapse. Of the antipsychotics, olanzapine may help reduce anxiety, agitation, and improve weight; particularly in patients with binge-purge subtype of AN. Cyproheptadine, amitriptyline, clomipramine and pimozide have also been tried with mixed success. Programs which combine pharmacotherapy with prominent behavioral therapy approaches show the best outcome.

### Course and Outcome

The course of AN varies greatly ranging from spontaneous recovery to a gradually deteriorating course resulting in death caused by

complications of starvation. Mortality ranges from 5% to 18%. Only 25% of patients improve completely from all symptoms with treatment. Binge eating-purging type patients show better recovery than restrictive subtype. Another half of patients improve partially, and continue to have some preoccupation about food and weight throughout life. Patients with childhood neuroticism, parental conflict, vomiting, laxative abuse and other comorbid psychiatric symptoms have the poorest outcome.

### BULIMIA NERVOSA

The term bulimia comes from Greek, meaning *ravenous hunger*, and is a disorder characterized by uncontrollable *food binges* and *food purges*. In contrast to AN, patients with BN generally maintain a normal body weight. BN can be considered as a failed attempt at AN, where despite their body weight concern, patients lack the superego strength to prevent their eating binges.

### Epidemiology

Bulimia is more common than anorexia, and the lifetime prevalence of BN is estimated to be around 2–4% in young women. In males, the rates of BN are less than in females, at around 1.5%. BN is ten times more common in women than in men, and has an onset in early adulthood, generally later than the onset of AN. During college years, about 20% of women of industrialized countries go through transient bulimic episodes, although most remit spontaneously. Prevalence of BN in India is not known although individual case reports are not uncommon.

### Etiology

The neurotransmitters related to satiety, serotonin and norepinephrine, are also associated with BN. Additionally, raised plasma endorphin levels in BN patients who vomit may explain the feeling of well-being which these patients experience after vomiting. Genetic predisposition is lesser than AN. Socially, patients of BN tend to be high achievers and respond to social and cultural pressures for slimness. These patients often suffer from other impulse control problems like alcohol abuse, shoplifting and self-destructive sexual relationships.

### Clinical Features

Bulimia nervosa is essentially characterized by three cardinal features: (1) binges, (2) purges and (3) body image disturbances.

*Binges* refer to periods of rapid consumption of food, accompanied by a sense of loss of control overeating. Food that is sweet, soft, high on calories and otherwise avoided; like cakes and pastries, are preferred. Stress, negative mood states, adverse comments about body shape and lapse in dieting regimes often precipitate them. Patients typically binge in secret, in the middle of the night, in bathroom or when otherwise alone. Food is gulped rapidly and often not even chewed and some patients will consume any food without consideration for taste. Generally, about 1,000–2,000 kcal of energy is consumed per binges, although *subjective binges* triggered by eating small quantities of food also happen in some. Abdominal bloating, pain, exhaustion or running out of stock generally ends the binges and patients often suffer immediate subsequent distress termed *postbinge anguish*.

*Purging* follows the binge to counter guilt, anguish and physical discomfort. The commonest purging method involves self-induced vomiting by inserting finger into the throat, although some patients vomit on will. At all other times, BN patients invariably follow a strict dieting pattern, where the type, quantity and time of eating are strictly predetermined.

*Body image disturbance* Bulimia patients suffer from a morbid fear of fatness, worry about their body image and harbor concern about their sexual attractiveness. These weight-related concerns are seen



in almost all EDs are therefore considered as *core symptoms*. In contrast to AN patients who are not interested in sex, BN patients are mostly sexually active. Bulimia patients also generally maintain body weight within the normal weight range, although some may be overweight or underweight.

Bulimia nervosa patients also suffer from high rates of comorbid mood disorders, impulse control disorders, substance-related disorders and a variety of personality disorders. Past history often reveals food fads, pica and sexual abuse in childhood. The diagnostic criteria for BN according to ICD-10 are provided in **Box 2**.

#### BOX 2 ICD-10 criteria for bulimia nervosa

- Recurrent episodes of overeating in which large amounts of food are consumed in short periods of time
- Additionally, persistent preoccupation with eating and a strong desire or a sense of compulsion to eat (craving)
- The patient attempts to counteract the fattening effects of food by one or more of the following: self-induced vomiting; self-induced purging; alternating periods of starvation; use of drugs like appetite suppressants, thyroid preparations
- Binge eating happens at least two times per week over a period of 3 months
- A self-perception of being too fat, with an intrusive dread of fatness
- There is often, but not always, a history of an earlier episode of anorexia nervosa, the interval between the two disorders ranging from a few months to several years.

### Differential Diagnosis

Differentiating BN from AN can be difficult at times as both the disorders share several core features and patients often have phases of AN and BN alternating during the course of ED. Most diagnostic guidelines give preference to the diagnosis of AN when symptoms of both are present and label the condition as AN binge-purge subtype. Only when body weight is maintained, the diagnosis of BN is made. Of other psychiatric disorders, while depression closely resembles AN, atypical depression mimics BN. Atypical depression, as the name suggests, is an atypical form of depression, where instead of lack of appetite, patients suffer from overeating and excessive sleep with prominent increased libido. Organic conditions that may resemble BN include the Klüver-Bucy syndrome and the Kleine-Levin syndrome. Klüver-Bucy syndrome, resulting from bilateral temporal lobe lesions, presents with hyperphagia and hypersexuality mimicking BN but is differentiated by additional presence of hyperorality, visual agnosia and docility. Kleine-Levin syndrome is a sleep disorder characterized by persistent episodic hypersomnia where patients may also experience hyperphagia and hypersexuality. Other conditions to keep in mind include temporal lobe epilepsy and central nervous system tumors.

### Management

In contrast to patients of AN, most patients of BN can be managed on outpatient department (OPD) basis and hospitalizations are rarely necessary, except for management of electrolyte imbalance or gastric/esophageal tears. BN patients are also less secretive as many consider the binges to be ego-dystonic (distressing) thereby actively partaking in therapy for decreasing binges.

Pharmacotherapy includes tricyclic antidepressants and SSRIs. Fluoxetine can reduce binge-purge episodes by 50%. A higher dose (60 mg) has been found better than 20 mg. Sertraline and fluvoxamine are alternative drugs.

Cognitive behavioral therapy (CBT) has shown robust evidence of effectiveness and many national guidelines (NICE: UK) now suggest it as a first-line therapy option with Level A clinical evidence base. CBT has more patient retention as compared to pharmacotherapy alone and the benefits of CBT are maintained

even 12 months post-therapy. CBT aims to modify patient's cognitive distortions about food, weight and body image; while behavior alteration focusses on interrupting the cycle of bingeing and dieting. Other psychotherapies which have shown promise in BN include interpersonal therapy and dynamic therapy.

### Course and Outcome

The outcome of BN is better as compared to AN, with 40–50% of treated patients showing complete remission. Untreated patients continue a chronic course with partial remission and exacerbations over the years. A longer duration of the illness at presentation, past history of AN, other comorbid disorders like depression and substance use predict poorer outcome. Patients who resist purging generally show better outcome.

#### IN A NUTSHELL

1. Around 2–10% of young women of western countries suffer from EDs. AN has a prevalence of 1% while BN has a prevalence of 2–4% in young women.
2. Eating Disorder Examination-Questionnaire is the most commonly used tools to generate ED diagnoses. The EAT is the most commonly used screening instrument for ED.
3. Disturbance in body image is considered as one of the core psychopathology of ED and is seen in most EDs. AN additionally has significantly low body weight while BN patients generally maintain body weight. Binges and purges may happen in both disorders.
4. Anorexia nervosa has significant genetic loading while bulimia has more environmental risk factors.
5. Treatment of both AN and BN includes psychotherapy (CBT) and pharmacotherapy. SSRIs, particularly fluoxetine has been found useful in treatment.

#### MORE ON THIS TOPIC

- Balhara YP, Mathur S, Kataria DK. Body shape and eating attitudes among female nursing students in India. *East Asian Arch Psychiatry*. 2012;22:70-4.
- Basker MM, Mathai S, Korula S, Mammen PM. Eating disorders among adolescents in a tertiary care centre in India. *Indian J Pediatr*. 2013;80:211-4.
- Berkman ND, Lohr KN, Bulik CM. Outcomes of eating disorders: a systematic review of the literature. *Int J Eat Disord*. 2007;40:293-309.
- Chakraborty K, Basu D. Management of anorexia and bulimia nervosa: an evidence-based review. *Indian J Psychiatry*. 2010;52:174-86.
- Chandra PS, Abbas S, Palmer R. Are eating disorders a significant clinical issue in urban India? A survey among psychiatrists in Bangalore. *Int J Eat Disord*. 2012;45:443-6.
- Fairburn CG, Cooper Z, Murphy R. Disorders of eating: bulimia nervosa. In: Gelder M, Andreasen N, Lopez-Ibor J, Geddes J. *New Oxford Textbook of Psychiatry*. 2<sup>nd</sup> ed. Oxford; New York: Oxford University Press; 2012.
- Goyal S, Balhara YP, Khandelwal SK. Revisiting Classification of Eating Disorders-toward Diagnostic and Statistical Manual of Mental Disorders-5 and International Statistical Classification of Diseases and Related Health Problems-11. *Indian J Psychol Med*. 2012;34:290-6.
- Hasan TF, Hasan H. Anorexia nervosa: a unified neurological perspective. *Int J Med Sci*. 2011;8:679-703.
- Mandal P, Arumuganathan S, Sagar R, Srivastava P. A classical case of bulimia nervosa from India. *Indian J Psychol Med*. 2013;35:309-10.
- Mendhekar DN, Arora K, Lohia D, et al. Anorexia nervosa: an Indian perspective. *Natl Med J India*. 2009;22:181-2.
- Mitchison D, Hay PJ. The epidemiology of eating disorders: genetic, environmental, and societal factors. *Clin Epidemiol*. 2014;6:89-97.
- Russell G. Disorders of eating: anorexia nervosa. In: Gelder M, Andreasen N, Lopez-Ibor J, Geddes J. *New Oxford Textbook of Psychiatry*. 2<sup>nd</sup> ed. Oxford; New York: Oxford University Press; 2012.
- Treasure J, Furth E van, Schmidt U. *Handbook of Eating Disorders*. 2<sup>nd</sup> ed. Southern Gate, Chichester; Hoboken, NJ: Wiley; 2003. p. 496.

## Chapter 21.13

# Anxiety Disorders

Shoba Srinath, Preeti Kandasamy

Transient fear and anxiety occur in all typically developing children. Fear is an adaptive response with the severity falling on a continuum. Children typically manifest stranger and separation anxiety during infancy and toddlerhood, fear of darkness and animals in preschool and performance-related anxiety in school age which follows a developmental sequence and are usually nonimpairing. Anxiety is considered pathological when it is severe and persisting with extensive degree of avoidance, subjective distress and impairment.

## EPIDEMIOLOGY

Anxiety disorders are one of the most prevalent psychopathology in children and adolescent. Community surveys across the world have reported the prevalence of anxiety disorder ranging from 2% to 24%. In India, epidemiological studies have shown a prevalence of 4.1% among children aged 4–16 years and 14.4% among adolescents. In clinical samples, the prevalence is about 20%.

## ETIOPATHOGENESIS

Etiology is multifactorial with nature and nurture contributing to it. Twin studies have thrown light on the importance of nonshared environmental factors as concordance rates are often not more than 50%. While some of the anxiety disorders such as post-traumatic stress disorder are more influenced by environmental stressors; in most other subtypes, there is interplay between stress and vulnerability factors.

Family studies have shown a greater prevalence of panic disorder among family members of children with separation anxiety disorder. Research finding shows that what is inherited could be the vulnerability for a disorder than the disorder per se. Parental factors could contribute in two ways, one, through heritability others through modeling, fostering avoidance and/or through unhealthy parenting style such as overprotective, overcontrolling or overly critical parenting styles.

Behavioral inhibition, defined as the tendency to be unusually shy or to withdraw in novel situations, has been extensively studied as a risk factor for anxiety disorder; however, not all children develop impairing levels of anxiety as they grow up. Insecure attachment is also said to contribute to anxiety disorders.

Neurobiological research has shown serotonin, gamma-aminobutyric acid (GABA) and glutamate dysregulation and amygdala hypersensitivity in anxiety disorders. Of note is Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) which is characterized by acute onset of obsessive compulsive disorder and tic disorder.

## CLINICAL FEATURES

The presenting complaints are often not the classical anxiety symptoms. Children may present with school refusal, somatic complaints, dissociative (conversion) symptoms, poor academic performance, poor social interaction or tantrums and the anxiety symptoms become evident on eliciting the context of the above complaints. Developmental differences in presentation should be considered while evaluating a child for anxiety symptoms. Young children may not recognize fear as unreasonable, they may present with somatic complaints, crying, irritability and anger outbursts when faced by anxiety provoking situations.

Symptoms of anxiety can be cognitive, such as nervousness, fearfulness, self-defeating thoughts or difficulty concentrating; or behavioral which includes excessive shyness, avoidance, reluctance or restlessness; and/or autonomic disturbance most commonly sweating, tremulousness, hyperventilation, palpitation, etc.

## Subtypes

Separation anxiety and specific phobias are common in middle childhood; social phobia and panic disorder are more common in adolescence.

*Separation anxiety disorder* is characterized by developmentally inappropriate and excessive worry about separation from attachment figure associated with distress when anticipating or experiencing separation, worry about losing major attachment figure or experiencing negative event such as getting lost.

*Social anxiety disorder* is marked fear of social situations associated with fear of being negatively evaluated during peer interaction and not just in interaction with adults. Selective mutism can be considered a severe form of social anxiety where there is failure to talk in specific social situations, e.g., a child refuses to speak at school, but speaks well at home and the symptoms cannot be explained by a communication disorder or lack of knowledge of spoken language.

*Specific phobia* is marked by significant fear and avoidance of specific objects such as animals, natural environment, blood-injection-injury or situational.

*Generalized anxiety disorder* is manifested as excessive anxiety and worry about a number of events. It is characterized by free-floating anxiety and worries about past and future events not restricted to specific theme or situation.

*Panic disorder* is characterized by abrupt surge of intense fear associated with palpitation, trembling, sweating, shortness of breath, dryness of mouth with fear of dying or losing control.

*Obsessive compulsive disorder* though currently not classified under the rubric of anxiety disorders, is of considerable importance to a pediatrician as it has a prevalence of 1%. Children commonly present with repeated thoughts of contamination, harm befalling family members and repeated washing, checking, arranging compulsions and can be secretive about it. In post-traumatic stress disorder, children have recurrent intrusive memories of traumatic events, nightmares and avoidance of trauma-related cues.

## DIFFERENTIAL DIAGNOSIS

A good clinical evaluation can rule out any other medical cause for the anxiety symptoms such as hypoglycemia, hyperthyroidism, cardiac arrhythmias, mitral valve prolapse, pheochromocytoma, seizure disorder, migraine, medications or substance abuse/withdrawal that can cause autonomic disturbance mimicking anxiety symptoms. Anxiety symptoms are a common occurrence along with many psychiatric diagnosis especially depressive disorders. *Vice versa*, 28% to 69% of children with anxiety have a comorbid depressive disorder. Attention deficit hyperactivity disorder and autism spectrum disorder can also have co-occurring anxiety disorders.

## APPROACH TO DIAGNOSIS

Given the high prevalence of anxiety disorders in community and clinic sample, it would be good practice to routinely enquire for anxiety symptoms in children presenting with any behavioral or emotional problems. As anxiety has a protective function, drawing the line between normal and pathology can sometimes be a challenge. Key factors that a clinician should consider are the level of impairment in the form of interference with school or

social functioning, subjective distress and most importantly ability of the child to recover when removed from the anxiety provoking situation. These could indicate the severity of the symptoms and dictate management plans.

As it is primarily, a clinical diagnosis evaluation should include a detailed history of the onset, development and context of anxiety symptoms whether it is stimulus specific or spontaneous, anticipatory or generalized; assessment of school functioning and impairment, good family psychiatric history and treatment history.

Predisposing factors including temperament of the child, genetic vulnerability; precipitating factors such as bullying, change of school, exam; parental anxiety and unhealthy parenting style would help in understanding the child's symptoms. Maintaining factors such as parental responses or access to rewarding activities in child with school refusal need to be elicited and addressed.

Young children may have difficulties in communicating or elaborating the cognitive, emotional and behavioral symptoms; however, most children can label their emotion and the distress associated with it. Because of the subjective nature of anxiety symptoms, it is important to assess severity of anxiety and associated distress from the child or adolescent's viewpoint. Self-report screening questionnaire or clinician-rated scale such as Screen for Child Anxiety Related Emotional Disorders (SCARED) or Pediatric Anxiety Rating Scale can be used.

## MANAGEMENT

### Nonpharmacological Treatment

It is the mainstay of treatment (**Box 1**). Cognitive behavioral therapy is one of the most effective interventions. Some components which can be done in a pediatric set-up includes educating the child and parent about anxiety disorder and working in collaboration with them, explaining the mind-body relationship, thought-feeling-behavior cycle, teaching relaxation strategies such as diaphragmatic breathing, asking child to maintain tension diary to help the child monitor and make the stress symptom association. It is often useful to use a visual analog scale or *Tension* thermometer to help the child rate the subjective unit of distress at baseline and during follow-up.

#### BOX 1 Nonpharmacological interventions for anxiety disorders

##### Generic interventions for all anxiety disorders

- Relaxation strategies
- Monitoring anxiety on a visual analog scale (Tension diary)
- Problem-solving skills rather than avoidant-focused coping
- Positive self-talk

##### Specific interventions

- Systematic desensitization and exposure for specific phobia
- Graded return to school for separation anxiety, school phobia
- Graded exposure to feared social situations, social skills training, and role play for social anxiety disorder.

*Parental interventions* include addressing parental anxieties, helping parents encourage children to face anxiety provoking situations through graded exposure; use of gentle disciplining and avoiding criticism and intrusiveness; practicing relaxation and remaining calm when faced with an anxiety provoking situation to help the child learn through modeling. Sending a note to the teacher with the child's consent can help a child with school-related stressor.

### Pharmacological Intervention

Drugs are used as an adjunct in children with severe symptoms. Given that majority of the children show improvement with nonpharmacological interventions in a short span and considering

the long-term side effects with psychotropics, it is important to consider a trial of psychotherapy before deciding on medication when symptom severity is mild to moderate. Avoid short-acting benzodiazepine; when indicated a short trial (2–4 weeks) of long-acting benzodiazepine such as clonazepam 0.25–1 mg HS, with a tapering dosage schedule should be used with caution to avoid dependence. Sedative side effects can be a limiting factor. Children with prominent autonomic arousal in performance situations would benefit from beta-blockers such as propranolol 10–40 mg SOS if not contraindicated. In children with severe symptoms requiring long-term pharmacological interventions, selective serotonin reuptake inhibitors (SSRIs) are the first-line drugs. Most commonly used are low doses of fluoxetine, sertraline or escitalopram. Avoid tricyclic antidepressants in view of cardiac side effects. **Box 2** provides list of clinical situations where referral should be made.

## OUTCOME

Prospective studies have found that majority of children are free from their anxiety disorders at follow-up, with relapse only in a few children. However, adolescents with anxiety disorders are at an increased risk to develop depression, substance dependence and educational underachievement.

## PREVENTION

Primary prevention should focus on enhancing child's coping skills as it is a protective factor. Pediatrician can play an important role in early diagnosis as anxiety disorders are often under-reported and under-recognized.

### IN A NUTSHELL

1. Anxiety disorders cause significant impairment in academic and social functioning of children.
2. Parental anxiety and unhealthy parenting styles can be important predisposing factors.
3. These disorders have varied clinical presentation, indirect presentations are most common and presence of comorbidity is the rule.
4. Nonpharmacological interventions are effective. Pharmacological interventions to be offered only when symptoms are severe. When indicated, SSRIs are first-line drugs.
5. School-related stressor such as bullying and academic difficulties needs to be explored and addressed.

## MORE ON THIS TOPIC

- Clark DM. Social anxiety disorder: recognition, assessment and treatment. NICE clinical guideline. From: <http://guidance.nice.org.uk/cg159>. Accessed October 29, 2014.
- Connolly SD, Bernstein GA; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with Anxiety disorders. *J Am Acad Child Adolesc Psychiatry*. 2007;46:267-83.
- Eapen V, Graham P, Srinath S. Where There is No Child Psychiatrist: A Mental Health Care Manual. 1<sup>st</sup> ed. The Royal College of Psychiatrists, Glasgow: Bell & Bain Ltd.; 2012.
- Piacentini J, Bennett S, Compton SN, et al. 24- and 36-week outcomes for the Child/Adolescent Anxiety Multimodal Study (CAMS). *J Am Acad Child Adolesc Psychiatry*. 2014;53:297-310.
- Russell PS, Nair MK, Mammen P, et al. ADad 5: the co-morbidity in anxiety disorders among adolescents in a rural community population in India. *Indian J Pediatr*. 2013;80:S155-9.
- Srinath S, Girimaji SC, Gururaj G, et al. Epidemiological study of child and adolescent psychiatric disorders in urban and rural areas of Bangalore, India. *Indian J Med Res*. 2005;122:67-79.



## Chapter 21.14

# Evaluation of Mental Well-Being

*Manju Mehta, Sneh Kapoor*

The role of sound mental health for healthy physical and emotional functioning is critical. Mental health is crucial in determining quality of life, relationships, vocation and productivity across the life span. It, then, becomes important to ascertain the role of mental well-being in the early formative years as a precedent to later development and functioning. Mental health problems in childhood cause difficulties not only for the child but also for the family and significant others. Thus, the understanding and adequate evaluation of mental well-being is important in childhood, and in some cases, starts right at infancy.

Evaluation of mental well-being of children often takes on a two-pronged approach. One may rely on a detailed clinical interview along with observation of the child in various settings, which are to be corroborated by reports of parents and teachers. Often, a clinician can also choose to use standardized scales to evaluate certain aspects of mental well-being such as cognitive development, social and adaptive functioning among others.

### DETAILED CLINICAL INTERVIEW: IDENTIFYING IMPORTANT SIGNS/SCREENING

A detailed clinical interview eliciting birth history, developmental milestones and any other significant medical conditions is the first step in evaluating the child for mental health issues. Following this, parents are asked questions pertaining to the child's present concerns or any concerns that the parents may have about the child's emotional or mental well-being, or any concerns regarding the child's behavior. Important signs to look out for *at home* could include sudden unexplained withdrawal from significant family members or some particular members of the family, excessive or age-inappropriate crying, aggression, sibling rivalry, excessive clinginess/withdrawal towards one parent/family member, excessive fear or avoidance of certain situations/places. Certain other complaints that the parents may come with may include incontinence/enuresis or age-inappropriate habits such as thumb sucking, nail biting. School-going children often report with complaints of frequent stomachache/headache/vomiting, or problems in adjusting to school life due to excessive social fear.

School-going children may report with the above concerns at home or may present with a different set of difficulties at school. Problems of sudden declining performance at school, loss of interest in class activities, withdrawal, poor participation, clinginess, school refusal/drop out or refusal to go home may be indicators of deeper rooted problems and could also be manifestations of childhood depression. Other problem behaviors or tell-tale signs could be inattention, hyperactivity, frequent out of seat behavior, irritability, aggression—both verbal and physical, bullying, etc.

### STANDARDIZED SCALES

Some important clinical scales that are often used in clinical practice to assess the mental well-being of children are discussed in this section. Some of the common scales are discussed below.

#### Development and Well-being Assessment

The Development and Well-Being Assessment (DAWBA) developed by Goodman et al. in 2000 is a set of interviews,

questionnaires and rating techniques that elicit information to help formulate a psychiatric diagnosis for children and adolescents between 5 years and 17 years of age. The diagnoses are based on the International Classification of Diseases, Tenth Revision (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and include common emotional, behavioral and hyperactivity disorders. Owing to its recent development, the test can be administered in both paper-pencil format, or by a computer for reduced cost and time taken.

#### Child Behavior Checklist and Youth Self-Report

The Child Behavior Checklist (CBCL) developed by Thomas Achenbach (2001) is a screening checklist devised to identify emotional and behavioral problems in children and adolescents. It is often used as a parent-rated or clinician-rated scale. The CBCL is for use with children/adolescents between 6 years and 12 years of age, and uses a Likert scale to assess for eight scales/syndromes. The Youth Self-Report (YSR), also developed by Achenbach, is a self-report screening tool for behavioral and emotional problems to be filled in by the concerned children or adolescents. It is standardized for use with children 11 years and older; and yields scores on eight empirically derived syndrome scales. These scales are listed below:

1. Anxious/depressed
2. Depressed
3. Somatic complaints
4. Social problems
5. Thought problems
6. Attention problems
7. Rule-breaking behavior
8. Aggressive behavior.

The 2001 revision also added six scales to screen for diagnostic categories according to the DSM:

1. Affective problems
2. Anxiety problems
3. Somatic problems
4. Attention deficit hyperactivity disorder (ADHD)
5. Oppositional defiant problems
6. Conduct problems.

The responses are to be rated in accordance with behavior over the past 6 months. The YSR and the CBCL are also scored on (optional) competence scales for activities, social relations, school and total competence.

#### Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ) is a brief behavioral screening questionnaire about 3–16 years old. It has various versions, all of which assess for 25 attributes, divided between five scales of: (1) emotional symptoms, (2) conduct problems, (3) hyperactivity/inattention, (4) peer relationship problems and (5) prosocial behavior (each with 5 items).

The same 25 items are included in questionnaires for completion by the parents or teachers of 4–16 years old (Goodman, 1997). For younger children (3–4 years old), a slightly modified informant version is used. Many clinicians use the SDQ as the initial self-report assessment before beginning the actual sessions or clinical assessment. These results can determine further assessments by guiding the clinician about other overlooked categories that may not have come up in the presenting problems. For example, a child that may be referred with complaints of oppositional behavior may also reflect on attentional problems on the SDQ, which may have been overlooked had the SDQ not been used during the initial assessment.



## Vineland Adaptive Behavior Scale

The Vineland Adaptive Behavior Scale (VABS) is designed to measure adaptive behavior of individuals from birth to age 90. The second revision of this scale contains five domains each with 2–3 subdomains. The domain scores yield an adaptive behavior composite. The main domains are:

- Communication
- Daily living skills
- Socialization
- Motor skills
- Maladaptive behavior (optional).

It is primarily used for measuring daily functioning and adaptive behavior and for screening purposes for diagnosis in the autism spectrum disorders or other genetic disorders. It can also be used as a screening for developmental delays or behavioral and emotional problems.

## Projective Testing

Tests such as *Draw-A-Person Test* as well as *Children's Apperception Test* are projective techniques. These tests are often employed for a deeper understanding of any conflicts or problems that the child may be facing that are not amenable to direct scrutiny or readily reported. Due to their ambiguous nature and the informal nature of activities involved (such as drawing, storytelling, etc.), these tests aid in rapport formation and are more accepted by children, who may feel daunted in a testing environment and may develop resistance to long scales and being repeatedly questioned about their behavior. In cases of deeper emotional problems and interpersonal conflicts, these tests yield valuable information that may not be reported directly on objective tests by parents or the children themselves.

## ASSESSMENT OF PSYCHOPATHOLOGY

Some commonly used clinical scales to assess common mental disorders that may occur during childhood, such as anxiety, depression, obsessive-compulsive disorder are enumerated in **Table 1**.

### MORE ON THIS TOPIC

Achenbach TM, Rescorla LA. Manual for the ASEBA preschool forms and profiles. Burlington, VT: University of Vermont, Department of Psychiatry; 2000.

Goodenough F. Measurement of intelligence by drawings. New York: World Book Co.; 1926.

Goodman R. The strengths and difficulties questionnaire: a research note. *J Child Psychol Psychiatry*. 1997;38:581-6.

**Table 1** Common scales to assess mental disorders in children

Disorder	Scale	Age range	Administered by
Anxiety	Beck anxiety inventory for youth	7–14	Child/adolescent
	Beck anxiety inventory	7	Child/adolescent, parent and clinician
	State trait anxiety inventory for children	9–12	Child/clinician
	Liebowitz social anxiety scale-child and adolescent version	7 and above	Child, parent, clinician
Obsessive-compulsive disorder	Children's Yale-Brown obsessive-compulsive scale	6–14	Clinician
Depression	Children's depression rating scale-revised	6–12	Clinician
	Kiddie schedule for affective disorders and schizophrenia	6–18	Clinician
	Children's depression scale	7–18	Clinician
	Child depression inventory	7–17	Child, parent, clinician
	Beck depression inventory for youth	7–14	Child

Goodman R, Ford T, Richards H, et al. The development and well-being assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry*. 2000;41:645-55.

Harris DB. Children's drawings as measures of intellectual maturity. New York: Harcourt, Brace & World; 1963.

Sparrow SS, Cicchetti DV, Balla DA. Vineland-II adaptive behavior scales: survey forms manual. Circle Pines, MN: AGS Publishing; 2005.

### IN A NUTSHELL

1. Early evaluation and identification is the key to facilitating promotion of mental well-being in children, and is the key to fostering later development and adequate functioning.
2. Evaluation of mental well-being of children often takes on a two-pronged approach: detailed clinical interview along with observation of the child in various settings; or use standardized scales to evaluate certain aspects of mental well-being such as cognitive development, social and adaptive functioning among others.

## Chapter 21.15

# Management of Psychological Illness

Paul Russell

Child psychiatric disorders can be broadly divided into those that have a developmental cause (e.g., autism), organic psychiatric illness secondary to disorders of the nervous system (e.g., trauma, infections) or other bodily systems (e.g., hypothyroid states resulting in depression), biologically mediated psychiatric illness where there are biochemical or electrophysiological abnormalities (e.g., psychoses and mood disorders) and psychologically mediated illnesses that happen because of psychological mechanisms of the mind that are maladaptive in nature (e.g., conversion disorder). This latter group of illnesses can be called as psychological illnesses.

Psychological illnesses (often described as having medically unexplained symptoms in primary care pediatric settings) are prevalent in 10% of children, with 11% among girls and 4% among boys. Recent research works support the view that childhood psychological illnesses have the propensity to continue into adulthood with significant impairment personally and illness burden to the society. This chapter will discuss the psychological illnesses in children with a psychological framework for its etiology and management.

### PATHOGENESIS

Though many biological models such as Hilgard's neodissociation model, Oakley's attention control model, Kozłowska developmental model, Stonnington's theory of mind model, and Brown's errors in information processing and representation model are all potentially plausible, the model that well explains the pathogenesis and has an effective treatment approach is the *psychodynamic model*. As these groups of disorders are psychological in nature and in order to understand the psychodynamic etiology with its consequent treatment techniques, the basic understanding of the human mind is essential.

### Understanding the Human Mind

The human mind is like an iceberg where the small visible tip, *the conscious*, is the first layer of the mind with all its contents fully available to our awareness (e.g., available to the memory). The *preconscious* is the second strata of the mind, of which the individual is mostly unaware, and has many psychological defense mechanisms that prevents re-entry of past life events and their associated unpleasant emotions (e.g., anxiety and sadness) from the unconscious to the conscious, and thus protects the child. Every traumatic life event, that is unpleasant to the child, is sent deep into the third level of the mind namely *the unconscious* that is totally unavailable to the child's awareness, by the primary defense mechanism of repression (Fig. 1). This defense mechanism of repression (mechanism by which events with their unpleasant emotions are kept away from consciousness) is effective enough to protect the child from emotional trauma most of the time.

### Response to Emotional Trauma

When the emotional trauma is overwhelming and the defense mechanism of repression is unable to repress the original traumatic event and the associated emotions into the unconscious

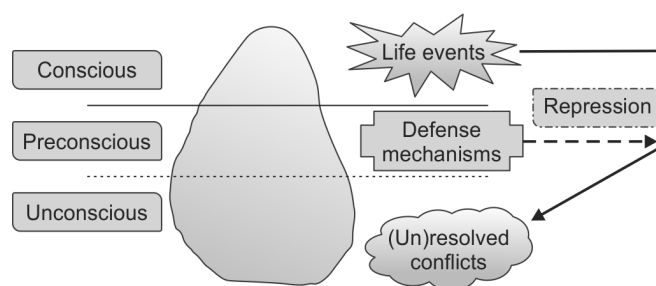


Figure 1 The structure and functioning of a normal mind

or, secondly, when similar traumatic events continue to happen, the original unresolved but repressed traumatic event gains more emotional strength and the trauma with its emotions escapes to the conscious, compounding the anxiety in the child. For this renewed traumatic emotions to be sent back to unconsciousness, other secondary defense mechanisms will have to be roped-in by the child's unconscious.

There are adaptive secondary defense mechanisms (e.g., humor, channelization, sublimation) and maladaptive secondary defense mechanisms (e.g., denial, regression, conversion). Depending on the type of secondary defense mechanism(s) used in addition to repression, the type of symptom presentation and thus the psychological illness varies. To explain this further, if the secondary defense mechanism of isolation (mechanism by which the life event and the emotions are isolated and thereby not interfering with the day to day thought process) and conversion (mechanism that converts isolated emotions into a physical symptom) are used after repression, the event is isolated from its emotions and the isolated emotions are converted into loss of bodily functions. Often the organ that perceived the traumatic event shows the bodily symptom, by the process of organ of choice, and specific organs are affected (e.g., child who had seen crime might become psychogenically blind). Similarly, isolation with dissociation (mechanism that splits a group of mental processes from the main body of consciousness) or isolation with somatization (mechanism by which thinking and feeling of bodily symptom is not differentiated) results in dissociative or somatoform/somatization disorders respectively.

In psychological illnesses, thus *primary gain* refers to the extent to which a bodily symptom diminishes the unpleasant emotions at the unconscious level (e.g., having a psychogenic seizure episode when the stern teacher at school reminds the student of the abusive father at home and the fight back at home between parents. Here the bodily symptom is produced unconsciously by psychological defense mechanisms, by which the child has diminished the overwhelming anxiety at that point in time. *Secondary gain* is achieved when the symptom presentation serves to help the individual avoid the situation generating the unpleasantness (e.g., having psychogenic seizures at home and thus can avoid meeting the stern teacher). Gaining attention, emotional support and tangible rewards with the aid of symptoms from persons in the environment are also examples of secondary gain. *Tertiary gain* refers to the homeostasis in the family that is brought about by the child's symptoms (e.g., parents not having fights and focusing on the child's symptoms that bring about peace at home). The treatment plan has to address all these forms of gains.

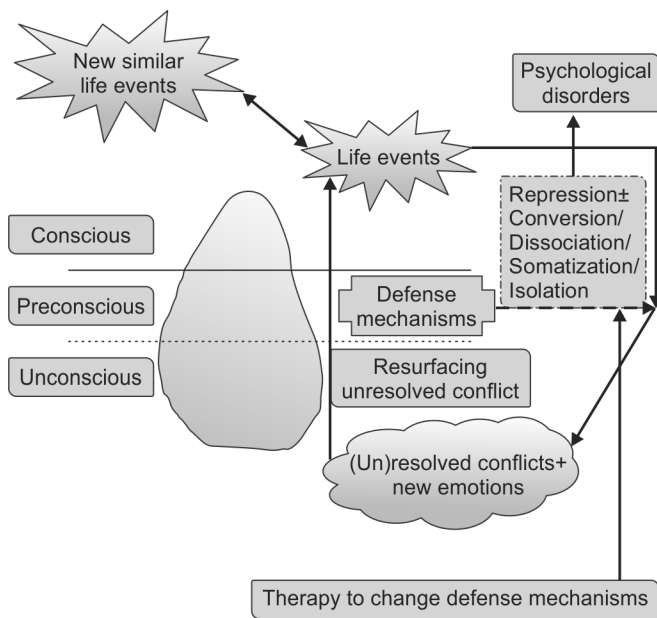
### PSYCHOLOGICAL ILLNESS

When the symptom is produced unconsciously (by psychological defense mechanism) for some unresolved unconscious conflict

(e.g., psychogenic seizures caused by unconscious psychological mechanisms to diminish the unpleasant emotions caused by factors the child is unable to identify), it is either a somatization/conversion/dissociative disorder (**Fig. 2**). The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) categorizes the psychological illnesses under the categories of dissociative disorder as well as somatic symptom disorder and related disorders, whereas the International Classification of Diseases (ICD-10) classifies these illnesses mainly under neurotic, stress-related and somatoform disorders (**Table 1**).

## DIAGNOSIS

These illnesses are generally of acute onset but can also have symptoms that may gradually worsen over time. In general,



**Figure 2** The mechanism of unresolved conflicts and defense mechanisms resulting in psychological disorders

**Table 1** The nomenclature of psychological illnesses in DSM and ICD diagnostic systems and their symptom presentation

DSM-5 illnesses	ICD-10 illnesses	Symptom presentation
Dissociative disorder	Dissociative/Conversion disorder	Dissociative identity Dissociative amnesia Depersonalization Derealization Trance and possession + symptoms of conversion for ICD-10
Somatic symptom disorder	Somatization disorder Somatoform pain disorder	Somatic symptoms with excessive symptom preoccupation and impairment
Illness anxiety disorder	Hypochondriacal disorder	Various somatic symptoms with excessive fear about an underlying illness and impairment
Conversion disorder		Paralysis Abnormal movement Swallowing symptoms Speech symptoms Seizures Sensory and special sensory impairments

psychological illnesses should not be considered as a diagnosis of exclusion although every somatic symptom in a pediatric setting should be investigated for a potential underlying physical illness. It should be remembered that psychological illnesses often concurrently exist with several medical and psychiatric conditions. Thus, initial diagnosis of psychological illness without a complete physical examination and other medical investigations is discouraged.

The diagnosis of any psychological illness has two components. Firstly, ruling out a physical cause and, secondly, ruling in a psychological cause for the somatic symptoms. If both these components are not considered together during diagnosis, the possibility of misdiagnosis and missed diagnosis will prevail especially in primary care pediatric settings, where medical diagnostic tests are less developed, and physical causes are not ruled out adequately. On the other hand, in tertiary care settings, overinvestigation for physical symptoms will happen and underdiagnosis of psychological illness can happen when psychological causes are not ruled out adequately. It should also be remembered that overinvestigation need not dispel fears but can exacerbate anxiety, as well as result in reinforcement and fixation of symptoms.

The treating pediatrician should request for medical investigations that keep with the symptom presentation and the potential organic diagnoses being entertained. Thus, laboratory investigations to exclude electrolyte disturbances, blood sugar disturbances, renal failure, systemic infection, toxins and medication, an electroencephalograph to distinguish pseudoseizures from a true seizure disorder; radioimaging to rule out an occult neoplasm or space occupying lesion may be required.

After ensuring the absence of a physical cause that can explain the presenting symptoms, the physician may use the DSM-5 diagnostic criteria for these disorders or, in busy settings, use appropriate measures for ruling in a psychological illness (e.g., Child Dissociative Checklist, Children's Somatization Inventory). Often, the psychological gains or stresses may not be apparent in the beginning, but they become evident later by their symbolic and temporal correlation to symptom onset or symptom worsening and symptom profile.

## DIFFERENTIAL DIAGNOSIS

The differential diagnoses for psychological illnesses range from life-threatening organic causes to normative behavior in children. Although there is a plethora of physical disorders that need to be considered as a differential diagnosis, which depends on the interpretation of the symptom clusters by the pediatrician, this chapter's focus is on illnesses that have medically unexplained symptoms.

### Normal Behavior

Developmentally, young children can present with physical symptoms without identifiable organic cause for a few hours or days after a minor injury. Cognitive difficulty in verbalizing the associated emotional distress is considered to be the cause for such physical symptoms. These symptoms are considered normal for children in this age group, and the role of psychological stressors is minimal.

### Symptom of Other Psychiatric Disorders

Physical symptoms can be part of many other psychiatric disorders like post-traumatic stress disorder, where peritraumatic conversion or dissociation symptoms are common. In these children, there is usually a historical evidence for catastrophic trauma (e.g., natural or man-made disasters that the child has witnessed or has

survived) in the past 6 months. Also, somatization, conversion or dissociation symptoms are often seen in anxiety disorders and depressive disorders among children. These disorders will have to be ruled out before the treatment plan is made.

### Factitious Disorder

The diagnosis of factitious disorder depends on evaluating two different dimensions in the child namely: (1) the awareness of the symptom production and (2) type of gains for the symptoms (**Fig. 3**). When the child voluntarily produces symptoms for some unresolved internal conflict (e.g., feigning bleeding for stresses caused by factors that the child is unable to identify, and often has to be uncovered with psychological tests), it is factitious illnesses. There is compelling need to produce symptoms for unknown psychological reasons, thus children with factitious illness can subject themselves through even invasive medical procedures and voluntarily hospitalizations.

### Malingering

If the child is voluntarily producing the symptoms for an identifiable and tangible external gain (e.g., feigning fits to avoid examination at school), it is malingering (**Fig. 3**). Inconsistencies between history and objective findings, as well as observations that are inconsistent should bring in the possibility of malingering or the Munchausen's syndrome among children with unexplained medical symptoms. Furthermore, in children, Munchausen by Proxy is also prevalent when a family member or caregiver can induce physical or psychological symptoms in the child for their own psychological benefits.

	External gain	Internal gain
Conscious symptoms	Malingering	Factitious
Unconscious symptoms	--	Somatization Conversion Dissociation

**Figure 3** Differential diagnosis for psychological illnesses

## TREATMENT

Children with psychological illnesses almost always present to the pediatrician or family physician as their first medical consultation because the presenting symptom is mostly medical in nature. Therefore, treatment from the prehospital to follow-up period of children, with medically unexplained symptoms, may change from a possible physical illness to a psychological illness.

### Prehospital Treatment

Treat patients as if their symptoms have a physical (developmental, neurochemical, neurophysiological or organic) origin as prehospital services (e.g., ambulance and triaging services) most often do not have the resources to distinguish a psychological illness from a physical illness.

## Hospital Treatment

### Rule Out Medical Cause

Pediatricians in emergency settings must be aware that the diagnosis of a possible psychological illness disorder does not eliminate the presence of underlying physical disease, and in acute care settings approach each child as if their symptoms have an organic basis and treat them accordingly. But again it should be reiterated here that the psychological illness diagnosis should not be made solely on the basis of negative medical reports.

### Arrange for Consultation

Consultation should be considered during the period of admission or discharge from casualty with other medical and surgical departments for any child with the first episodes of psychological illnesses. Organizing a psychiatric consultation is necessary when a physical cause is eliminated in the casualty or afterwards. Arranging for a psychiatric consultation minimizes the stigma and hospitalization by directing these patients to appropriate outpatient follow-up care in psychiatry. Despite the symptom genesis being in the mind, do not query the reality of the symptoms but acknowledge impairment and impacting of the symptoms on the child and family respectively. Before referring to psychiatry try to comprehend the family's viewpoint about the illness, level of certainty for physical causes, agreement with investigations, level of conviction for psychological causes and views about the psychiatric referral and treatment.

### Control of Dangerous Symptoms

Besides, if the child has symptoms that are dangerous to self or others in the surrounding a sedative, antianxiety agent can be administered. Usually a short-acting benzodiazepine that dissolves in the mouth (e.g., lorazepam 0.5–1 mg as a stat dose) can be given along with suggestion, in an authoritative and yet a not confrontative manner, that symptoms are likely to abate soon. Suggestions such as these will calm the child down in acute care settings but is not an end by itself for the psychological treatments.

### Outpatient Therapy

If the pediatrician or the family care physician decides to treat the child, instead of referring to a mental health professional, the following steps need to be followed.

### Face-Saving Measures

The child might be given some face-saving measures whereby the symptoms are acknowledged and a way out of the symptoms is given (e.g., for child with paraplegic symptoms, a supportive walker is provided initially and slowly graded down to tripod stick, walking stick and walking without any support) as the psychotherapy progress. The treating pediatrician at this point should stop all oral and parenteral medication given as the treatment for the physical symptom (e.g., analgesics for pain symptoms). As face-saving measure bandages, ointment and various physical therapies can be suggested. These measures should be accompanied by the information to the child that all medical tests indicate normal bodily functions, and the lost abilities can be recovered or pains controlled.

### Shifting from Medical to Psychological Model of Illness

While arranging the consultation, it is important that the pediatrician discusses with the family about the psychological nature of the illness. Make families aware of the high prevalence of medically unexplained symptoms among children. Furthermore, do not express a sense of awkwardness when communicating the diagnosis of a psychological illness, as such expressions might worsen the stigma and treatment compliance.



It is important to introduce the psychological model of illness to them, as by now the parents have come to believe that there is a possible medical illness with their child. It is important for the family to understand that neither the cause nor the effect of the symptoms has physically damaged the child. Firstly, teach the family about the mind-body relationship and how mind controls the body (e.g., on seeing a snake, fear happens in the mind and it commands the body to react). Secondly, the bodily reaction can vary from person to person for the same emotion of fear (e.g., run away, call for help, killing the snake or having psychogenic seizure). Thirdly, that some of these reactions are culturally accepted and understood (adaptive reaction like running away) and others are not (maladaptive reaction like having a psychogenic seizure). Fourthly, while adaptive reactions are mediated by adaptive defense mechanisms, maladaptive reactions are mediated by maladaptive defense mechanisms (as discussed before in detail). So one of the main goals is to help the child use more adaptive mechanisms instead of maladaptive defense mechanisms for handling various life events.

### *Shifting from Malingering to Psychological Model of Illness*

Following this, parents almost always change from a medical model for the symptoms, but often fail to recognize the difference between the psychological model and malingering model for the past symptoms, and as a result punishment ensues to stop as well as prevent such symptoms adding to the child's woes. Parents have to learn the difference between the psychological and malingering model as discussed before (**Fig. 3**).

### *Addressing of Secondary Gains*

While addressing the gains, start with the removal of secondary gains. Take an inventory of people, situation and type of secondary gains the child is obtaining (e.g., family members, peers, teachers, neighbors at home, school, neighborhood and play ground in the form of making the child sit down, massaging, avoiding going to school or giving attention). After identifying the nature of the secondary gains, explain to the family or others that such secondary gains work as rewards for perpetuating the demonstration of physical symptoms and has to be stopped (e.g., if the parents out of fear of symptoms occurring on going to school, allow the child to stay at home, it provides the child the chance to avoid many other possible unpleasant situations at school, not only the stern teacher, and thus acts as a secondary gain). Educate the parents that rewards like attention and tangible rewards should be contingent only on the child going to school without getting symptomatic and no reward is given whenever the child becomes symptomatic. When the child becomes symptomatic, it is best to ignore the symptom (and not the child as we are only against the symptom and not the child!): the most difficult step for the parent to follow, especially when the symptoms are so worrisome. Finally, also prepare the family to anticipate worsening of the symptoms when steps are taken to stop secondary gains, as children are not going to give up on symptoms that were so useful to them. If and when the worsening happens, instead of the parents getting worried, it helps them to reason out the cause for this aggravation in order to stay on course with your therapy.

### *Tertiary Gains*

When the physical symptoms in the child is the only way of keeping the family cohesive and the child understands his or her role in the family homeostasis (e.g., preventing divorce and thereby collapse of the family), the tertiary gains have to be addressed with marital and family therapies. As these therapies are time consuming and need a fair amount of professional training, an appropriate referral

to a mental health professional adept in addressing these concerns is needed. However, the pediatrician may have to look at the child rearing consensus among parents, enhance the limit setting roles of the parents, remove the role modeling of physical symptoms in the family, address power struggles among parents and siblings as well as improve verbal communication in the family that is making the child symptomatic. In some children, the primary and tertiary gain may be closely related and can be addressed together. Also, whenever indicated, group therapy is organized to learn relaxation, to build self-esteem, assertiveness and communication in the child.

### *Addressing the Primary Gains*

Discuss and guide the parents through understanding the maladaptive mechanisms (e.g., somatization, conversion and dissociation), the child is using and to help the child use more adaptive mechanism (e.g., channelization) for exhausting the isolated unpleasant emotions (e.g., channelize the emotions into doing something constructive). Teach the child to reframe his or her experiences in a positive light (e.g., a stern teacher need not remind him of his abusive father instead another similar person in the child's life, who is firm and yet the child is fond of). Also, sternness does not equate with abusiveness in two different persons' behavior. Help the child to get back to school and face the teacher in a graded manner (e.g., starting from seeing teacher's photographs, to watching his videos, to meeting the teacher in nonacademic settings, to sitting and enjoying his or her classes eventually!). Teach the child to change from emotional coping and use problem-solving coping (e.g., emotional or behavioral venting like crying or acting-out respectively relieves unpleasant emotions temporarily but does not solve the problem). Teach the child who might be crying, about the stern teacher, the multiple practical steps to get familiar with or even befriend the teacher!). Help children to identify and communicate emotional distress as such and not as physical symptoms. If there is suspected catastrophic traumatic events as a cause of psychological illnesses, trauma-related treatment is specifically warranted. Over time, an important goal of therapy is for the child to learn increasingly adaptive and flexible ways to manage their emotions and to integrate past, current, and new experiences so that physical symptoms need not arise due to psychological gains.

### *Follow-up Care*

If psychological illnesses in children can be identified early, it is relatively easy to treat and can prevent the development of more severe mental health problems. However, during follow-up as many as 83% of the children have been found to have other psychiatric disorders, while only 26.1% were still suffering from the psychological illnesses. In cases with comorbidity, pharmacologic interventions may be needed if concurrent depressive and anxiety disorders are identified. Hospitalization is indicated only if outpatient therapy is not effective, when life-threatening physical symptoms are noted or when removing the child from his or her environment is very essential for controlling the perpetuating symptoms (e.g., secondary gains) in disturbed family settings.

### *PREVENTION*

Children with recurrent somatic complaints should be identified by pediatricians, screened and provided simple coping strategies for their symptoms (e.g., distraction techniques). Secondly, teachers need to identify children with chronic school absenteeism because of physical symptoms and support them in developing problem-solving coping skills in situations they find difficult at school. These simple approaches can prevent symptoms reaching a disorder level with impairment.

### IN A NUTSHELL

1. Psychological illness, although not strictly a standard nomenclature terminology, describes different constellations of clinical presentations indicative of a child experiencing and communicating psychological distress through physical symptoms not explained by medical findings.
2. Despite the existence of many integrative pathogenic models to explain these disorders, psychological treatments that address the different types of gain remain the mainstay for treatment.
3. Medications play a role only if the child has life-threatening symptoms or if there is a concurrent psychiatric illness. Early identification and appropriate treatment of these illnesses result in better long-term outcomes.

### MORE ON THIS TOPIC

- Fiertag O, Taylor S, Tareen A, Garralda E. Somatoform disorders. In: Rey JM. IACAPAP e-Textbook of Child and Adolescent Mental Health. Geneva: International Association for Child and Adolescent Psychiatry and Allied Professions; 2012.
- Garralda ME. Practitioner review: assessment and management of somatisation in childhood and adolescence: a practical perspective. *J Child Psychol Psychiatry*. 1999;40:1159-67.
- Lieb R, Pfister H, Mastaler M, Wittchen HU. Somatoform syndromes and disorders in a representative population sample of adolescents and young adults: prevalence, comorbidity and impairments. *Acta Psychiatr Scand*. 2000;101:194-208.
- Pehlivanürk B, Unal F. Conversion disorder in children and adolescents: a 4-year follow-up study. *J Psychosom Res*. 2002;52:187-91.
- Silberg J. Guidelines for the evaluation and treatment of dissociative symptoms in children and adolescents: International Society for the Study of Dissociation. *J Trauma Dissoc*. 2004;5:119-50.

# Section 22 NUTRITION AND NUTRITIONAL DISORDERS

Section Editors KE Elizabeth, Piyush Gupta

## Chapter 22.1

### Nutrient Groups and Nutritional Requirements

KE Elizabeth, S Bindusha

*Nutrition* is defined as the process by which the organism utilizes food. It signifies the dynamic process in which the food that is consumed is absorbed, metabolized and used for nourishing the body.

*Nutrients* are the chemical substances in the food that the body uses for functions that supports growth, tissue maintenance, and repair. There are six categories of nutrients: carbohydrates, protein, fats, vitamins, minerals, and water. Each category except water consists of a number of different substances. Nutrients which are not synthesized in the body or not synthesized adequately by the body are known as *essential nutrients*. They need to be provided by the diet and include carbohydrates, essential amino acids, essential fatty acids, vitamins, minerals, and water. *Nonessential nutrients* can be synthesized by the body (examples: glucose, cholesterol).

#### ENERGY

Energy requirement of an individual is defined as the level of energy intake from food that balances energy expenditure when the individual has a body size, composition, and level of physical activity, consistent with long-term good health, also allowing for maintenance of economically essential and socially desirable activity. In children, it includes the energy needs associated with the deposition of tissues at rates consistent with good health. Energy requirement must be assessed in terms of *energy expenditure* rather than in terms of energy intake. Energy intake may vary from day-to-day; on some days, it may be above the energy expenditure and sometimes, below it. Body energy reserves help to maintain normal energy expenditure over short periods even when the daily intake is below expenditure.

The energy expenditure consists of three components—basal energy expenditure, thermic effect of food and activity thermogenesis (**Fig. 1**). Basal energy expenditure (BEE) is the minimum energy expended that is compatible with life. Resting energy expenditure (REE) is the energy expended to maintain normal body functions and homeostasis. REE is 10–20% more than BEE. REE constitutes 60–70% of the total energy expenditure. Energy expended for growth is also part of REE. Growth requires 12–15% of total energy expenditure in infants. Thermic effect of food (TEF) is the increase in energy expenditure associated with consumption, digestion, and absorption of food. Thermic effect constitutes about 10% of total energy expenditure. Thermic effect varies from 5–30% depending on the composition of diet. A diet rich in protein has more thermic effect than a diet rich in fat. Spices, caffeine, capsaicin, and green tea increase the thermic effect of food. Activity

thermogenesis is the energy required for daily work, movement, and exercise. Energy expended for activity varies depending on the level of activity.

The traditional unit of energy is 1 kilocalorie (kcal/Cal). It is the amount of heat needed to raise the temperature of 1 kg of water by 1° Celsius from 14.5°C to 15.5°C. The international unit of energy is Joule. 1 calorie = 4.184 joule. 1 Joule = 0.239 calorie. Definitions of terms used for dietary reference intakes are listed in **Box 1**.

#### BOX 1 Definitions: Dietary Reference Intakes

##### Recommended Dietary Allowance (RDA)

The average daily dietary intake level of a nutrient that is sufficient to meet the nutrient requirement of nearly all healthy individuals in a particular life stage and gender group. RDA meets the needs of 97–98% of the population. RDA is usually fixed at 2 standard deviations above the average requirement. It is for the age in physiological state and not for the present weight of an individual.

##### Estimated Average Requirement (EAR)

The average daily nutrient intake level estimated to meet the requirement of half of the healthy individuals in a particular life stage and gender group. In infants it is the amount of the nutrient that results in maintenance of satisfactory rates of growth and development and/or prevention of specific nutritional deficiencies.

##### Adequate Intake (AI)

Recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake by a group of apparently healthy people, which is assumed to be adequate—used when an RDA cannot be determined. In the Indian context, this is referred to as 'Acceptable Intake'.

##### Tolerable Upper Intake Level (UL)

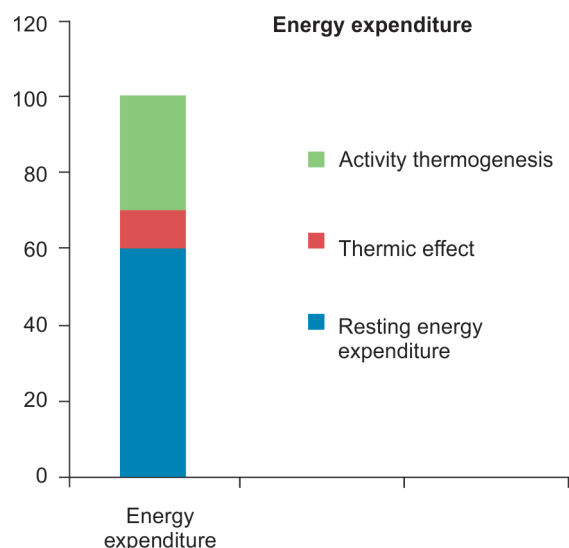
The highest average daily nutrient intake level that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases.

##### Dietary Reference Intakes (DRIs)

Dietary reference intakes include RDAs for those nutrients for which RDA is reliably established and other reference intakes where RDA is not established. These reference intakes include adequate intake (AI) and tolerable upper intake level (UL).

#### Energy Expenditure in Critically ill Children

Almost 16–20% of critically ill hospitalized children especially in those less than 2 years of age have been reported to develop severe acute malnutrition (SAM), following admission to a pediatric intensive care unit. Many children may also develop acute fluid and electrolyte malnutrition. The nutritional requirements and the nature of fuel utilization in critically ill children have not yet been defined. Overfeeding can lead to many side effects, including diet-induced thermogenesis, increased carbon dioxide production, and fatty deposition in the liver. Underfeeding, on the other hand, may result in depletion of fat and protein stores and malnutrition.



**Figure 1** Energy expenditure in health

Numerous equations have been used to estimate the caloric needs of the critically ill child. They calculate the predicted basal metabolic rate (PBMR) and then add the correction factor for the illness to calculate the predicted energy expenditure (PEE). Harris-Benedict and Food and Agriculture Organization/World Health Organization equation for PBMR is the most commonly employed (**Box 2**). The accuracy of the stress-related correction to PBMR in critically ill children is yet to be determined. There are various methods to calculate energy expenditure that include indirect calorimetry and bioelectrical impedance analysis. Another quick method is to give 2/3rd of the recommended dietary allowance (RDA) with 10% extra for the stress and the illness; the advantage is that it is easy and is not technology dependent.

#### **BOX 2** Equations for calculation of predicted basal metabolic rate (PBMR)

##### **Harris-Benedict equation (kcal/day)**

Males:  $66.473 + (13.7516 \times \text{Wt}) + (5.0033 \times \text{Ht}) - (6.755 \times \text{age})$

Females:  $66.50955 + (9.5634 \times \text{Wt}) + (1.8496 \times \text{Ht}) - (4.6756 \times \text{age})$

##### **WHO equation (kcal/day)**

3 years Boy:  $(60.9 \times \text{Wt}) - 54$

Girl:  $(61 \times \text{Wt}) - 51$

3–10 years Boy:  $(22.7 \times \text{Wt}) + 495$

Girl:  $(22.5 \times \text{Wt}) + 499$

10–18 years Boy:  $(17.5 \times \text{Wt}) + 651$

Girl:  $(12.2 \times \text{Wt}) + 746$

##### **Correction factors (% of PBMR added to PBMR)**

Elevated temperature + 12% per °C above 37°C (98.6°F)

ARDS +20%

Sepsis +10–30% depending on severity

Trauma +10–30% depending on severity

Surgery +10–30% depending on severity

## **CARBOHYDRATES**

Carbohydrates are the major source of energy. Carbohydrates consist of simple sugars (monosaccharide and disaccharide) and complex carbohydrates (polysaccharides, e.g., maltodextrin).

**Table 1** Glycemic index of common food items

Low glycemic index (55 or lower)	Medium glycemic index (56–69)	High glycemic index (70 or higher)
Apple	Sugar	Glucose
Orange	Brown rice	French bread
Mango	Chapathi	Baked potato
Banana	Sweet potato	Cake
Grapefruit	Cherry	Cornflakes
Milk		White rice
Milk chocolate		Watermelon
Carrot (raw)		Carrot (cooked)

Glucose, galactose and fructose are the common monosaccharides. Fructose is the sweetest sugar. Sucrose (2 glucose) and lactose (glucose + galactose) are the most common disaccharides. Invert sugar which contains unlinked glucose and fructose in a ratio of 1:1 is also available in nature. It is sweeter than sugar. Honey is an invert sugar. Starch, glycogen and fiber are examples of complex carbohydrates. Maltodextrin is a glucose polymer obtained by the partial hydrolysis of corn starch. Usually 45–65% of calories in food are from carbohydrates. Added sugar should constitute no more than 2.5% of total caloric intake.

Carbohydrates provide 4 calories per gram. Dietary fiber provides 2 calories per gram on an average even though humans cannot digest fiber. Fiber is converted to fatty acids by intestinal bacteria, which are absorbed from the intestine. The main function of fiber is to provide bulk to the food and prevent constipation. High fiber diet decreases the rate of glucose absorption and may prevent cardiovascular disease and colonic cancer.

**Glycemic index** It is the measure of the extent to which blood glucose is raised by 50 g portion of a carbohydrate containing food compared to 50 g of glucose or white bread. Food items are classified according to their glycemic index (**Table 1**). Food items with glycemic index 70 or above are classified as high, 56–69 as medium and 55 or less as low glycemic indexed food. Sugar, white bread, cake and baked or mashed potato are examples of food with high glycemic index. Grapes, tomato, apple, orange, carrot, banana, and apple are examples of food with low glycemic index. The method of cooking and processing also affects the glycemic index of the food.

## **PROTEIN**

The word protein means *of prime importance*. Proteins are needed for different biological functions. Proteins help in body building and tissue repair. They form enzymes, hormones, immunoglobulins and also help in transporting other nutrients. Proteins are made up of amino acids. There are 24 amino acids out of which 8 amino acids are essential for all ages. They are valine, leucine, isoleucine, lysine, tryptophan, methionine, threonine, and phenylalanine. Histidine is essential in infants. Arginine, cysteine, tyrosine, and taurine are also essential for low birthweight babies. The best quality protein should provide amino acids similar to the tissue protein. Breastmilk protein and egg protein are the best quality proteins. Egg protein is considered as the *reference protein* for the ease of making it available for laboratory references. The quality of protein depends on the extent to which the amino acid pattern resembles the reference protein. *Limiting amino acid* is the one found in lowest quantity in that protein compared to the reference protein. The overall quality of a specific protein can be increased by supplementing it with the limiting amino acid. The quality of soy



**Table 2** Protein quality of food items

Protein	Biological value	Net protein utilization	Protein efficiency ratio
Egg	96	96	3.8
Cow's milk	90	85	2.8
Meat	74	76	3.2
Fish	80	74	3.5
Rice	80	77	1.7
Wheat	66	61	1.3
Bengal gram	74	61	1.1

protein becomes equivalent to milk protein when supplemented with methionine, which is deficient in soya. Lysine is the limiting amino acid in cereals whereas methionine is the limiting amino acid in pulses. A cereal pulse combination provides a better quality protein than cereal or pulse alone. Measures of protein quality are summarized in **Box 3**. Protein quality of common food is summarized in **Table 2**.

**BOX 3** Measures of protein quality

*Digestibility coefficient* (DC) is the amount of absorbed nitrogen compared to the total nitrogen present in the food item.  $DC = \frac{\text{Absorbed nitrogen}}{\text{Total nitrogen}} \times 100$ .

*Biological value* (BV) is the amount of retained nitrogen compared to absorbed nitrogen.

$BV = \frac{\text{Retained nitrogen}}{\text{Absorbed nitrogen}} \times 100$ .

*Net protein utilization* (NPU) refers to the amount of retained nitrogen compared to the total nitrogen present in the food item.  $NPU = \frac{\text{Retained nitrogen}}{\text{Total nitrogen}} \times 100$ .

*Protein efficiency ratio* (PER) refers to the gain in weight of experimental animals per unit weight of protein consumed.

**FATS (LIPIDS)**

Fats are concentrated sources of energy. One gram of long chain fat provides 9 calories. Fats help in absorption of fat-soluble vitamins and are precursors of sex hormones and long chain polyunsaturated fatty acids (LCPs). Fats are categorized as *saturated* fats and *mono/poly unsaturated* fats (**Table 3**). Unsaturated fat contains double bonds between the carbon atoms in one or more of the fatty acids in it. If only one double bond is present it is monounsaturated fat, if more than one double bonds are present it is polyunsaturated fat. Saturated fats are stable and are solid in the room temperature. Animal fat in meat, butter and cheese, coconut oil and palm oil contain mainly saturated fats. Hydrogenation of vegetable oils will convert the unsaturated fats in them to saturated fats. Hydrogenation increases the storage life and baking quality of the oils. But saturated fat increases the blood level of low-density lipoprotein (LDL) cholesterol.

**Essential Fatty Acids**

The *essential fatty acids* are polyunsaturated fatty acids. They are linoleic acid and alpha linolenic acid. The essential fatty acids were previously designated as vitamin F. These essential fatty acids constitute a major component of the phospholipids of central nervous system. They are also needed for the production of prostaglandins and thromboxanes. Essential fatty acids are essential for normal fetal and infant growth, brain growth and visual acuity.

**Table 3** Fatty acid composition of oils

Oil	Saturated fatty acids (%)	Monounsaturated fatty acids (%)	Polyunsaturated fatty acids (%)	
			Omega 6	Omega 3
Coconut oil	92	6	1.6	0.4
Corn oil	13	25	61	1
Groundnut oil	18	49	33	0
Olive oil	14	77	8	1
Sunflower oil	11	20	69	0
Safflower oil	10	13	77	0
Palmolein	40	48	11	1
Hydrogenated vegetable oil	76	19	3	2

Linoleic acid is an omega-6 fatty acid. It is present in vegetable oils, meat and human milk. Alpha linolenic acid is an omega-3 fatty acid which is present in fish oil. Essential fatty acids are converted to long chain polyunsaturated fatty acids (LCPs). Arachidonic acid and adrenic acid are the derivatives of linoleic acids. These fatty acids are needed for production of prostaglandins and prostacyclins. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are derivatives of linolenic acid (omega-3). DHA is found in large amounts in brain, retina and testes. Fish is a very good source of omega-3 fatty acids. Omega-6: omega-3 ratio of 5:1 or less is ideal for cardiovascular health. High omega-6 and low omega-3 content as in groundnut and sunflower oil, respectively can lead on to free radical injury, angiotoxicity, and impaired immune function.

Medium chain triglycerides (MCTs) are fatty acids containing 8–10 carbon atoms. They can be absorbed directly into the portal veins without the help of lipase or bile salts. Hence, MCTs will be absorbed even in conditions with fat malabsorption. Coconut oil and cotton seed oil are rich sources of MCTs.

There are two types of dietary fats—visible and invisible fat. Average indian diet provides 25–30% of calories as fats. The type of fat consumed is as important as the amount of fat consumed for healthy life. Not more than 10% of energy should be derived from saturated fatty acids. Approximately 10% should be obtained from monounsaturated fatty acids and 10% from polyunsaturated fatty acids. EFAs should provide 1–3% of the total calories.

**VITAMINS AND MINERALS**

Vitamins are chemical substances in the food that perform specific functions in the body. They are classified as *water soluble* and *fat soluble* vitamins. B complex vitamins and vitamin C are water soluble, whereas vitamin A, D, E and K are fat soluble. The stores of water-soluble vitamins are limited in our body. Exception is vitamin B<sub>12</sub>. Fat-soluble vitamins are stored in the fatty tissue and liver. These stores can last for months to years, even when the dietary intake is low. Excessive consumption of fat soluble vitamins especially A and D can lead to toxicity. Vitamin deficiency diseases and toxicity are discussed later in this section.

Minerals are classified into macrominerals and microminerals (**Fig. 2**). *Macrominerals* are elements present in higher concentration in the body. They constitute more than 0.01% of bodyweight. Calcium, phosphorous, sodium, potassium and magnesium are the major macrominerals. *Microminerals/trace elements* are elements present in concentration less than 0.01% of body weight. Trace elements essential for human growth and function include iron, iodine, zinc, copper, chromium, selenium, manganese, cobalt, molybdenum, nickel, vanadium, silicon, arsenic, fluorine and tin.

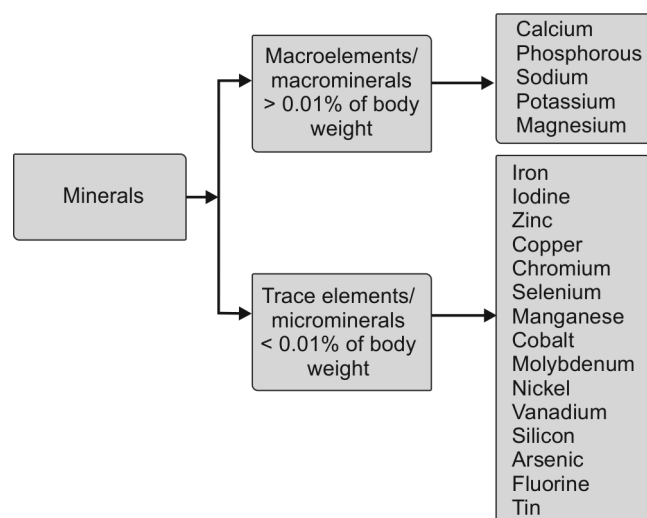


Figure 2 Minerals

Recommended dietary allowance of energy and major nutrients as recommended by Indian Council of Medical Research (2011) are summarized in **Table 4**.

### Calcium

Calcium is a major element in the body and is mainly present in the skeletal tissue. 99% of body calcium is present in the bone. Nonskeletal calcium has important functions like neuromuscular excitation, blood coagulation, and membrane permeability. Calcium is vital for body functions and hence the body tries to maintain calcium level even when there is dietary calcium deficiency. The calcium present in the bones has an important role in maintenance of serum calcium levels. Serum calcium level is maintained within normal limits by the interplay of vitamin D, parathyroid hormone, thyrocalcitonin, cortisol and sex hormones which control absorption and excretion of calcium and phosphorous and bone turnover.

Milk and milk products are the major sources of dietary calcium. When consumption of milk is low, cereals become the major dietary source of calcium. *Raggi, rajkeera* (amaranth), gingelly seeds, sea food, fish, mutton and green leafy vegetables are good sources of calcium. 20–25% of dietary calcium is absorbed. Vitamin D increases the intestinal absorption of calcium. Presence of phosphate in the milk and oxalates and phytates in the grains decrease calcium absorption. Calcium: phosphorous ratio of

2:1 is optimal for calcium absorption. Excessive intake of animal protein and sodium will increase the urinary loss of calcium. RDA of calcium for infants is 500 mg/day, 1–9 years–600 mg/day and 10–18 years is 800 mg/day. RDA for adult male and female is 600 mg/day which increases to 1,200 mg/day during pregnancy and lactation.

### Phosphorous

Phosphorous along with calcium is needed for the normal growth of bone and teeth. It is also a component of nucleic acid, phosphate esters, ATP, 2, 3-DPG and buffer systems. It is important in cellular metabolism, oxygen transport and acid base balance. Cereals, pulses, nuts and oil seeds are rich sources of phosphorous. 80% of phosphorous in the plant sources is present as phytate which is not absorbed. Phytate levels are low in polished rice and germinated seeds. All protein rich foods are rich in phosphate. Phosphorous deficiency can occur in low birth weight babies, children with malnutrition and those on parenteral nutrition. RDA of phosphorous for infants is 750 mg/day, 1–9 year–600 mg/day and 10–18 year is 800 mg/day.

### Sodium

Sodium is the principal action of extracellular fluid and is involved primarily in the maintenance of osmotic equilibrium and extracellular fluid volume. Sodium functions as the osmotic skeleton of the extracellular fluid. Maintenance of normal sodium levels are needed to maintain the normal size and shape of cells. The most common cause for hyponatremia is acute diarrheal disease. Hyponatremia can also occur due to excessive renal loss and excessive sweating. Salt is the major dietary source. Recommended intake of salt is less than 5 g/day. Requirement of sodium is 2–3 mEq/kg/day. RDA of sodium is 400 mg/day for infants, 600 mg/day for children between 1–3 years and 1,000 mg/day for children between 4 years and 6 years.

### Potassium

Potassium is the most abundant cation of intracellular fluid. Eighty percent of body potassium is in the skeletal muscles. Concentration of potassium in the extracellular fluid is around 4.5 mEq/L while the cells have about 150 mEq/L. Total body potassium content corresponds closely to lean body mass and nitrogen content. Potassium contributes to intracellular osmolality. Enzymes involved in glycolysis and oxidative phosphorylation are potassium dependent. It is involved in the maintenance of acid-base balance. Potassium deficiency and excess rarely occurs due to inadequate or excess intake. Deficiency of potassium occurs in

Table 4 Recommended dietary allowances of energy and nutrients

	Energy (kcal)	Protein (g)	Fat (g)	Calcium (mg)	Iron (mg)	Zinc (mg)
Infants 0–6 months	92 cal/kg	1.16/kg		500		
Infants 6–12 months	80 cal/kg	1.69/kg	19	600		
Children 1–3 years	1060	16.7	27	600	9	5
Children 4–6 years	1350	20.1	25	600	13	7
Children 7–9 years	1690	29.5	30	600	16	8
Boys 10–12 years	2190	39.9	35	800	21	9
Girls 10–12 years	2010	40.4	35	800	27	9
Boys 13–15 years	2750	54.3	45	800	32	11
Girls 13–15 years	2330	51.9	40	800	27	11
Boys 16–18 years	3020	61.5	50	800	28	12
Girls 16–18 years	2440	55.5	35	800	26	12

Source: Indian Council of Medical Research (ICMR); 2011.

diarrhea, malnutrition, diabetic ketoacidosis, and diuretic therapy. Hypokalemia produces skeletal muscle paralysis, abdominal distension and ileus.

Potassium is abundant in fruits and green vegetables. Cereals, pulses, nuts and oil seeds also contribute to significant amounts of potassium. Requirement is 2–3 mEq/kg/day. The ideal desirable sodium: potassium ratio in diet is 1:1.

## Magnesium

About 60–70% magnesium is present in bones, 25–30% in muscles, 6–8% in soft tissue and 1% in extracellular fluid. Magnesium forms complexes with phospholipids of cell membranes and nucleic acids. Magnesium is an important cofactor of the kinases, and is needed for the energy transfer reactions involving ATP and creatine phosphate. Magnesium is also important for maintaining electrical potential in nerves and muscle membranes. Magnesium deficiency leads to neuromuscular dysfunction. Serum magnesium is maintained in a narrow range like that of calcium. There is close association between calcium and magnesium. They have mutually reinforcing as well as opposing actions. Severe magnesium deficiency can lead to tetany and convulsions. Hypocalcemia and hypokalemia are always associated with magnesium deficiency and are reversed by magnesium repletion.

Plants form major source of magnesium. Magnesium is the metal in chlorophyll. Animal products, legumes and cereals are good sources of magnesium. About one-third of dietary magnesium is absorbed from the usual Indian diet. Dietary deficiency of magnesium will not occur unless associated with malabsorption syndromes or disease states like malnutrition. Requirement of magnesium is 3–6 mg/kg/day. RDA of magnesium is 30 mg for infants below 6 months and 45 mg for infants between 6 months and 12 months. Children between 1 year and 3 years will require 50 mg/day, 4–6 years: 70 mg/day; and 7–9 years: 100 mg/day. Adolescents will require an intake between 120 mg/day and 240 mg/day. RDA for adult male is 340 mg/day and female 310 mg/day.

## ANTIOXIDANTS

Free oxygen radicals and reactive oxygen species play a role in aging and various disease processes. Human body has an efficient system to protect itself from free radicals with antioxidants and enzyme systems. Antioxidants are substances whose presence in relatively low amounts significantly inhibits the rate of oxidation of targets. Vitamin E, beta carotene, vitamin C, phytochemicals like flavonoids, flavones, flavonols, cinnamic acid, coumarin derivatives, phytoalexin derivatives, trace elements like selenium, copper, zinc, magnesium and amino acids like cysteine and taurine are naturally occurring antioxidants.

Carotenoids consist of (a) provitamin A carotenoids like beta carotene; and (b) nonprovitamin A carotenoids like lycopene, lutein, canthaxanthin, and astaxanthin. All carotenoids are versatile antioxidants. Beta carotene acts by trapping free radicals produced during inflammation and is effective at low oxygen tension in the tissues. Carotenoids can also modulate the level of inflammatory mediators like prostaglandins and leukotrienes. Increased carotenoid levels have been associated with decreased LDL oxidation. Higher intake of food rich in carotenoids was found to reduce the occurrence of adult macular degeneration. Studies have also demonstrated a low incidence of coronary vascular diseases and cancers of prostate and breast.

Vitamin C can react with a wide range of reactive oxygen species, including superoxide, singlet oxygen and hypochlorite.

Vitamin C is a chain-breaking antioxidant and it protects lipids and membranes by scavenging peroxy and hydroxyl radicals. Vitamin C can also reduce heavy metal toxicity. Reduced glutathione reduces dehydroascorbate back to active vitamin C and vitamin C and glutathione are complementary to each other. A combination of vitamin C with vitamin E is more effective than vitamin C alone. Vitamin C and reduced glutathione acts on lipoic acid to regenerate vitamin E. Intake of vitamin C more than 500 mg/day has been found to reduce coronary vascular disease, hypertension, and cancers of oral cavity, esophagus, ovary, stomach and colon in adults.

Vitamin E is the primary chain-breaking antioxidant of lipids, lipoproteins, and membranes. Vitamin E acts as a peroxy radical scavenger, creating a tocopheryl radical. This radical will decompose unless converted back to tocopherol by reduced glutathione, vitamin C and coenzyme Q<sub>10</sub>. Vitamin E supplementation has been found to be associated with decreased incidence of atherosclerosis, Alzheimer's disease and overall cancer risk. Studies also suggest that vitamin E may act as a cell response modifier and improve cell mediated immunity. Vitamin E supplementation was also found to normalize serum IgE levels and heal the lesions of atopic dermatitis.

Flavonoids are one of the largest classes of polyphenols, and more than 4,000 different flavonoids have been identified. Their antioxidant properties, physiologic activities, and bioavailability vary according to major subclasses. Flavonoids can scavenge free radicals and block LDL oxidation. Flavonoids can also act as chelators and inhibit spontaneous generation of hydroxyl radicals.

Glutathione peroxidase is a selenium dependent enzyme which is a major antioxidant system. Selenium deficiency will lead to suboptimal level of glutathione peroxidase and hence oxidant injury. Copper, zinc, and manganese are indispensable metals for the activity of superoxide dismutase, which is the main oxygen scavenger in the body. Hence, dietary deficiencies of these minerals result in peroxidative damage and mitochondrial dysfunction. Deficiency of copper or zinc also enhances cytochrome P-450 activity in microsomes of liver and lung, and stimulates generation of reactive oxygen radicals.

### IN A NUTSHELL

1. Food supplies a variety of nutrients and energy that the body requires.
2. Optimum proportion and quality of items such as carbohydrate, protein, fat, vitamins and minerals are required for growth, survival and well being.
3. Intake of each food item should be guided by RDA, EAR, AI, tolerable UL, DRI to prevent excess and deficiency.
4. Diet should provide protective foods and antioxidants.
5. Energy expenditure in ill children varies from that of healthy children.

### MORE ON THIS TOPIC

Brown JE. Nutrition Basics: Nutrition through Life-Cycle. 4<sup>th</sup> ed. USA: Wadsworth; 2011.

Dietary Guidelines for Indians: A Manual, 2<sup>nd</sup> ed. Hyderabad: National Institute of Nutrition; 2011.

Elizabeth KE. Nutrition and Child Development. 4<sup>th</sup> ed. Hyderabad: Paras; 2010.

Elizabeth KE. Nutrition and Child Development. 5<sup>th</sup> ed. Hyderabad: Paras; 2015.

## Chapter 22.2

# Nutritive Values of Foods

Neetu Sharma, Piyush Gupta

## FOOD GROUPS

Indian Council of Medical Research (ICMR) in 2011 identified four main food groups in our diet. These are (a) cereals and pulses, (b) milk, egg and meat products, (c) vegetables and fruits, and (d) oils, fats, nuts and oilseeds based on their predominant nutrients (**Table 1**). To fulfill the nutritional requirement of the body it is important to include each group in daily diet, in the recommended proportion.

Food can also be categorized according to their functions:

- **Energy rich food** Carbohydrate rich foods like cereals, millets, sugar, starchy vegetables and the fat rich foods such as oil, ghee, butter, nuts and oilseeds are rich in calories. Intake of these foods is a must for physical activity and maintenance of overall health, growth, and recovery from illness.
- **Body building food** Protein rich foods, e.g., pulses, legumes, and nuts; milk and other dairy products, egg, meat, fish, belong to this group. This category is vital for growth spurt, maturation, and bone development.
- **Protective food** Protective food comprises of vitamin and mineral rich food sources such as fruits and vegetables, eggs, milk and milk products. Food material from this group is required to fight infections in children and prevent oxidative damage.

An in-depth learning about food groups allows us to comprehend the types of nutrients, and their impact on our body. This is vital not only in determining what constitutes a balanced diet, but also in assessing nutritional adequacy, as an aid for nutritional counseling, while briefing therapeutic diet to the patients and understanding food labeling.

## CEREALS

Cereals (e.g., wheat, rice, corn, oats and barley) form the major staple food in most parts of the world. They furnish generous amounts of energy and nutrients at low cost and have a significant position in the Indian dietaries. Rice and wheat are the most widely consumed cereals.

Cereals are an economical source of energy, mainly contributed by starch and fat, and a significant source of protein (6–12%), although of low biological value (incomplete protein). Cereals are better utilized when supplemented by the more complete proteins of milk, meat and eggs as they supply the amino acids lacking in cereals. Whole grain cereals are considerable sources of iron, phosphorous and thiamine. During milling of rice, the bran which is the outer layer of the kernel is discarded. Bran is rich in fiber and minerals. It is also a good source of thiamine and riboflavin. Polished rice thus obtained is lower in vitamins and minerals than parboiled rice. Parboiling is a process of hydrothermal treatment of paddy which drives nutrients, especially thiamine, from the bran into the grain, making it more nutritious.

Cereals are easily digestible, supply roughage and have a laxative property. Incorrect cooking practices lead to loss of water soluble vitamins, i.e., by cooking in large volume of water and draining away the excess of it. Nutritive value of some common cereals is presented in **Table 2**.

## PULSES

Pulses, alternatively called legumes, are the essential components of vegetarian diets due to their high protein content (20–40%). Proteins are needed for growth and repair of body tissues such as muscles, organs, skin, hair and blood. Except for *soybean*, pulse proteins are deficient in methionine and tryptophan. Groundnut and *soybean* are rich in oils. They are also good sources of Ca, Mg, Zn, Fe, K and P, and are fairly rich in niacin, but poor in riboflavin and contain small amounts of carotene.

Germination improves the nutritive value of pulses. The ascorbic acid, riboflavin, niacin, choline and biotin content increase considerably, and antinutritional factors (phytates, tannins) and toxic factors are eliminated. Fermentation increases digestibility, palatability and improves availability of essential amino acids. Such proteins can be of advantage in treating protein malnutrition as they are less expensive than animal proteins.

Some commonly consumed pulses are: green gram (*mung*), red gram (*tuvar/arhar*), black gram (*urd*), bengal gram (*chana*), lentil (*masur*), peas and soybean (**Table 3**).

## Vegetables

Vegetables vary widely in their composition and nutritive value, depending on the part of the plant which is used as a vegetable. Water is the major constituent of vegetables (about 99%). Vegetables contribute to the bulk of the diet and are low in calories, proteins and fats, though are rich sources of minerals and vitamins. Vegetables are of great use in weight reducing diets as they provide satiety due to bulk and contribute few calories. The bulk and water content also helps to relieve constipation.

Green leafy vegetables (GLV) such as spinach (*palak*), fenugreek (*methi*), *chaulai*, cabbage are good sources of iron, ascorbic acid, calcium and B-group vitamins. Some of these leafy vegetables contain oxalic acid which combines with calcium and forms an insoluble salt making it unavailable for absorption. However, GLV are essential, for the generous amounts of iron, ascorbic acid and vitamin A they provide in the diet.

Tuberous vegetables such as potato, sweet potato and yam (*garadu* or *ratalu*) are good sources of carbohydrates but are poor in proteins, vitamins and minerals. Carrots have rich amounts of beta-carotene (**Table 4**).

## Fruits

Fruits are valued for their minerals, vitamins and digestible fiber. Citrus fruits and guava are rich in ascorbic acid whereas yellow fruits contain carotenoids (precursors of vitamin A). Fiber content is more in fresh fruits than in fruit juices. Bananas provide calories in a nonresidue diet. They act as a mild laxative in constipation. Fruits are not good sources of calcium, phosphorous and iron. However, dried apricots, dates, grapefruit are fair sources of iron and calcium.

Apart from these micronutrients, vegetables and fruits are also rich sources of phytonutrients which act as natural antioxidants. Eating a wide variety of fruits and vegetables is recommended as a preventive measure against various free-radical mediated diseases (coronary artery disease, cancer, inflammatory bowel disease, etc.). A daily intake of at least 300 g of vegetables (green leafy vegetables: 50 g; other vegetables: 200 g; roots and tubers: 50 g) and in addition, fresh fruits (100 g) is recommended for an Indian adult. Nutritive values of some common fruits per 100 g of edible portion are given in **Table 5**.



**Table 1** Food grouping systems

Food group	Main nutrients
<b>Cereals, millets and pulses</b>	
<i>Cereals</i>	
Rice, wheat, ragi, <i>bajra</i> , maize, sorghum ( <i>Jowar</i> ), barley, riceflakes, wheat flour	Energy, protein, invisible fat, vitamin B <sub>1</sub> , vitamin B <sub>2</sub> , folic acid, iron, fiber
<i>Pulses</i>	
Bengal gram, blackgram, greengram, redgram, lentil (whole as well as dhals), peas, rajmah, soyabeans, beans, etc.	Energy, protein, invisible fat, vitamin B, vitamin B <sub>2</sub> , folic acid, calcium, iron, fiber
<b>Vegetables and fruits</b>	
<i>Green leafy vegetables</i>	
Amaranth, spinach, gogu, drumstick leaves, coriander leaves, mustard leaves, fenugreek leaves	Invisible fats, carotenoids, vitamin B <sub>2</sub> , folic acid, calcium, iron, fiber
<i>Other vegetables</i>	
Carrots, brinjal, lady's-fingers, capsicum, beans, onion, drumstick, cauliflower	Carotenoids, folic acid, calcium, fiber
<i>Fruits</i>	
Mango, guava, tomato	Carotenoids
Ripe, papaya, orange, sweet lime, watermelon	Vitamin C, fiber
<b>Milk and meat products</b>	
Milk, curd, skimmed milk cheese	Protein, fat vitamin B <sub>2</sub> , calcium
Meat, chicken, liver, fish,	Protein, fat, vitamin B <sub>2</sub>
Egg, meat	
<b>Oils, fats, nuts and oilseeds</b>	
<i>Fats</i>	
Butter, <i>ghee</i> , hydrogenated oils, cooking oils like groundnut, mustard, coconut	Energy, fat, essential fatty acids

Source: Dietary Guidelines for Indians. 2<sup>nd</sup> ed. National Institute of Nutrition, Indian Council of Medical Research; 2011.

**Table 2** Nutritive value of common cereals (per 100 g of edible portion)

Name of foodstuff	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)	Crude fibers (g)	Minerals (g)	Iron (mg)	Calcium (mg)
Bajra	361	11.6	5.0	67.5	1.2	2.3	8.0	42
Maize, dry	342	11.1	3.6	66.2	2.7	1.5	2.3	10
Ragi	328	7.3	1.3	72.0	3.6	2.7	3.9	344
Rice, raw, milled	345	6.8	0.5	78.2	0.2	0.6	0.7	10
Rice, puffed	325	7.5	0.1	73.6	0.3	3.8	6.6	23
Wheat, whole	346	11.8	1.5	71.2	1.2	1.5	5.3	41
Wheat, flour (refined)	348	11.0	0.9	73.9	0.3	0.6	2.7	23
Wheat, bread (brown)	244	8.8	1.4	49.0	1.2		2.2	18

Source: Nutritive values of Indian foods. National Institute of Nutrition, Indian Council of Medical Research;2012.

**Table 3** Nutritive value of some commonly consumed pulses (per 100 g of edible portion)

Name of foodstuff	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)	Crude fibers (g)	Mineral (g)	Iron (mg)	Calcium (mg)
Bengal gram, <i>dal</i>	372	20.8	5.6	59.8	1.2	2.7	5.3	56
Black gram, <i>dal</i>	347	24.0	1.4	59.6	0.9	3.2	3.8	154
Green gram, whole	334	24.0	1.3	56.7	4.1	3.5	4.4	124
Green gram, <i>dal</i>	348	24.5	1.2	59.9	0.8	3.5	3.9	75
Moth beans	330	23.6	1.1	56.5	4.5	3.5	9.5	202
Rajmah	346	22.9	1.3	60.6	4.8	3.2	5.1	260
Soybean	432	43.2	19.5	20.9	3.7	4.6	10.4	240

Source: Nutritive values of Indian foods. National Institute of Nutrition, Indian Council of Medical Research;2012.

**Table 4** Nutritive value of some common vegetables (per 100 g of edible portion)

Name of foodstuff	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)	Crude fibers (g)	Minerals (g)	Iron (mg)	Calcium (mg)
<b>Roots and tubers</b>								
Carrot	48	0.9	0.2	10.6	1.2	1.1	1.03	80
Colocasia	97	3.0	0.1	21.1	1.0	1.7	0.42	40
Onion big	50	1.2	0.1	11.1	0.6	0.4	0.6	46.9
Potato	97	1.6	0.1	22.6	0.4	0.6	0.48	10
Radish white	17	0.7	0.1	3.4	0.8	0.6	0.4	35
<b>Leafy vegetables</b>								
Bathua leaves	30	3.7	0.4	2.9	0.8	2.6	4.20	150
Cabbage	27	1.8	0.1	4.6	1.0	0.6	0.80	39
Fenugreek leaves	49	4.4	0.9	6.0	1.1	1.5	1.93	395
Lettuce	21	2.1	0.3	2.5	0.5	1.2	2.40	50
Mustard leaves	34	4.0	0.6	3.2	0.8	1.6	16.30	155
Spinach	26	2.0	0.7	2.9	0.6	1.7	1.14	73
<b>Other vegetables</b>								
Bitter gourd	25	1.6	0.2	4.2	0.8	0.8	0.61	20
Brinjal	24	1.4	0.3	4.0	1.3	0.3	0.38	18
Cauliflower	30	2.6	0.4	4.0	1.2	1.0	1.23	33
Cucumber	13	0.4	0.1	2.5	0.4	0.3	0.60	10
French beans	26	1.7	0.1	4.5	1.8	0.5	0.61	50
Jackfruit, tender	51	2.6	0.3	9.4	2.8	0.9	1.70	30
Ladies fingers	35	1.9	0.2	6.4	1.2	0.7	0.35	66
Pumpkin fruit	25	1.4	0.1	4.6	0.7	0.6	0.44	10
Tinda, tender	21	1.4	0.2	3.4	1.0	0.5	0.90	25

Source: Nutritive values of Indian foods. National Institute of Nutrition, Indian Council of Medical Research;2012.

**Table 5** Nutritive value of some common fruits (per 100 g of edible portion)

Name of foodstuff	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)	Crude fibers (g)	Minerals (g)	Iron (mg)	Calcium (mg)
Apple	59	0.2	0.5	13.4	1.0	0.3	0.66	10
Banana, ripe	116	1.2	0.3	27.2	0.4	0.8	0.36	17
Grapes pale green variety	71	0.5	0.3	16.5	2.9	0.6	0.52	20
Guava, country	51	0.9	0.3	11.2	5.2	0.7	0.27	10
Jambu fruit	62	0.7	0.3	14.0	0.9	0.4	0.43	15
Lemon	57	1.0	0.9	11.1	1.7	0.3	0.26	70
Lichi	61	1.1	0.2	13.6	0.5	0.5	0.70	10
Mango, ripe	74	0.6	0.4	16.9	0.7	0.4	1.30	14
Watermelon	16	0.2	0.2	3.3	0.2	0.3	7.90	11
Orange	48	0.7	0.2	10.9	0.3	0.3	0.32	26
Papaya, ripe	32	0.6	0.1	7.2	0.8	0.5	0.50	17
Pineapple	46	0.4	0.1	10.8	0.5	0.4	2.42	20
Pomegranate	65	1.6	0.1	14.5	5.1	0.7	1.79	10
Tomato, ripe	20	0.9	0.2	3.6	0.8	0.5	0.64	48

Source: Nutritive values of Indian foods. National Institute of Nutrition, Indian Council of Medical Research;2012.

## Milk and Milk Products

Milk and milk products are rich sources of calcium, protein and riboflavin, good sources of vitamin A, phosphorous, thiamine; and poor sources of iron and ascorbic acid (Table 6). The principal milk protein is casein, others

are lactalbumin and lactoglobulin. Milk is the only sources of vitamin B<sub>12</sub> for strict vegetarians and the only natural source of lactose. Milk from different sources varies in composition and nutritive value. The milk from one species is best suited for the needs of infants of that species only.

## Egg, Meat and Fish (Table 7)

### Egg

It consists of approximately 11% shell, 58% white and 31% yolk. Egg protein is considered to be one of the best proteins, as it has all the *essential amino acids* in adequate amounts. In egg protein is a standard or *reference protein*, against which quality of other proteins is assessed. Egg supplies generous amounts of both fat and water soluble vitamins. Vitamin C is present in small quantity. Calcium, phosphorous, iron, zinc are also present in egg. Iron and vitamin A are contained only in the yolk. Boiling/heating denatures *avidin*—a substance present in raw egg which binds biotin (B-complex vitamin) making it unavailable to the body. Egg is easily digestible and completely absorbed, hence, suited for convalescing patients. Since, it is low in fiber it is advised in patients with a gastrointestinal illness. Rich cholesterol content of yolk is avoided in obese or hypertensive children.

### Meat

Meats contain about 15–20% proteins of high nutritive value, with good amounts of essential amino acids. Fat content of meat varies between 5% and 40%. Organ meats (liver and kidney) are iron rich. Meat also provides zinc and B-vitamins. It is a poor source of calcium. Liver is a rich source of vitamin A. High meat diet is advised to patients with anemia and protein-energy malnutrition.

### Fish

It is an excellent source of proteins (16–20%) of good biological value, and of unsaturated fats especially omega-3 fats. Vitamin A and D are found in fish liver oils. B-vitamins and ascorbic acid present in raw fish are heat labile. Fish is also rich in calcium and phosphorous.

### Others

#### Fats and Oils

Fats provide fat-soluble vitamins and fatty acids essential for human nutrition, add palatability to the diet, and induce satiety. Certain elements/compounds in fat work as antioxidants and lessen blood cholesterol besides adding natural flavor like tocotrienols in palm oil, lignans in sesame oil and oryzanol and tocotrienols in rice-bran oil. The composition of minor elements gets modified if the oil is refined. Increase in blood lipid and thrombogenicity, and decrease in insulin sensitivity with risk of cardiovascular disease (CVD), obesity, stroke and cancer are associated with the saturated fatty acids. However, polyunsaturated fatty acids (PUFA), especially n-3 PUFA, are antiatherogenic, enhance insulin sensitivity and glucose utilization, and reduce adiposity. Appropriate functioning of nervous, immune, vascular and renal systems requires an adequate balance of the two categories of PUFAs, i.e., linoleic and linolenic acids in the diet. They are also vital for vision and

**Table 6** Nutritive value of milk (per 100 mL)

Name of foodstuff	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)	Minerals (g)	Iron (mg)	Calcium (mg)
Milk buffalo's	117	4.3	6.5	5.0	0.8	0.2	210
Milk cow's	67	3.2	4.1	4.4	0.8	0.2	120
Milk goat's	72	3.3	4.5	4.6	0.8	0.3	170
Cheese	348	24.1	25.1	6.3	4.2	2.1	790
Whole milk powder (cow's milk)	496	25.8	26.7	38.0	6.0	0.6	950

Source: Nutritive values of Indian foods. National Institute of Nutrition, Indian Council of Medical Research;2012.

**Table 7** Nutritive value of egg, meat, fish (per 100 g of edible portion)

Name of foodstuff	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)	Minerals (g)	Iron (mg)	Calcium (g)
<b>Fish and other sea foods</b>							
Hilsa	273	21.8	19.4	2.9	2.2	2.1	180
Katla	111	19.5	2.4	2.9	1.5	0.9	530
Pabda	114	19.2	2.1	4.6	1.1	1.3	310
Parsley fresh	140	17.5	5.9	4.3	1.5	2.7	850
Pomfrets white	87	17.0	1.3	1.8	1.5	0.9	200
Puti	106	18.1	2.4	3.1	1.4	1.0	110
Rohu	97	16.6	1.4	4.4	0.9	1.0	650
Sarputi	161	16.5	9.5	2.3	1.5	0.5	220
Singhi	124	22.8	0.6	6.9	1.7	2.3	670
Tengra fresh	144	19.2	6.4	2.3	2.1	2.0	270
<b>Meat and poultry</b>							
Beef meat	410	79.2	10.3	0.2	1.6	18.8	68
Egg, hen	173	13.3	13.3		1.0	2.1	60
Mutton, muscle	194	18.5	13.3		1.3	2.5	150
Pork, muscle	114	18.7	4.4		1.0	2.2	30

Source: Nutritive values of Indian foods. National Institute of Nutrition, Indian Council of Medical Research;2012.

brain growth. An appropriate blend of saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA) can be achieved by consuming more than one type of vegetable oils and eating foods rich in alpha-linolenic (ALA) acid such as legumes, green leafy vegetables, fenugreek and mustard seeds.

Fats are defined as *visible* and *invisible* fats. Visible fats refer to those that are used during cooking like ghee, vegetable oils, butter and *vanaspati*, whereas invisible ones are those that are found as integral components in various foods. The ones present in ready-to-eat and processed food are referred as *hidden fats*.

### Nuts and Oil Seeds

These are good sources of energy and contain good quality proteins in small amounts. Nuts contain appreciable amounts of carbohydrates, B-group vitamins and some minerals such as calcium, phosphorous and iron (**Table 8**). Oilseed proteins are of inferior quality as they lack methionine. But, being rich in lysine, they can be used to supplement cereals for development of weaning foods.

**Table 8** Nutritive value of nuts and oilseeds (per 100 g of edible portion)

Name of foodstuff	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)	Crude fibers (g)	Minerals (g)	Iron (mg)	Calcium (mg)
Almond	655	20.8	58.9	10.5	1.7	2.9	5.1	230
Cashewnut	596	21.2	46.9	22.3	1.3	2.4	5.8	50
Coconut, dry	662	6.8	62.3	18.4	6.6	1.6	7.8	400
Coconut, fresh	444	4.5	41.6	13.0	3.6	1.0	1.7	10
Groundnut	567	25.3	40.1	26.1	3.1	2.4	2.5	90
Pistachio nut	626	19.8	53.5	16.2	2.1	2.8	7.7	140
Walnut	687	15.6	64.5	11.0	2.6	1.8	2.6	100

Source: Nutritive values of Indian foods. National Institute of Nutrition, Indian Council of Medical Research;2012.

**Table 9** Nutritive value of sugar and jaggery (per 100 g of edible portion)

Name of foodstuff	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)	Minerals (g)	Iron (mg)	Calcium (mg)
Honey	319	0.3	0.0	79.5	0.2	0.7	5
Jaggery (cane)	383	0.4	0.1	95.0	0.6	2.6	80
Jaggery (date palm)	353	1.5	0.3	86.1	2.6	3	63.0

Source: Nutritive values of Indian foods. National Institute of Nutrition, Indian Council of Medical Research;2012.

**Table 10** Nutritive value of condiments and spices (per 100 g of edible portion)

Name of foodstuff	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)	Crude fibers (g)	Minerals (g)	Iron (mg)	Calcium (mg)
Asafoetida	297	4.0	1.1	67.8	4.1	7.0	7.0	690
Cardamom	229	10.2	2.2	42.1	20.1	5.4	5.4	130
Chilies dry	246	15.9	6.2	31.6	30.2	6.1	6.1	160
Cloves dry	286	5.2	8.9	46.0	9.5	5.2	5.2	740
Coriander	288	14.1	16.1	21.6	32.6	4.4	4.4	630
Cumin seeds	356	18.7	15.0	36.6	12.0	5.8	5.8	1080
Fenugreek seeds	333	26.2	5.8	44.1	7.2	3.0	3.0	160
Ginger fresh	67	2.3	0.9	12.3	2.4	1.2	1.2	20
Mango powder	337	2.8	7.8	64.0	13.7	4.9	4.9	180
Turmeric	349	6.3	5.1	69.4	2.6	3.5	3.5	150

Source: Nutritive values of Indian foods. National Institute of Nutrition, Indian Council of Medical Research;2007.

### Sugar and Jaggery

They are used as sweetening agents. They contribute calories and palatability to the diet. Some amount of iron is also obtained from jaggery (**Table 9**). However, excessive amounts of sugar should be avoided as it might cause dental caries in small children. The most commonly used sugar is sucrose (table sugar).

### Condiments and Spices (Table 10)

These are used as flavoring substances and have an indispensable position in cooking, although they have limited nutritive value. Chilies and coriander (*dhania*) have little amounts of  $\beta$ -carotene. Most of them contain tannin which interferes with absorption of iron. Garlic is considered to have antibacterial property. Turmeric, ginger, garlic, cumin and cloves are rich in antioxidants. Excessive amounts of condiments should be avoided as they may lead to peptic ulcers.

### Beverages

Quenching thirst and providing body fluid is the main usage of beverages. Normal requirement of the body water varies with calories consumed. Water is required to regulate temperature and eliminate body wastes.



### Tea and Coffee

Tannin and caffeine, present in tea and coffee, provide stimulating effects, tea and coffee. Caffeine induces alertness, energy and overall sense of well-being. Higher intake of caffeine, over 200 mg can lead to anxiety, nervousness, higher blood pressure, arrhythmia, increased cholesterol and physiological dependence and can affect fetal growth. A cup of tea or coffee contains 50 mg and 100 mg caffeine roughly. Tea and coffee should not be taken 1 hour before and after meal because it interferes with iron and casein absorption. Tea also contains theophylline and theobromine, polyphenols and flavonoids which are associated with decrease risk of coronary heart disease and stomach cancer.

### Soft Beverages

There are two main categories of soft drinks, i.e., synthetic and natural drinks. Synthetic drinks are best avoided as they contain artificial colors, flavors and preservatives, and no nutrients. Carbonated beverages, as most of the synthetic drinks usually are, also affect appetite adversely and damage teeth enamel due to the phosphoric acid content. Natural drinks like fresh fruit juice, *lassi*, coconut water, and butter milk are healthier options. Butter milk and coconut water are ideal drinks as oral rehydration fluid. They should be avoided in hyperkalemia, acute adrenal insufficiency, and those with low urine output.

## FOOD PYRAMID

The food pyramid, a valuable roadmap for healthy diet planning, rests on the concept of energy density which combines nutritional values with portion sizes to cater to different needs or situations such as, the high energy density requirement in children and elderly people, or low energy density needs in case of obesity. Since no single food offers all essential nutrients in sufficient amount, a diet can be balanced only if it consists of food from all different food groups. Not all foods in a food group contain the same nutrients. So within each food group, the food selection should be assorted or diverse rather than a single one to fulfill the requirements of essential ingredients. Lastly, ensuring a proportionate intake of each selected food is as vital as is the assortment or balance itself. To sum up, a diet can be considered optimum only if it has a proper representation from different food groups in required proportions.

As illustrated in the **Figure 1**, in each of the food groups, a specific number of serving is recommended and healthy choices are emphasized. For example, in the *first layer of the pyramid* (at the bottom) are the cereals and milk, advised to be taken in adequate amount, as cereals/millet are used as staple food and are major sources of most nutrients, in this category, whole grains and emphasized; low-fat dairy products are encouraged.

Vegetables and fruits are at the *second layer of the pyramid* and unlimited amounts of fresh or frozen forms of each are recommended. Vegetables and fruits are rich sources of minerals, vitamins and phytonutrients. Fruits and vegetables are also rich in complex carbohydrates and fiber. Dietary fiber is important for proper bowel function, to reduce chronic constipation, and reduce plasma cholesterol. Some vegetables and fruits provide very low calories, whereas some others such as potato, sweet potato, tapioca and yam and banana are rich in starch which provides energy in good amount. Therefore, vegetables and fruits can be used to increase or decrease calories in our diet.

The *third layer of pyramid* about the use of protein and fat dictates that it should be used in moderation. The intake of



**Figure 1** Food pyramid

Source: Dietary Guidelines for Indians. 2<sup>nd</sup> ed. National Institute of Nutrition, Indian Council of Medical Research; 2011.

PUFA should be 8–10% of energy intake. Ideally a ratio of polyunsaturated/saturated (PUFA/SFA) of 0.8–1.0, and linoleic/ $\alpha$ -linolenic (n-6/n-3) of 5–10 is required. The intake of trans-fatty acids should not exceed 1% of energy intake. A combination of oils like soyabean, sesame, mustard, and sunflower should be used to achieve minor components in the diet. The use of *ghee*, butter, *vanaspati*, animal food, processed food should be minimized. Prefer fish over meat and poultry. Use of reheated oil and fat should be avoided. Ill effects of excess dietary fats are initiated early in life. Use of skimmed milk is advocated beyond 2 years of age. Consumption of fish, beans, and low-fat dairy products are encouraged from this layer. Increased amount of protein is needed for growing and ill children.

The *top (fourth) layer* consists of processed food and sugar that should be used as little as possible.

Food pyramid also offers the right combination of food intake to match with the physical activity. Daily physical activity, from lifestyle activities throughout the day as well as planned exercise, is an important component for weight management, especially of school children and adolescents. The ICMR food pyramid also cautions against intake of alcohol and tobacco.

### Balanced Diet

A diet can be termed as 'balanced' if it contains all nutrients in right quantity and required proportion offering diversity of belonging to the four basic good groups (**Table 11**). Though these quantities and proportions would differ as per age, physical activity, gender and physiological status, normally in a balanced diet, around 50–60% of total calories would come from carbohydrates, preferably complex carbohydrates, 20–30% from visible and invisible fats, and 10–15% from proteins. Besides, several nonnutrients like antioxidants, phytochemicals and dietary fiber should also be the parts of a balanced diet. While phytochemical like polyphenols, flavones save from oxidant damage, antioxidants like vitamin C and E, beta-carotene, riboflavin and selenium save from free radical damages. Some of the best sources of antioxidants in our everyday food are garlic, ginger, clove, cumin and turmeric.

**Table 11** Balanced diet for infants, children, adolescents (number of portions)

Food groups	g/portion	Infants (months)				Years					
		6–12	1–3	4–6	7–9	10–12		13–15		16–18	
						Girls	Boys	Girls	Boys	Girls	Boys
Cereals and millets	30	0.5	2	4	6	8	10	11	14	11	15
Pulses	30	0.25	1	1	2	2	2	2	2.5	2.5	3
Milk (mL) and milk products	100	4*	5	5	5	5	5	5	5	5	5
Roots and tubers	100	0.5	0.5	1	1	1	1	1	1.5	2	2
Green leafy vegetables	100	0.25	0.5	0.5	1	1	1	1	1	1	1
Other vegetables	100	0.25	0.5	1	1	2	2	2	2	2	2
Fruits	100	1	1	1	1	1	1	1	1	1	1
Sugar	5	2	3	4	4	6	6	5	4	5	6
Fat/Oil (visible)	5	4	5	5	6	7	7	8	9	7	10

Source: Dietary Guidelines for Indians. 2<sup>nd</sup> ed. National Institute of Nutrition, Indian Council of Medical Research; 2011

\*Quantity indicates top milk. For breastfed infants, 200 mL top milk is required. One portion of pulse may be exchanged with one portion (50 g) of egg/meat/chicken/fish. For infants introduce egg/meat/chicken/fish around 9 months.

## Recommended Dietary Allowance

The recommended dietary allowances are the quantities of nutrients that must be obtained from food to meet the physiological needs of healthy individuals according to their age and gender.

## DIETARY HABITS

With the passage of time, there has been a major change in the perception and discourse on dietary habits. Initially, this area used to be generally confined to the understanding and correction of nutritional deficiencies. Whereas lately, in the wake of constantly emerging evidences on diet pattern contributing to certain health risks, now it is considered to be a determinant of chronic diseases. This is all the more apparent in the astronomical increase in the lifestyle-related diseases due to the globalization and fast-paced lifestyle that have prompted people to opt for calorie rich, inexpensive, convenient-to-carry and ready-to-consume foods with long shelf-life containing excess salt, sugar and trans-fat, thus leading to harmful effect. Among the disorders that are on rise—obesity, cardiovascular diseases, hypertension, diabetes and certain types of cancers are of serious concern due to their increasing incidence in the younger age group. Hence, it is imperative that the awareness about healthy food culture is disseminated in the early phase of childhood for a healthy generation.

The dietary habits vary according to socioeconomic status, customs and traditions. **Box 1** offers a few tips for developing healthy dietary habits in childhood. **Table 12** depicts recommendations for a healthy lifestyle diet. This diet replaces the saturated fats with unsaturated fats which results in a decrease in the level of low-density lipoprotein (LDL) cholesterol and also emphasizes an increase in physical activity. In case of inadequate decrease in LDL, the amount of soluble fiber in the diet can be increased. The LDL-lowering power can also be enhanced by the food products that contain plant sterols.

## Cooking Methods

Cooking destroys harmful germs, makes food palatable and helps in digestion. Faulty cooking process and method can result in the loss of nutrients. Avoid repeated washing of food grains

prior to cooking, and do not reheat the leftover oil after deep-frying. Once cut, vegetables should neither be washed nor soaked in water for long. Cooking should be done in utensils with lid, and water should be used in adequate amount so that no excess

### BOX 1 Healthy dietary habits

- Exclusive breastfeeding should be provided till 6 months of age and it should be continued till two years or more.
- Complementary feeding should start with home based semisolid foods comprising cereal-pulse-nut and sugar/jaggery combinations that provide good quality protein, adequate calories and other protective nutrients, after 6 months. Energy density can be enhanced by using *Amylase-Rich Foods (ARFs)*. Details of ARFs are provided in the next Chapter.
- When a child starts learning to eat, they need help by parents. Many a times child push out food because they have not learn the skill of moving food inside or swallow solids. This is not a sign showing child is not interested in food. In fact, if food is regularly given to the baby, the ability to swallow develops automatically.
- Feeding is more successful when it is given in suitable feeding situation, i.e., all family members taking meal at same time so child develops interest in feeds, use separate bowl for the child, feed when child is alert and happy.
- Avoid food fads and discard erroneous food beliefs.
- During illness it is must to provide adequate and appropriate diets. Frequent small quantities, energy-rich cereals-pulse diet with milk and vegetables should be given to the child. Continue breastfeeding and give plenty of fluids during illness. Child should never be starved.
- Also assess whether foods prepared are safe or not. Talk to family to know whether following practices are fulfilled or not.
- Caregiver washes hands and utensils.
- Caregiver uses clean and safe water. In case, water is not deemed safe for drinking, one of the usual methods of purification is to boil it for around 10–15 min.
- Caregiver uses freshly prepared foods. If it is not consumed immediately, it should be stored either hot over 60°C or refrigerated below 10°C.
- Ensure good intake of polyunsaturated fatty acids (PUFA), whole grain cereals, vegetables and fruits in all age groups.

water is thrown away after the cooking. Cooking can be done by boiling, steaming, frying, roasting, baking and pressure cooking. While boiling leads to the loss of heat labile vitamins, microwave preserves nutrients but cooks unevenly. Processes of cooking that lead to loss of nutrients, such as deep frying, cooking at high temperatures, adding baking soda while cooking pulses, and cutting of vegetables in to small pieces, should be minimized. Nutritive value of the food can be enhanced by sprouting of grams, malting of cereals, and parboiling of grains. Prior to cooking, removal of pesticide residue from the food products is equally important and can be done by washing thoroughly in running water, blanching, and peeling.

### Processed Food

Restrict intake of preserved and processed foods like chips, salted biscuits, pickles, sauce, salted butter, and cheese. Processed foods

**Table 12** Therapeutic lifestyle change (TLC) diet

Diet component	Recommended intake
Total fat	25–35%
Saturated fat	< 7%
Monounsaturated fat	Up to 20%
Polyunsaturated fat	Up to 10%
Cholesterol	< 200 mg/day
Fiber	20–30 g/day
Protein	Approximately 15%
Total calories	As needed to maintain desired weight
Salt	< 5 g per day
Tobacco, alcohol	Nil

**Table 13** Approximate calorific value of some cooked preparation

Preparation	Quantity for one serving	Calories (kcal)
<b>1. Cereal</b>		
Rice	1 cup	170
Phulka	1 no.	80
Paratha	1 no.	150
Puri	1 no.	80
Bread	2 slices	170
Poha	1 cup	270
Upma	1 cup	270
Idli	2 nos.	150
Dosa	1 no.	125
Khichdi	1 cup	200
Wheat porridge	1 cup	220
Semolina porridge	1 cup	220
Cereal flakes with milk (corn/wheat/rice)	1 cup	220

Contd...

<b>2. Pulse</b>		
Plain dal	½ cup	100
Sambar	1 cup	110
<b>3. Vegetable</b>		
With gravy	1 cup	170
Dry	1 cup	150
<b>4. Nonvegetarian</b>		
Boiled egg	1 no.	90
Omelette	1 no.	160
Fried egg	1 no.	160
Mutton curry	¾ cup	260
Chicken curry	¾ cup	240
Fish fried	2 big pieces	190
Fish cutlet	2 nos.	190
Prawn curry	¾ cup	220
Keema kofta curry	¾ cup (6 small koftas)	240
<b>5. Savoury snacks</b>		
Bajji or pakora	8 nos.	280
Besan ka pura	1 no.	220
Chat (dahi pakori)	5 pieces	220
Cheese balls	2 nos.	250
Dahi vada	2 nos.	180
Vada	2 nos.	140
Masala vada	2 nos.	150
Masala dosa	1 no.	200
Pea-kachori	2 nos.	380
Potato bonda	2 nos.	200
Sago vada	2 nos.	210
Samosa	1 no.	200
Sandwiches (butter 2 tbsp)	2 nos.	200
Vegetable puff	1 no.	200
Pizza (cheese and tomato)	1 slice	200
<b>6. Chutney</b>		
Coconut/groundnut/til	2 tbsp	120
Tomato	1 tbsp	10
Tamarind (with jaggery)	1 tbsp	60
<b>7. Sweets and Desserts</b>		
Besan barfi	2 small pieces	400
Chikki	2 pieces	290
Fruit cake	1 piece	270
Rice puttu	½ cup	280
Sandesh	2 nos.	140
Double ka meetha	½ cup	280
Halwa (kesari)	½ cup	320
Jelly/jam	1tbs	20
Custard (caramel)	½ cup	160
Srikhand	½ cup	380
Milk chocolate	25 g	140
Ice cream	½ cup	200

Source: Dietary Guidelines for Indians. 2<sup>nd</sup> ed. National Institute of Nutrition, Indian Council of Medical Research; 2011.

Contd...

lack dietary fiber and micronutrients, and their frequent intake enhances the risk of exposure to various chemical additives and excessive intake of fat, salt, sugar and calories. Always read food labels for their nutrients and the additive presence and prefer fortified processed food.

Since people comprehend in terms of food intake rather than nutrients, it is constructive to explain in terms of food items and their quantity. Indian Council of Medical Research has provided approximate calorific value of some commonly cooked Indian preparations (**Table 13**).

### MORE ON THIS TOPIC

Gopalan C, Rama Sastri BV, Balasubramanian SC. Nutritive Value of Indian Foods. Hyderabad: National Institute of Nutrition, ICMR; 2012.

Indian Council of Medical Research. Nutrient Requirements and Recommended. Dietary Guidelines for Indians-A Manual. Hyderabad: National Institute of Nutrition, ICMR; 2011.

National Heart, Lung, and Blood Institute. Your Guide to Lowering Your Cholesterol with TLC. National Institutes of Health, US Department of Health and Human Services; NIH Publication No. 06-5235. 2005.

World Health Organization. Diet, Nutrition and the Prevention of Chronic Diseases. WHO Technical Report Series No.916. Geneva: WHO; 2003.

### IN A NUTSHELL

1. Eat variety of foods to ensure a balanced diet.
2. Ensure provision of extra food and health-care to pregnant and lactating women.
3. Promote exclusive breastfeeding for 6 months and encourage breastfeeding till 2 years or as long as one can.
4. Feed home based semisolid foods to the infant after 6 months.
5. Ensure adequate and appropriate diets for children and adolescents, both in health and sickness.
6. Eat plenty of vegetables and fruits.
7. Ensure moderate use of edible oils and animal foods and very less use of *ghee*/butter/*vanaspati*.
8. Avoid overeating to prevent overweight and obesity.
9. Exercise regularly and be physically active to maintain ideal body weight.
10. Restrict salt intake to minimum.
11. Ensure the use of safe and clean foods.
12. Adopt right precooking processes and appropriate cooking methods.
13. Drink plenty of water and take beverages in moderation.
14. Minimize the use of processed foods rich in salt, sugar and fats.



## Chapter 22.3

# Infant and Young Child Feeding

JP Dadhich

Optimal nutrition during the first 2 years of life is important to lay down a strong foundation for growth and development of children. Recently, the focus has been drawn to the first 1,000 days of nutrition that include both intrauterine period (270 days of pregnancy) plus the first 2 years of life (730 days). The following infant and young child feeding practices, as recommended in the WHO/UNICEF global strategy for infant and young child feeding practices are imperative to achieve optimal growth, development and health.

- *Early initiation of breastfeeding* within one hour;
- *Exclusive breastfeeding* for the first 6 months of life;
- *Complementary feeding starting after 6 months* of life to meet their evolving nutritional requirements and to fill the nutritional gap between the total needs of the infant and the amount being provided by breastfeeding.

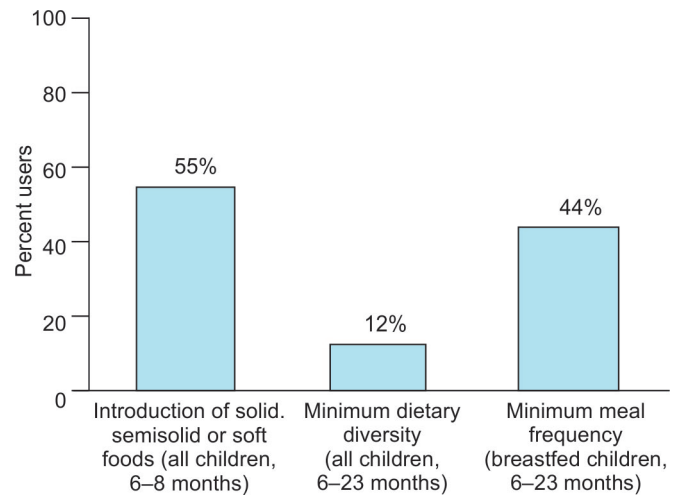
Infants should receive nutritionally adequate and safe complementary foods while breastfeeding continues for up to 2 years of age or beyond. Breastfeeding has been dealt with in the section on newborn care. Present chapter will mainly focus on the complementary feeding component of infant and young child feeding.

## COMPLEMENTARY FEEDING

Complementary feeding implies giving other foods in addition to breastmilk. These other foods are called complementary foods (WHO, 2004). National Nutrition Institute-Indian Council of Medical Research (NIN-ICMR) recommends home based semisolid foods to the infant after 6 months of age. Appropriate complementary feeding has been recognized as an important preventive strategy for child deaths, preventing 6% of child deaths. Improvement of complementary feeding through strategies such as counseling about nutrition in food secure populations and nutrition counseling, food supplements, conditional cash transfers, or a combination of these, in food-insecure populations could substantially reduce stunting and related burden of disease. Apart from being important to provide appropriate nutrients, introduction of diverse foods during infancy might have a protective effect on asthma, food allergy, and food sensitization with increased expression for regulatory T-cells marker.

## Status of Complementary Feeding in India

The proportion of children in India, who are fed with appropriate complementary feeding practices like timely initiation at 6 months consuming appropriate number of variety of food groups (i.e., three or more food groups for breastfed children and four or more food groups for nonbreastfed children); and minimum frequency of feeding (i.e., feed solid or semisolid food at least twice a day for infants of 6–8 months, 3 or more times for other breastfed children, and 4 or more times for nonbreastfed children) is depicted in the **Figure 1**. It is evident that in India, complementary foods is not introduced to 45% infants at appropriate time (6–8 months), minimum dietary diversity is available to only 12% children between 6 months and 23 months, and 56% are not fed with minimum frequency required. Coupled with the fact that more than half of infants are not exclusively breastfed during first 6 months, sub-optimal complementary feeding contributes significantly to child undernutrition in India.



**Figure 1** Complementary feeding indicators for India

Source: NHFS-3, 2005-06.

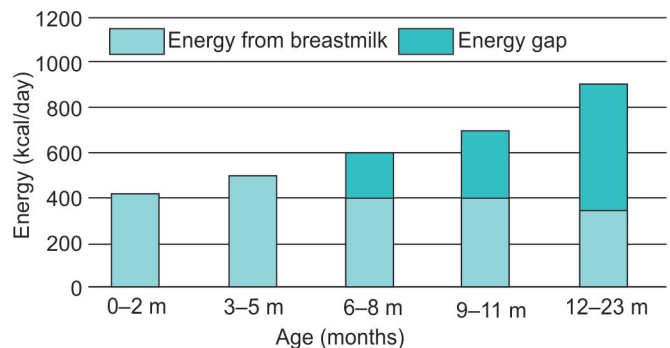
## Attributes of Complementary Feeding

Attributes of appropriate complementary foods include (a) timely start; (b) adequate in amount, variety and frequency; and (c) properly fed and safe.

### Timely Start

Breastmilk is sufficient to promote growth and development till 6 months of age. Complementary foods should be introduced after 6 months of age along with continued breastfeeding when need for energy and nutrients exceeds that is provided by breastmilk (**Fig. 2**). Also, around this age, infant's development and behavior makes him/her ready for foods other than breastmilk. Gradually, infant's tendency to push solids out decreases; infant starts showing interest in other people eating and reach for food; holds objects and like to put things in his/her mouth; starts moving the food around the mouth with better control of tongue and starts chewing the food. Also, the digestive systems are mature enough to begin to digest a range of foods.

Adding complementary foods before 6 months of age may decrease the intake of breastmilk resulting in a low nutrient diet and increase the risk of illness especially diarrhea. Likewise, adding complementary foods too late may lead to suboptimal growth and development and risk of nutritional deficiencies and malnutrition.



**Figure 2** Energy gap to be filled by complementary foods after 6 months of age

Reproduced with permission: From *Infant and young child feeding: model chapter for textbooks for medical students and allied health professionals*. WHO;2009.

### Adequate in All Food Groups

Complementary foods should be adequate in amount, containing various food groups to provide sufficient energy, protein, and micronutrients with optimum frequency as required for the age. Complementary foods should not replace breastfeeding and should be provided in addition to breastfeeding. Sequencing of complementary feeding in relation to breastfeeding does not affect total energy intake. Three or more food groups for breastfed children and four or more food groups for nonbreastfed children from food groups as mentioned below:

**Staples** Each community has a staple food, which is the main food eaten. Examples include cereals (rice, wheat, maize, and millets), roots (potato) and pulses. Cereals are the main source of energy. Cereals are usually milled to flour which is used to make bread (*chapati*) or make porridge. Cereals also provide proteins but are not very good source of micronutrients, millets (bajra, ragi) being an exception. Cereals also contain phytates which may interfere in the absorption of iron, zinc and calcium. It becomes important to use cereals with other sources of protein (like pulses and oil seeds like groundnuts) and micronutrients (like vegetables and fruits). Pulses and oil seeds contains fats, hence are a source of energy. Pulses with low fat contents are bengal gram, green gram, kidney beans, etc. Pulses and oil seeds with high fat content are ground nut, soybean, sesame, etc. Pulses and oil seeds also contain phytates interfering absorption of micronutrients. Beans contain antinutrients interfering utilization of nutrients by the body. Antinutrients could be removed by soaking the beans and throwing away the water. A cereal pulse combination in the ratio 2:1 is recommended for infant feeding.

**Fats and sugars** Oils and fats are concentrated source of energy and may be added to complementary foods to increase energy density without much increase in the volume. Fats and oils are also a good source of vitamin A. Sugar and jaggery are also energy-rich and can be added to foods to increase the energy content.

**Foods of animal origin (milk, curd, eggs, meat, fish)** Foods of animal origin are rich source of good quality proteins. Flesh and organs of animals are good source of micronutrients like vitamin A, zinc and calcium. Animal liver is a rich source of iron, vitamin A and folates, while egg yolk is a good source of vitamin A.

**Vegetables and fruits** Addition of vegetables and fruits to child's diet enrich it by providing vitamin A, iron, vitamin C and zinc.

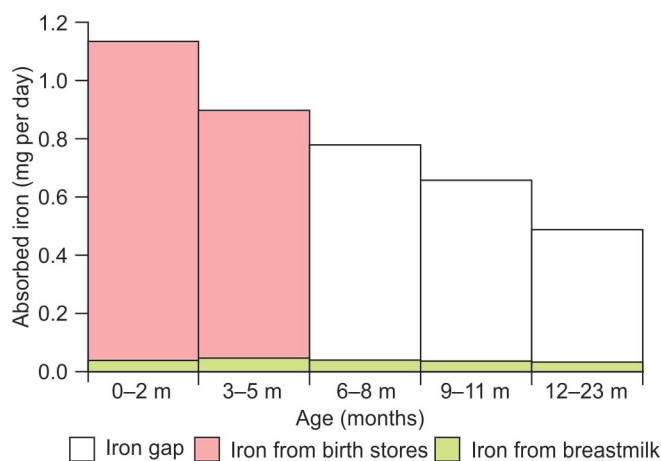
A balanced diet for infants and young children should include appropriate amounts of above mentioned food group, as given in the **Table 11** of previous chapter.

### Iron Gap

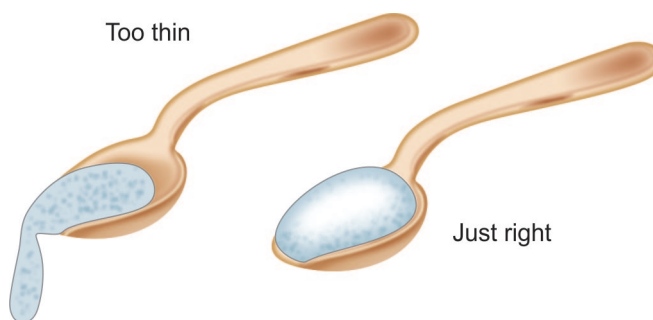
Full-term infants are born with adequate iron store and get some iron in breastmilk, thus do not require additional iron for first six months of life. After six months of life, breastmilk iron is grossly inadequate and most of iron demand needs to be met with complementary foods. This is important to provide iron rich foods to children during this period to fill iron gap. Iron rich foods include green leafy vegetables, legumes, dried fruits, meat, fish and poultry products. Bioavailability of iron from plant foods is not optimum, addition of fruits rich in vitamin C increases the absorption of iron from plant foods. It is important to note that with increasing age (6–24 months) requirement for iron decreases (**Fig. 3**).

### Texture, Frequency and Amount of Complementary Foods

Complementary foods should be of right consistency (**Fig. 4**); soft; prepared with easy to digest, inexpensive, locally available and culturally acceptable ingredients; and easy to prepare at home.



**Figure 3** Iron need and supply in infants and young children  
Reproduced with permission: From *Complementary feeding—family foods for breastfed children*. WHO; 2000.



**Figure 4** Consistency of complementary foods (6–8 months)  
Reproduced with permission: From *Complementary feeding—family foods for breastfed children*. WHO; 2000.

These foods should be energy dense with variety to provide all nutrient demands of a growing child. Complementary foods may be started after 6 months with small amounts of mashed and semi-solids (e.g., porridge); quantity is increased with age, maintaining frequent breastfeeding. Gradually, food consistency, amount and variety are increased with age. Infant can be fed with finger foods by 8–9 months of age and by 12 months, family foods can be eaten. Frequency of complementary feeding should also increase with age as outlined in **Tables 1** and **2**. Certain food items need to be avoided in infants and young children, e.g., tea and coffee (interfere with iron absorption), aerated beverages (no nutritional value), too much sugary drinks and fruit juices (cause decreased appetite for other nutritious foods and also may cause loose stools), and nuts (may cause choking).

### Continued Breastfeeding

It is crucial to continue breastfeeding till 2 years of age and beyond as breastmilk remains an important source for energy, proteins and micronutrients like vitamin A and vitamin C for infants and young children even in the second year of life. It plays an important role in preventing undernutrition and morbidities. It can provide about one-third of energy needs, half of protein and 75% of the vitamin A requirements of a child of this age (**Fig. 5**). Thus, breastmilk helps a child to get enough energy and high quality nutrients from breastfeeding during the second year of life.

**Table 1** Practical guidance on the quality, frequency and amount of food to offer children 6–23 months of age who are breastfed on demand

Age	Energy needed per day in addition to breastmilk	Texture	Frequency	Amount of food an average child will usually eat at each meal
6–8 months <sup>1</sup>	200 kcal	Start with thick porridge, well mashed foods Continue with mashed family foods	2–3 meals per day Depending on the child's appetite, 1–2 snacks may be offered	Start with 2–3 tablespoonful per feed, increase gradually to ½ of a 250 mL cup
9–11 months	300 kcal	Finely chopped or mashed foods, and foods that baby can pick up	3–4 meals per day Depending on the child's appetite, 1–2 snacks may be offered	½ of a 250 mL cup/bowl
12–23 months	550 kcal	Family foods, chopped or mashed if necessary	3–4 meals per day Depending on the child's appetite, 1–2 snacks may be offered	¾ of a 250 mL cup

<sup>1</sup>The age ranges should be interpreted as follows: a child 6–8 months is 6 months or older ( $\geq 180$  days) but is not yet 9 months old ( $< 270$  days).

Reproduced with permission. From *Infant and young child feeding: model chapter for textbooks for medical students and allied health professionals*. WHO;2009.

**Table 2** Age-wise complementary foods

Age	Type of supplement	Example of food to be given
7th–8th months	Semisolid	Ready to eat infant mixes, well blended porridge, <i>kheer</i> , well mashed lentil with a boiled vegetable, potato and spinach puree, blended rice <i>khichri</i> , vermicelli <i>khichri</i> , sweet dalia
9th–12th months	Semisolid - solid	Poha with curd, potato with curd, millet <i>khichri</i> , <i>upma</i> , <i>idli</i> , <i>moong dal</i> mixture
Above 1 year	Solid	<i>Roti</i> , <i>cheela</i> , <i>parantha</i> , <i>laddoo</i> , biscuits, rice, <i>dal</i> (family food)

Source: IBFAN Asia, Navdanya, IHES, BPNI (2009). Complementary foods for children and young children (recipe for the people by the people).

## Responsive Feeding

Responsive feeding means the reciprocity between child and caregiver (Black and Aboud, 2011). It is important to make feeding a pleasurable experience for the infant. It also helps in ensuring intake of adequate amount of variety of foods. Responsive feeding is a three-step process:

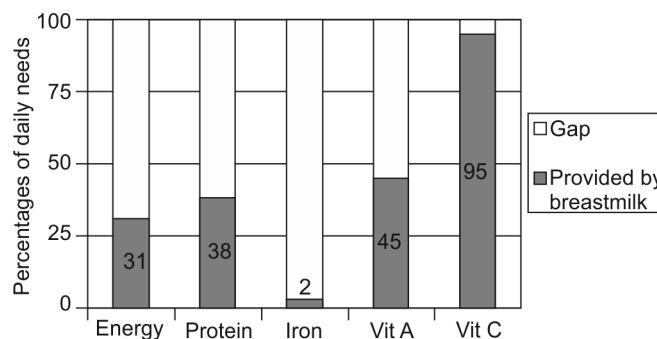
1. The child signals requests through motor actions, facial expressions, or vocalizations.
2. The caregiver recognizes the signals and responds promptly in a manner that is emotionally supportive, contingent on the signal, and developmentally appropriate.
3. The child experiences a predictable response to signals.

Responding to the child with smiles and eye contact; talking to the child while feeding; feeding the child slowly with patience increase food intake; experimenting with different food combinations, tastes, textures; minimizing distractions during meals are few practices which helps in achieving responsive feeding.

## Maintaining Safety of Food

Complementary foods should be hygienically prepared, stored and fed. This can be achieved by:

- Washing caregiver's and child's hands before preparing, handling and eating food
- Using clean water and raw materials to cook food
- *Storing foods safely* Keeping food covered and serving shortly after preparation



**Figure 5** Nutrition provided by breastmilk in second year of life and gaps to be filled by complementary foods

Reproduced with permission from infant and young child feeding counseling—a training course, the '4 in 1 course' (integrated course on breastfeeding, complementary feeding and infant feeding and HIV), Breastfeeding Promotion Network of India (BPNI), Delhi.

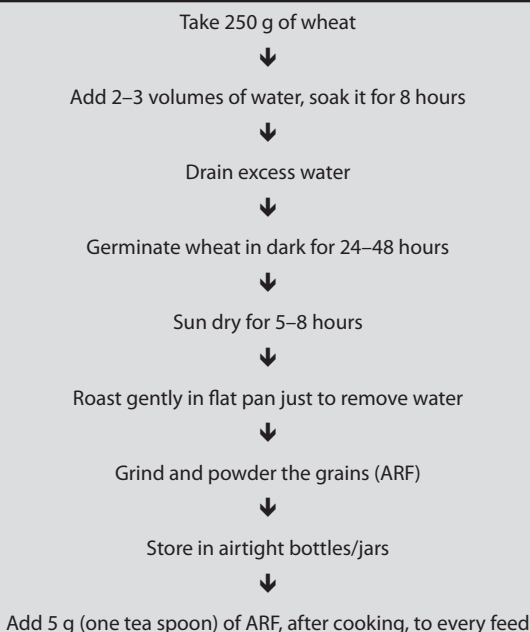
- Using clean utensils to prepare and serve food
- Using clean bowls and cups when feeding child.

## Amylase Rich Foods

Thick and viscous food prepared from cereals is difficult to swallow. Amylase (an enzyme) liquefies it and make easy to swallow without compromising the energy density. It increases acceptability of the food. Amylase rich food is prepared using the method shown in **Box 1**.

## Types of Complementary Foods

Complementary foods may be especially prepared foods, which may be either instant food mixes or freshly prepared foods or modified family foods. Instant infant food mixes may be prepared using roasted and powdered cereals, pulses, groundnuts, jaggery, etc. These mixes are stored in airtight containers and may be used for more than a month. Such foods are useful in families where frequent cooking in a day is not possible. Instant foods may be reconstituted for use by taking 4 tablespoon (about 50) of instant mix and 100 mL of boiled water, mixing thoroughly. Some oil/*ghee*, and sugar may be added to make it more palatable as well as to increase the calorie density. If available, some fruit/vegetable may also be added to it to make it more nutrient rich.

**BOX 1 Preparation of amylase rich food (ARF)****BOX 3 Recipes for fresh complementary foods****Suji Halwa**

*Ingredients:* Suji (roasted) 200 g, groundnut (roasted) 40 g, jaggery 100 g, Oil 10 mL, water 800 mL.

*Method of preparation:*

1. Grind groundnuts coarsely after removal of skin.
2. Heat oil in a pan, add *Suji* and fry till light brown.
3. Add groundnuts to *Suji* and mix well.
4. Add jaggery and water to the above and cook till it leaves sides.

*Nutritive values per 100 g:* Calories 408, protein 9.05 g, Iron 2.02 mg.

**Dalia Porridge**

*Ingredients:* Dalia (Broken wheat) 25 g, moong dal 20 g, milk 60 mL, sugar 30 g, ghee/oil 15 g.

*Method of preparation:*

1. Roast broken wheat in a pan.
2. When half-done add *dal* and continue roasting till light brown.
3. Add water to the above, cook till soft and slightly thick (semisolid).
4. Remove from fire. Add milk, sugar and oil. Boil for a few minutes and serve.

*Nutritive value per 100 g:* Calories 310, protein 6.5 g, Iron 1.5 mg, carotene 497 µg.

Two examples of such foods (adapted from a publication of FNB, Ministry of Women and Child Development, Government of India) are given in **Box 2**. Complementary foods can also be prepared fresh using commonly available food ingredients at home. These foods provide variety. Some examples of such foods are given in **Box 3**.

**Epilogue**

Along with breastfeeding, optimum complementary feeding with home prepared, age appropriate foods is crucial for ensuring optimum health and nutrition for the infants and young children.

**BOX 2 Recipes of instant food mix for complementary feeding****1. Wheat Food Mix**

*Ingredients:* Wheat 100 g, roasted bengal gram dal 30 g, groundnut 20 g, Sugar 50 g.

*Method of preparation:*

- Clean and roast wheat and groundnut separately (remove the outer skin of groundnut).
- Grind roasted Bengal gram dal and roasted groundnut and wheat separately to a fine powder. Mix all the ingredients thoroughly and add powdered sugar.
- Fill in dry airtight container and store.

*Nutritive value per 100 g:* Calories 386, protein 11.64 g, iron 3.75 mg, carotene 51.5 µg.

**2. Chidwa Mix**

*Ingredients:* Chidwa (rice flakes) 100 g, Bengal gram 30 g (roasted and de-husked), ground nut 20 g (roasted).

*Method of preparation:*

- Roast *Chidwa* and grind.
- Grind roasted groundnut (without skin) and Bengal gram separately.
- Mix all thoroughly. Store in a dry-airtight container.

*Nutritive value per 100 g:* Calories 381, protein 12.39 g, iron 15.63 mg, carotene 22.6 µg.

**IN A NUTSHELL**

1. Optimal nutrition during the first 2 years of life is important for growth and development of children.
2. Complementary feeding after 6 months of age along with continued breastfeeding is required to meet the evolving nutritional requirements and to fill the nutritional gap.
3. Appropriate complementary feeding is crucial in preventing undernutrition, disease and mortality in children.
4. Attributes of appropriate complementary foods include timely start; adequate in amount, variety and frequency; properly fed and safe.
5. Wholesome complementary foods may be prepared using ingredients available in the household.

**MORE ON THIS TOPIC**

Complementary Feeding: Family foods for breastfed children. Geneva: WHO; 2000.

Dietary Guidelines for Indians—a Manual. Hyderabad: National Institute of Nutrition (NIN)-Indian Council of Medical Research; 2011.

Guiding principles for complementary feeding of the breastfed child. Geneva: PAHO-WHO; 2001.

Infant and young child feeding: model chapter for textbooks for medical students and allied health professionals. Geneva: WHO; 2009.

Nutritious recipes for complementary feeding of infants and young children. Food and Nutrition Board-Ministry of Women and Child Development, Government of India; 2008.

Shah D, Singh M, Gupta P, et al. Effect of sequencing of complementary feeding in relation to breastfeeding on total intake in infants. *J Pediatr Gastroenterol Nutr.* 2014;58:339–43.

Saha KK, Frongillo EA, Alam DS, et al. Appropriate infant feeding practices result in better growth of infants and young children in rural Bangladesh. *Am J Clin Nutr.* 2008;87:1852–9.



## Chapter 22.4

# Feeding During Childhood and Food Allergy

KE Elizabeth, S Bindusha

Childhood and adolescence are periods of continuous growth and development. During the preadolescent period the child grows, on an average, 6–7 cm in height and 2–3 kg in weight every year and simultaneously development and maturation of various tissues and organs take place. So, they need more nutritious food in proportion to their weight than adults. Energy requirement of children depends on their basal metabolism, rate of growth, body size, age and activity. Enough calories should be provided for growth and to prevent protein being utilized for energy. Excessive calorie intake will lead to obesity. Children require adequate protein intake for growth and maintenance needs. Young children require around 1.8 g of protein per kg body weight, which decreases over years to 1.2 g/kg in late childhood. Proteins with high biological value should be included in their diet. Young children are at high-risk for iron deficiency due to rapid growth, increase in hemoglobin mass and increase in the total iron mass during growth. Lack of iron rich food in the diet adds on to this. Calcium is needed for adequate mineralization of growing bone. Milk and milk products are the major sources of calcium. Children who do not consume these are at risk of calcium deficiency. Vitamin D deficiency is also prevalent in our country, even though major part of our country lies near the equator. Dark pigmentation of skin, excessive clothing and lack of exposure to the sunlight especially during the peak hours are considered to be the causes. Zinc is essential for growth and zinc deficiency during childhood can lead to stunting.

## FOOD FOR PRESCHOOL AND SCHOOL CHILDREN

Young children between 1 year and 5 years should be given foods which are rich in energy and protein and low in bulk (example: legumes, pulses, nuts, edible oil or ghee, sugar, milk and eggs). Young children will consume more calories if small frequent feeds are given. The energy gap could be corrected by adding vegetable oil, ghee or sugar to the food. Food items which do not swell much on cooking like potato and banana are also energy dense. Vegetables including green leafy vegetables and locally available seasonal fruits should be part of their daily menu. Majority of children take more than three meals per day. Snacks make a useful contribution to the nutrient requirements, particularly in older children and adolescents. Snacks should be carefully chosen so that they are nutrient rich. Frequent changes in the menu are often liked by children. Older children and adolescents should consume plenty of milk to fulfill the high calcium requirements. Excessive salt intake should be avoided particularly by children having a family history of hypertension. School children should be encouraged not to miss breakfast and practice healthy eating using the food guide pyramid.

## FOOD FOR ADOLESCENTS

Adolescence is a period of rapid growth and is spread almost over a decade. This is a transitional stage in human development. It is characterized by rapid increase in height and weight, hormonal changes, sexual maturation and wide swings in emotion. Adolescent growth spurt starts at about 10–12 years in girls and 2 years later in boys. Development of critical bone mass is essential during this period as this forms the ground for maintaining mineral

integrity of the bone in later life. The pattern and proportion of various body components like body water, muscle mass, bone and fat increase during the entire childhood and adolescence to reach adult values by about 18 years. Adolescent girls are at greater physiological stress than boys because of menstruation. Their nutritional needs are of particular importance as they have to prepare for motherhood. All these rapid anabolic changes require more nutrients per unit body weight. The growth during this period is under the influence of nutrition, genetic and hormonal factors.

An adolescent boy is expected to consume 2,700–3,000 kcal/day, as equivalent to the requirement of an adult sedentary male. Adolescent girl requires 2,300–2,400 kcal, more than an adult sedentary female. Carbohydrates should make up 45–65% of energy intake; protein 10–30%; and fat 25–35%. Dietary fat should come primarily from sources of polyunsaturated and monounsaturated fatty acids, such as fish, nuts, and vegetable oils. Trans fats, found in hydrogenated oils used primarily in bakery products, should be avoided altogether because they increase serum levels of low density lipoprotein. Dietary intake of total cholesterol, found in animal products, should be limited to 300 mg/day.

Growing children and adolescents particularly require more calcium. Though recommended dietary allowances for calcium are about 800 mg/day only, it is desirable to give higher quantities of calcium for adolescents to achieve high peak bone mass. Adolescents are also at risk of vitamin D deficiency also due to inadequate exposure to sunlight. Adequate intake of iron should be ensured as iron is needed to build up the muscle mass and to prevent the development of anemia due to menstrual loss in girls. Malnutrition among adolescents may be due to various reasons other than unavailability of food. Many adolescents consume less food due to lack of time as they are engaged in a period of stressful studies. Breakfast is often missed or eaten hurriedly. Food fads and fast food culture also leads to malnutrition. Fast foods are high in calories, fat and sodium but fail to provide enough vitamins and minerals needed during this stage. Very little information is available about the nutrient composition of fast foods. Food additives like ajinomoto and coloring agents used for preparation of fast foods are antinutrients. Soft drinks also provide only empty calories. They may contain antinutrients. Consumption of soft drinks will kill the appetite and promote skipping of meals.

Peer pressure, media influence and rapid changes in the body size and shape may make them uncomfortable about their bodies. Some children especially girls eat less food as they want to remain slim. In some families, adolescent girls eat last and least due to ignorance and poverty. Psychological problems and eating disorders like anorexia nervosa and bulimia may also interfere with adequate nutrition. Adolescence is the period during which experimentation starts in all fields. Adolescence is the vulnerable stage for developing wrong food habits. Distinctive likes and dislikes for food may develop in this age. Developing unhealthy food habits may lead to nutrient deficiency. Dietary experimentation in the form of strict vegetarianism without proper knowledge about the healthy meal plans may also lead to malnutrition. In addition to consumption of a nutritious well balanced diet, appropriate lifestyle practices and involvement in physical activity such as games or sports should be encouraged among children and adolescents.

## FOOD ALLERGY

*Food allergy* is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food. The immune response may be IgE mediated, non-IgE mediated or a combination of both. *Food intolerance* is a nonimmune reaction that occurs after ingestion of food due to metabolic, toxic, pharmacologic or undefined mechanisms.

## Epidemiology

The prevalence of food allergy is increasing globally. Food allergy is more prevalent in the developed countries. Incidence of food allergy is 3–6% in children and 1–3% in adults. Children may outgrow their allergies over time. Food allergy that starts in adulthood often persists. Allergy to milk, egg, soy, or wheat is more likely to be outgrown than allergy to tree nuts or peanut. Resolution of a food allergy can occur as late as the teenage years.

## Pathogenesis

The major food allergens are egg, milk, peanut, tree nuts, fish, shellfish, wheat, and soy. Food allergens can cause symptoms when eaten either in the raw form or after being cooked. Cross reactivity can occur between different allergens which have structural similarity. Chemical additives in the food can produce adverse reactions which do not have immunological basis and hence considered as food intolerance.

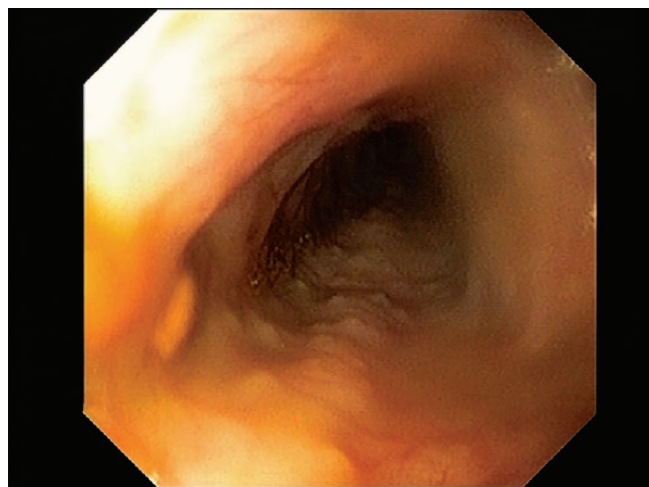
IgE-mediated reactions are characterized by an acute onset of symptoms generally within 2 hours after ingestion of the trigger food. IgE-mediated reactions to foods typically involve the skin, gastrointestinal tract, and respiratory tract. Exposure to the allergen will stimulate the Th2 lymphocytes, which will stimulate the B-cells to differentiate into plasma cells and produce allergen specific IgE antibodies. Once IgE antibodies are formed they will bind to the tissue mast cells and basophils. Once the allergen specific antibodies have bound to the mast cells, the patient is considered as sensitized to that allergen. On re-exposure to the food, antigenic proteins in the food bind to and cross-link the IgE antibodies on the mast cells, which trigger the release of symptom-causing mediators, such as histamine and leukotrienes. Sensitization alone is not sufficient to define food allergy. An IgE-mediated food allergy requires both the presence of sensitization and the development of specific signs and symptoms on exposure to that food. Non-IgE-mediated immunologic reactions (e.g., cell mediated) include food protein induced enterocolitis, proctocolitis, and enteropathy syndromes. These conditions primarily affect infants or young children who present with abdominal complaints, such as vomiting, abdominal cramps, diarrhea, and occasionally blood in the stool and failure to thrive or poor weight gain. Examples of food allergy with mixed IgE- and non-IgE-mediated causes include eosinophilic esophagitis and atopic dermatitis.

## Clinical Features

Allergic reactions occur if the specific IgE is above a critical level. Symptoms of IgE-mediated food allergy can occur within minutes to hours of ingesting the trigger food and can vary in severity from mild to life-threatening. Severity of allergic reactions varies based on the amount of food ingested, preparation of the food and ingestion of other foods along with the trigger food. Severity can also be influenced by the patient's age, presence of comorbidities like asthma, as well as rapidity of absorption. The rate of absorption increases if the food was eaten on empty stomach or close to the time of exercise, leading to a more severe reaction. IgE-mediated reactions commonly affect the skin, gastrointestinal tract (Fig. 1), airways and rarely the circulatory system. Food induced anaphylaxis is a severe allergic reaction due to systemic release of mediators. It progresses rapidly and may possibly lead to death. Non-IgE mediated food allergy syndromes present predominantly with abdominal symptoms. Clinical features of various food allergy syndromes are summarized in Table 1.

## Diagnosis

Specific IgE can be demonstrated by positive allergic skin prick test or immunoassay of serum. These tests will identify foods that might provoke an IgE-mediated allergy. But they cannot be considered diagnostic of food allergy unless supported by history. Double-blind placebo-controlled food challenge (DBPCFC) is the most



**Figure 1** Cow milk protein allergy: endoscopic changes  
Source: Dr Rimjhim Shrivastava, Pediatric Gastroenterologist, Raipur, Chhattisgarh.

specific test for diagnosing food allergy. It can reliably differentiate between sensitization and allergy. Single blind or open food challenges may also be done in young children. A food challenge is indicated if specific IgE test results do not correspond to the history or if a screening test result for specific IgE is positive and the food was not introduced into the patient's diet till then. Diagnostic algorithm for food allergy is depicted in Flow chart 1.

## Treatment

The safest treatment for food allergy is strict avoidance of the causal food or foods. This holds good for all food allergy syndromes irrespective of the mechanism of allergy. Indiscriminate use of elimination diets without firm diagnosis should be discouraged, as it will lead to malnutrition. Once the offending antigen is found out that alone needs to be avoided. Patients should be educated on how to read ingredient labels on the food items to avoid their allergens. In many western countries, food-labeling laws require food manufacturers to declare in plain language on the food packaging whether one of the common allergens or a product derived from them is used as an ingredient. Similar laws are not in place in our country, and care is required to identify hidden forms of allergens.

Drug therapy depends on the symptoms. If patient presents with anaphylaxis intramuscular injection of 1/1,000 solution of adrenaline 0.01 mL/kg may be lifesaving. Children who have experienced anaphylaxis, and whose allergens are not clearly identified should be prescribed preparations of adrenaline like epipen for use in emergencies. Hydrocortisone, H1 and H2 antihistamines are used for urticaria. Steroids are used for treatment of eosinophilic gastroenteritis.

## Prognosis

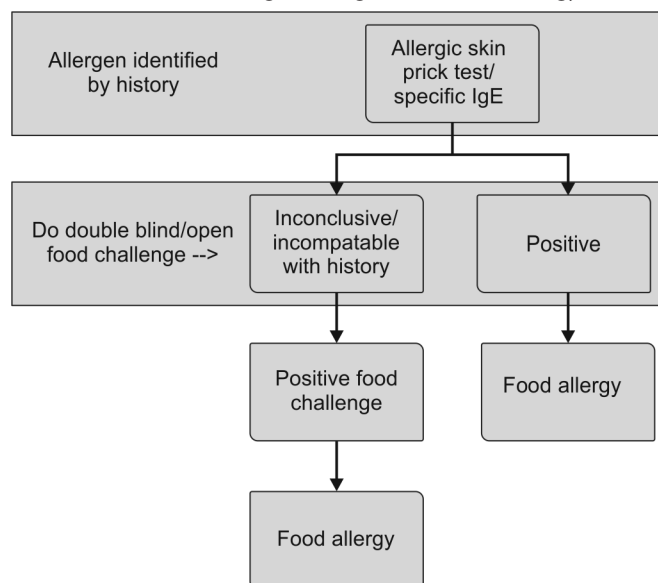
As age advances most children will be able to tolerate previously allergic food. Tolerance usually develops by 3 years of age. This is due to maturation of the gastrointestinal barrier system and development of immunological tolerance.

## MORE ON THIS TOPIC

- Burks W, Tang M, Sicherer S, et al. ICON: food allergy. *J Allergy Clin Immunol.* 2012;129:906-20.
- Elizabeth KE. *Nutrition and Child Development.* 4<sup>th</sup> ed. Hyderabad: Paras; 2010.
- Lucas BL, Sharon A Feucht SA, et al. *Nutrition in Childhood.* Krause's Food and Nutrition Care Process. 13<sup>th</sup> ed. Missouri: Saunders; 2012. pp. 389-409.

**Table 1** Food allergy: disorders, pathology, and clinical features

Disorder	Pathology	Clinical features	Food allergen
Urticaria/angioedema	IgE mediated	Common-acute urticaria	Milk, egg, peanut, tree nut, fish, shellfish, wheat and soy
Anaphylaxis	IgE mediated	Rapid progression, shock Multi organ involvement	Any, but commonly peanut, tree nut, fish, shellfish, milk and egg
Food-associated, exercise-induced anaphylaxis	IgE mediated	Food triggers anaphylaxis only if exercise follows ingestion	Wheat, shellfish and celery
Oral allergy syndrome (pollen-associated)	IgE mediated	Pruritus and mild edema in the oral cavity, rarely progress beyond mouth Anaphylaxis—very rare increase after pollen season	Raw fruit and vegetables birch pollen—apple, peach, pear and carrot ragweed—melons
Immediate gastrointestinal hypersensitivity	IgE mediated	Immediate vomiting, pain	Milk, egg, peanut, tree nut, fish, shellfish, wheat and soy
Atopic dermatitis	Combined IgE and cell mediated	Food allergy in 35% with moderate to severe rash	Major allergens, especially egg, milk
Eosinophilic esophagitis	Combined IgE and cell mediated	Gastroesophageal reflux, vomiting, dysphagia, food impaction	Multiple allergens
Eosinophilic gastroenteritis	Combined IgE and cell mediated	Ascites, weight loss, edema, obstruction	Multiple allergens
Food protein induced enterocolitis	Cell mediated	Usually in infants vomiting, diarrhea, poor growth, lethargy	Milk, soy, rice, oat, meat
Food protein induced allergic proctocolitis	Cell mediated	Usually in infants Mucus and blood in stools	Cow's milk—through breastfeeds
Heiner syndrome	Cell mediated	Pulmonary infiltrates, failure to thrive, iron deficiency anemia	Cow's milk

**Flow chart 1** Diagnostic algorithm for food allergy

National Institute of Nutrition. Dietary Guidelines for Indians: A Manual. 2<sup>nd</sup> ed. Hyderabad: ICMR; 2011.

National Institute of Nutrition. Nutrient Requirements and Recommended Dietary Allowances for Indians - Report of the Expert Group of the Indian Council of Medical Research. Hyderabad: National Institute of Nutrition; 2012.

Stang JS, Larson N. Nutrition in Adolescence. Krause's Food and Nutrition Care Process. 13<sup>th</sup> ed. Missouri: Saunders; 2012. pp. 410-30.

## IN A NUTSHELL

### Healthy Eating Practices

The following principles are recommended for the healthy eating campaign.

1. Moderation in all things. Ensure a balanced diet by including all food groups every day. Food pyramid will help in the choice of balanced diet. Include cereal pulse combination, roots and tubers in adequate quantities, vegetables and fruits liberally, milk, milk products and meat in moderation and oils, fats and sugars sparingly.
2. Variety is the spice of life. Ensure variety within each food group. Food fads must be avoided as it may evolve as a social handicap.
3. Knowledge about what is enough—adolescent boy should eat as much as his father eats and the adolescent girl should eat a little more than what the mother eats.
4. Some people claim that vegetarianism is healthier. This depends on the degree of vegetarianism. Vegetarians have low-risk of obesity, hypertension, coronary arterial disease and colon cancer. Vegans are at risk of calcium, iron and vitamin B<sub>12</sub> deficiency. Whole grains and germinated seeds are beneficial for them. Lacto-ovo-vegetarians have very little nutritional risk except iron deficiency due to lack of heme iron. Fruitarians who eat only fruits are at the risk of protein, sodium, calcium and other mineral deficiency.
5. Micronutrients and antioxidants including beta-carotene, vitamin A, vitamin C, folic acid, iron, iodine and zinc are essential for healthy life.



## Chapter 22.5

# Undernutrition: Prevalence and Etiology

Piyush Gupta, Neetu Sharma

Adequate food and nutrition are essential for proper growth and physical development, optimum work capacity, normal reproduction, adequate immunity, and resistance to infections. Inadequate diet may produce several forms of undernutrition in children, the most important being protein-energy malnutrition (PEM), and micronutrient malnutrition like nutritional iron deficiency anemia (IDA), vitamin A deficiency (VAD), and iodine deficiency disorders (IDD). Undernutrition can be categorized as macronutrient (protein, fat, and carbohydrates) and micronutrient (vitamins and minerals) deficiency.

### MACRONUTRIENT MALNUTRITION

Nutritional deficiency of macronutrients results in a syndrome of protein-energy malnutrition (PEM). *Severe acute malnutrition* (SAM), the most severe and life-threatening form of PEM, is often associated with infection; and contributes to high child mortality. Early onset of malnutrition can also have lasting effects on growth and long-term functional status. The magnitude of macronutrient malnutrition cannot be fathomed easily from the prevalence of *marasmus* and *Kwashiorkor* as they represent only the tip of the iceberg. Moderate and mild undernutrition may remain unrecognized because clinical criteria for their diagnosis are imprecise and difficult to interpret accurately.

### MICRONUTRIENT MALNUTRITION

Micronutrients deficiencies are termed as *hidden hunger*, as they do not give rise to apparent manifestations till the condition becomes severe. Micronutrient malnutrition continues to affect over 2000 million people worldwide. It is difficult to assess the true burden of micronutrient malnutrition as it requires laboratory facilities, advanced technology and other resources. There are several reasons for micronutrient deficiencies. The population

may be deficient because they have poor access to micronutrient rich food due to poverty, defective crop growing pattern, deficient soil quality, inappropriate climate, or geographical isolation. Traditional dietary fads may also hinder intake, absorption, or utilization of micronutrient rich foods. Cereal-pulse based Indian diets are qualitatively deficient in iron, calcium, vitamin A, riboflavin and folic acid, due to low intake of green leafy vegetables, fruits, and foods of animal origin. The food distribution within the family is also inequitable.

Micronutrient deficiency is clinically evident only in the later stages of the disease; manifesting with impaired work capacity, learning disability, increased susceptibility to infections, and greater risk of death. For the country, it translates into loss of economic productivity, and hike in investment on health and education. According to WHO, over 2 million child deaths (around 20% of total) are attributable to zinc, vitamin A, iron, and iodine deficiency. These micronutrients cannot be synthesized endogenously and have to be supplied in the diet.

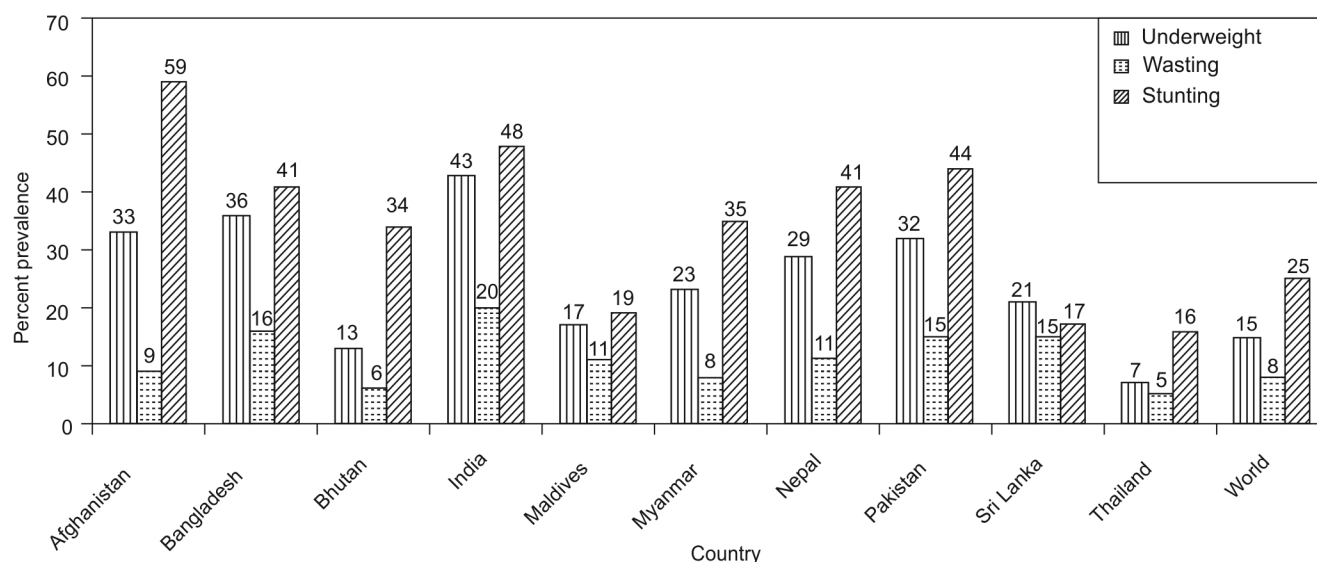
### PROTEIN-ENERGY MALNUTRITION

#### Global Prevalence

More than one-fourth of under-five children worldwide (about 150 million) are underweight; 27% (182 million) are stunted, while 10% are wasted. Almost two-thirds of undernourished children live in Asia, 29% in Africa, and 3% in Latin America and the Caribbean. Despite an overall decline in the prevalence of stunting, child malnutrition still remains a major public health problem in developing countries (**Fig. 1**). In South Asia, every other child can be classified as underweight. **Figure 2** depicts the global prevalence of underweight in children below 5 years of age. It is now recognized that about 53% of all deaths in young children are attributable to underweight.

#### India

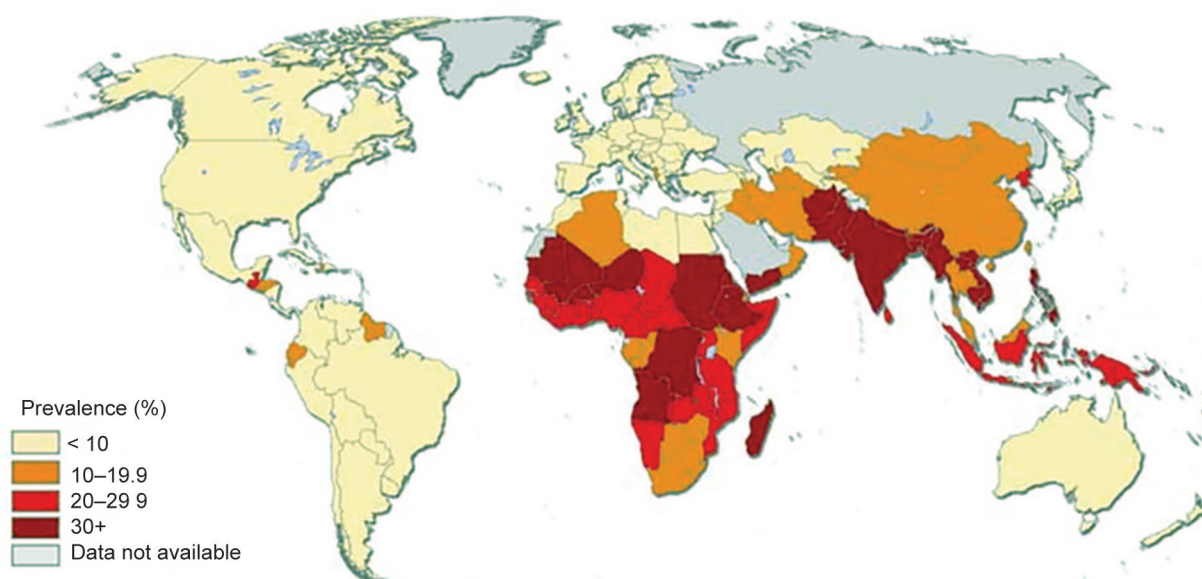
There has been a significant decline in the prevalence of severe protein energy malnutrition in India, over past few decades. The proportion of children under 3 years of age who were underweight decreased from 53% in National Family Health Survey (NFHS)-1 (1992-1993) to 47% in NFHS-2 (1998-1999), and 46% in NFHS-3 (2004-2005). Similarly, prevalence of stunting decreased from 52% in NFHS-1 to 45% in NFHS-2 and 38% in NFHS-3. According to NFHS-3 (2005-2006) survey report, 43% of children



**Figure 1** Prevalence of malnutrition in under-five children

Source: The State of the World's Children 2014. New York. The United Nations Children's Fund.





**Figure 2** Global prevalence of underweight in children under 5 years of age, 1995–2004  
Reproduced with Permission from Deonis M et al. WHO.

under five years of age were underweight, and almost half (48%) were stunted (**Fig. 3**). Wasting (weight for height  $< 80\%$  or  $< 2SD$  of expected) was less prevalent, affecting 20% of children under 5 years of age.

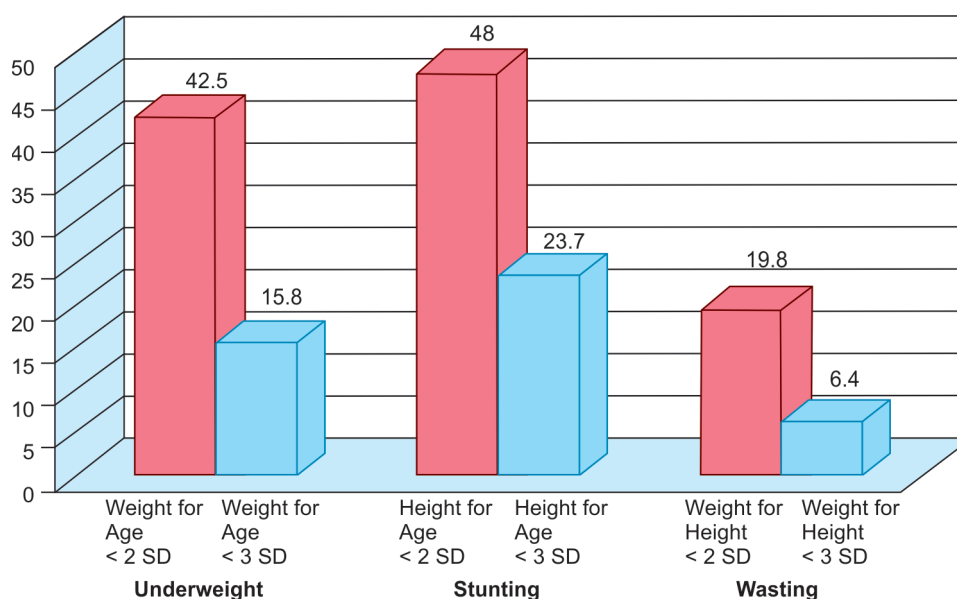
*Statewise situation* Malnutrition varies widely across region, states, age, gender and social groups, being worst in children under two, in the populous northern states, in rural areas, and among tribal populations and scheduled castes. The proportion of children under 5 years of age who are underweight ranged from 20% in Sikkim and Mizoram to more than 50% in Madhya Pradesh, Jharkhand and Bihar. Other states where more than 40% of children were underweight are Meghalaya, Chhattisgarh, Gujarat, Uttar Pradesh, and Odisha. The overall prevalence of underweight (46%

versus 33%), stunting (51% versus 40%), and wasting (21% versus 17%) are higher in rural settings, compared to the urban areas.

### Etiology

#### *Maternal Malnutrition and Lack of Breastfeeding*

In postnatal life also, these infants receive less attention from the mother who is overworked and weak. The nutritional status of children is also strongly related to maternal nutritional status. Undernutrition is more common for children of mothers whose body mass index is below 18.5 than for children whose mothers are not underweight. Malnourished mothers have a high incidence of low birthweight and growth retarded babies with poor nutritional reserve. These low birthweight babies are more likely to become



**Figure 3** Nutritional status of under-five children in India (NFHS-3)

malnourished. Lack of exclusive breastfeeding for first 6 months makes the child prone to early onset malnutrition. Artificial feeding is often disastrous for the baby because of the poor quality of the substitute milk, excessive dilution and use of unhygienic feeding bottles and nipples. High pressure advertising by baby food manufacturers and social demands on the urban educated working women has encouraged early discontinuation of breastfeeding. Unfortunately, evaporated dry milk powders and packaged foods are expensive. Poor mothers tend to economize on their use and offer diluted milk formula to the infant. Unhygienic feeding practices in the preparation of milk formula result in frequent episodes of diarrhea and diminished absorption of food by the infant.

### *Delayed Introduction of Complementary Feeding*

According to NFHS-3 data, only 56% of infants aged 6–9 months received complementary semisolid foods as recommended. In most rural households, introduction of semisolid foods is delayed, often beyond one year. Most of the times, it is the diluted animal milk in small quantities, which is used to supplement breastfeeds.

### *Infections*

Frequent infections contribute to undernutrition. Diarrhea, pneumonia, malaria, measles, whooping cough, and tuberculosis precipitate acute malnutrition and aggravate the existing nutritional deficit. During infections, child's appetite is impaired. There may be iatrogenic restriction of food by the parents. The body tissues are catabolized and metabolic demands are escalated. Protein may be lost because of tissue breakdown and in pus and exudates. Also, malnutrition may adversely affect the immune status and make the malnourished individuals more vulnerable to infections. This sets up a vicious cycle of malnutrition-infection-malnutrition.

### *Food Quality and Quantity*

Nonavailability of food, either due to poverty or inaccessibility is considered an important determinant of malnutrition. The poor cannot purchase adequate amount of food of the desired quality for meeting their and their family's nutritional requirements. On the other hand, food becomes inaccessible for people in situations such as civil wars, or natural calamities. Natural disasters such as floods, earthquakes, and droughts shift the precarious nutritional balance towards the negative side. However, it is the poor quality of food, rather than a quantitative deficit, which is responsible for malnutrition in majority of cases.

### *Social Factors*

Repeated pregnancies, inadequate child spacing, food taboos, broken homes and separation of a child from parents are responsible for quantitative and qualitative deficit of food and nutrients. Share of women and preschool children is disproportionately less compared with the economically active male adults. Families may also have irrational beliefs about the nutritional needs of infants and nutritional quality of common foods. Some foods are erroneously believed to be hot or cold in nature or likely to cause liver disease.

Undernutrition has a strong negative relationship with the mother's education. The percentage of children who are severely underweight is almost five times as high for children whose mothers have no education as for children whose mothers have 12 or more years of education. Risk of undernutrition is generally lower for first and consistently increases with increasing birth order. Short birth intervals are associated with higher levels of undernutrition. Rapid succession of pregnancies adversely affects the nutritional status of the mother leaving her malnourished and inappropriate lactation. Per capita availability of food in large families is low and unequally distributed.

## VITAMIN A DEFICIENCY (VAD)

(Also see Chapter 22.9)

Vitamin A deficiency of sufficient duration or severity can lead to xerophthalmia, childhood blindness, anemia, decrease host resistance to infection, and increased risk of mortality in under-five children. Vitamin A supplementation is shown to reduce the risk of death by 23–30% in children 6–59 months old.

Vitamin A deficiency (VAD) in a community is assessed by the prevalence of night blindness and serum retinol level ( $< 0.7 \mu\text{mol/L}$ ) in preschool children. Regions are categorized as having mild, moderate, or severe VAD, based on cut-offs listed in **Table 1**.

**Table 1** Indicators for recognizing vitamin A deficiency in the community

<i>Vitamin A deficiency in the community</i>	<i>Prevalence of night blindness in preschool children</i>	<i>Serum retinol <math>&lt; 0.70 \mu\text{mol/L}</math> in preschool children</i>
Mild	0–1%	2–10%
Moderate	1–5%	10–20%
Severe	$> 5\%$	$> 20\%$

Source: World Health Organization, 2009.

## Global Situation

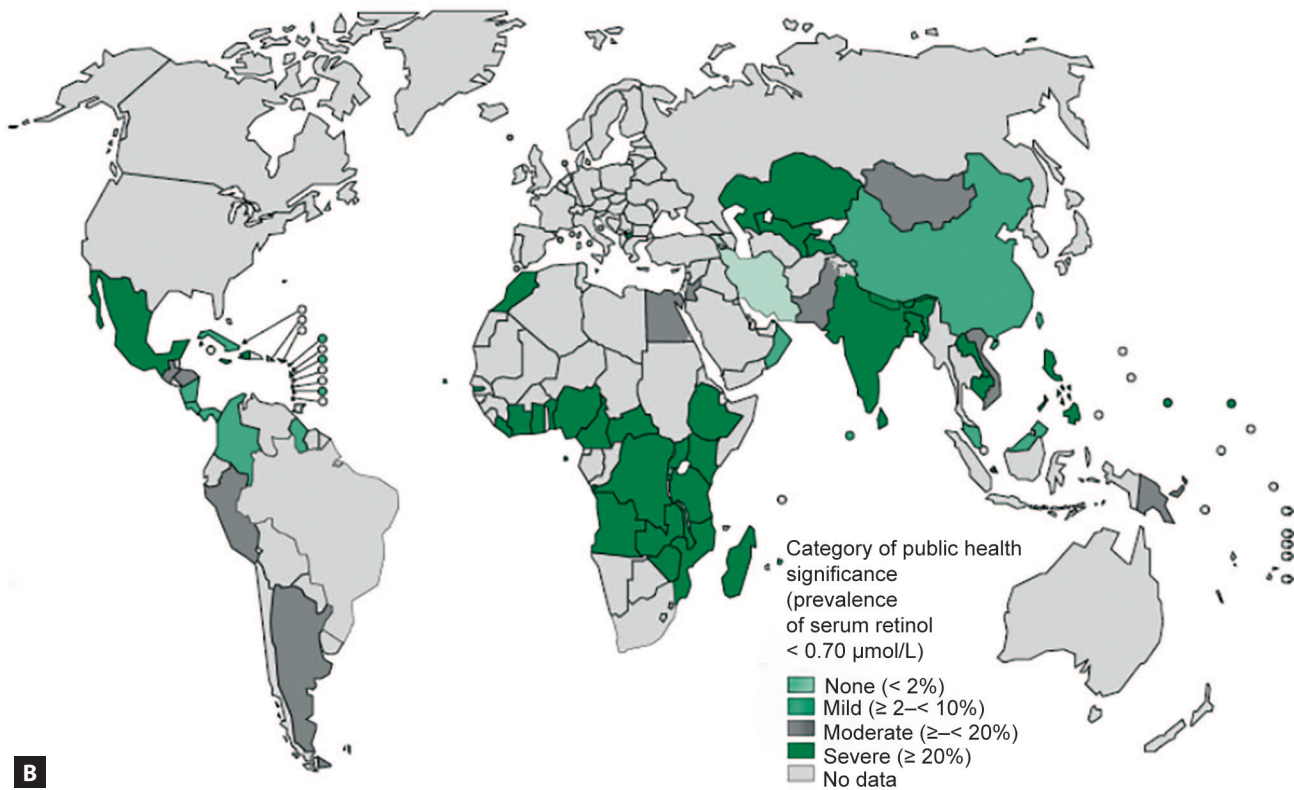
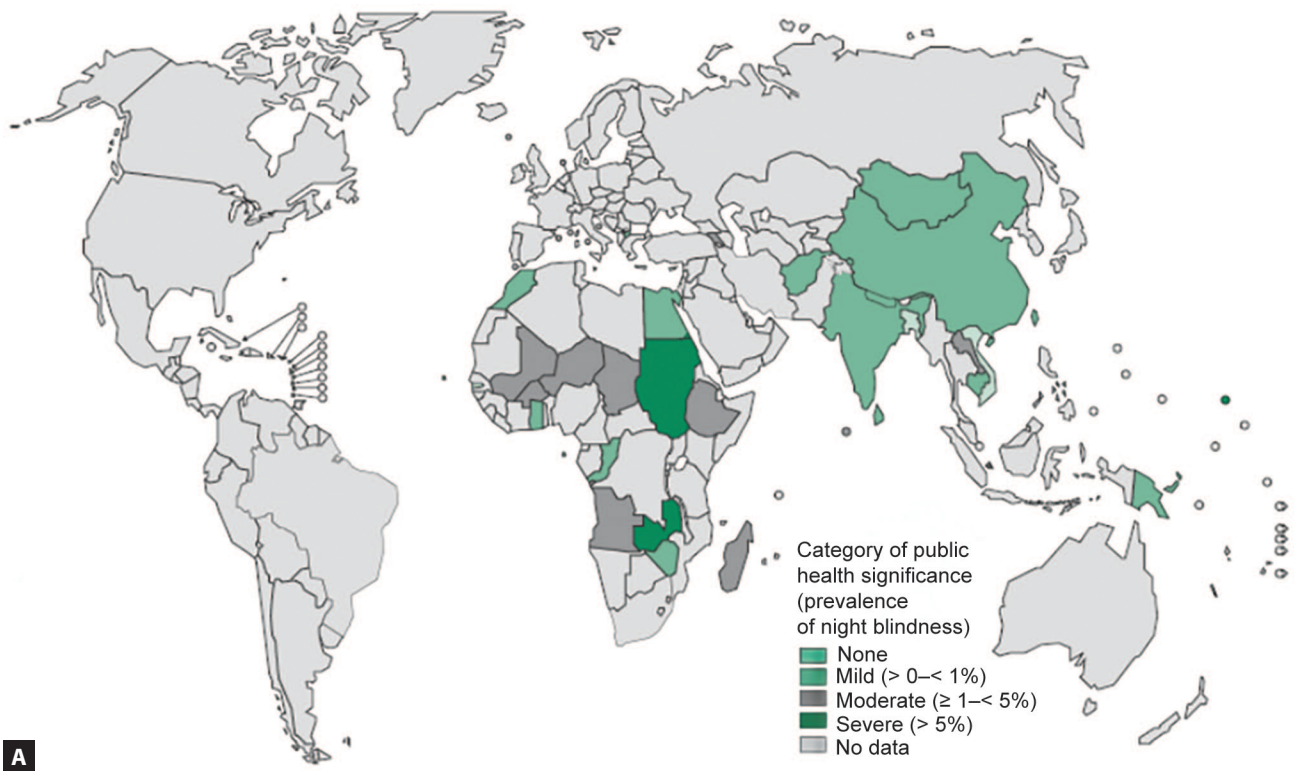
Night blindness affects more than 5 million preschool children and almost 10 million pregnant women, corresponding to 1% and 8% of global population, respectively. Biochemical deficiency affects 33.3% (190 million) of the preschool age population and 15.3% (19.1 million) of the pregnant women. Highest prevalence of VAD is accounted for by South-East Asia and Africa. **Figures 4A and B** categorizes the countries by degree of vitamin A deficiency in preschool children.

## India

As per WHO estimates, the prevalence of night blindness in under-five children and pregnant women in India is 0.6% and 12.1%; while that of biochemical deficiency (retinol  $< 0.7 \mu\text{mol/L}$ ) is 62% and 16.4%, respectively. Thus, subclinical vitamin A deficiency is a significant problem in preschool children, while overt vitamin A deficiency rampant in pregnant women. The National Nutrition Monitoring Bureau (NNMB) micronutrient survey (2006) indicates that there has been substantial decline in prevalence of Bitot spots in preschool children. The current prevalence of Bitot spots is only 0.7%; and prevalence of night blindness is less than 0.5%. According to countrywide data from department of women and child development, the overall prevalence of Bitot spots in India is 0.2%; ranging from 0.1% in Haryana and Himachal Pradesh to 3% in Mizoram. Prevalence of VAD is maximum in southern states of India; which may be related to dietary habits.

## Etiology

Dietary deficiency is the predominant etiology. Low intake of protective foods such as vegetables particularly green leafy vegetables, fruits and cereal-pulse based diets makes the Indian food deficient in vitamin A. Lack of exclusive breastfeeding also contributes to deficiency. Vitamin A absorption is hampered in chronic diarrhea, malabsorption states, and chronic liver disease. Depletion of vitamin A also occurs during acute infections. Frequent episodes of diarrhea, respiratory tract infections and measles increase the vitamin A demands making children prone to its deficiency during these states. Knowledge and practices of



**Figures 4A and B** Vitamin A deficiency as assessed by prevalence of (A) night blindness and (B) biochemical deficiency in preschool children (1995–2005 WHO survey data)  
Reproduced with permission from WHO, 2009.



women on vitamin A deficiency is poor and there is no prioritization for intake of dark green leafy vegetables and yellow colored fruits, which are rich in vitamin A.

## IRON DEFICIENCY ANEMIA

(Also see Chapter 38.6)

Iron deficiency anemia (IDA) is the most widespread micronutrient deficiency in the world, affecting more than 1.5 billion people. It is generally assumed that 50% of cases with anemia are due to iron deficiency. Anemia can result in impaired cognitive performance, suboptimal behavioral and motor development, in coordination, delayed language development and scholastic achievement, as well as increased morbidity from infectious diseases. Anemia in pregnancy is associated with increased maternal and child mortality and increased prevalence of low birthweight infants.

### Global Situation

Anemia affects 1.62 billion people (24.8%) across the world. Infants, children and pregnant women are the most vulnerable. Prevalence of anemia is highest in preschool age children (47.4%). One-fourth (25.8%) of all school-age children are anemic. South-East Asia and Africa are the worst affected (Fig. 5).

### Prevalence in India

Anemia is highly prevalent among the under-five children, and pregnant women, in every state of India. Among children 6–35 months it has increased from 74% in NFHS-2 to 79% in NFHS-3. The prevalence of anemia is highest in the age group of 12–23 months; this may partly be attributed to the initiation of weaning-infection coupled with poor nutritional supplementation.

### Etiology

Iron deficiency may be secondary to inadequate intake, decreased absorption, and/or increased losses. During infancy, milk is usually a major part of the diet. Both human milk and cow's milk provide relatively small quantities of iron (0.2–0.4 mg/L), but the bio-availability of iron from human milk is considerably higher than that of cow's milk. Hence, infants fed on cow's milk often develop iron deficiency anemia. Cereals and pulses which form the staple in complementary food are relatively poor in iron. Vegetables and iron rich animal proteins form a very small part of the diet. The Indian diet also contains large quantities of phytates, oxalates, phosphates, etc., all of which interfere with iron absorption.

Heavy parasitic infestation is an important cause of anemia in older children. Hookworm infestation results in large amount of blood loss. It is estimated that a hookworm can, on an average, remove 0.03–0.2 mL of blood per day. Chronic inflammation and infection can lead to depression of several indicators of iron status, like serum iron and increase in free erythrocyte protoporphyrin.

Puberty menorrhagia is an important cause of anemia among adolescent females. Anemia status of the child is closely linked with the anemia status of the mother. Each pregnancy and parturition results in large amounts of blood loss and several such pregnancies at short intervals make these women severely anemic. Children born to such mothers also have low iron stores. Children born to sociodemographically deprived mothers are also more likely to be anemic due to the inappropriate choice of food or due to food fads. Low-birthweight infants have a higher risk for iron deficiency as they have less iron stores at birth.

## IODINE DEFICIENCY DISORDERS (IDD)

(Also see Chapter 22.13)

Iodine deficiency disorders (IDD) refer to the wide spectrum of effects of iodine deficiency on growth and development. It includes

endemic goiter, endemic cretinism, impaired mental function and increased stillbirths and perinatal and infant mortality. Children living in iodine-deficient areas on an average have lower intelligence quotient (about 13 points) as compared to children living in iodine-sufficient areas.

### Global Situation

Iodine deficiency disorders (IDD) are a major health problem particularly among preschool children and pregnant women. It is the leading cause of preventable brain damage in the world. Globally, two billion people are at risk of iodine deficiency disorders due to insufficient iodine intake. Nearly 266 million school-aged children in the world have insufficient iodine intake. Some 38 million children are born every year unprotected against the risk of iodine deficiency. Among the 130 countries which reported data for IDD in 2006 (comprising 91.1% of the total global population) IDD is currently a significant public health problem in 118 countries (Fig. 6).

### Prevalence in India

About 350 million people, who do not consume iodized salt, are at risk for IDD. A recent study (IJMR, 2013) has reported 263/325 districts of India as IDD endemic (prevalence > 10%). Only 70% households consume adequately iodized salt. About 90,000 stillbirths and neonatal deaths occur every year due to maternal iodine deficiency. Around 54 million persons are estimated to have goiter, 2.2 million have cretinism and 6.6 million suffer from mild psychomotor handicaps. The overall prevalence of total goiter rate (TGR) among rural children (6–12 years) was about 4% (NNMB, 2001). The prevalence of goiter was highest in Maharashtra (11.9%) and West Bengal (9%).

### Etiology

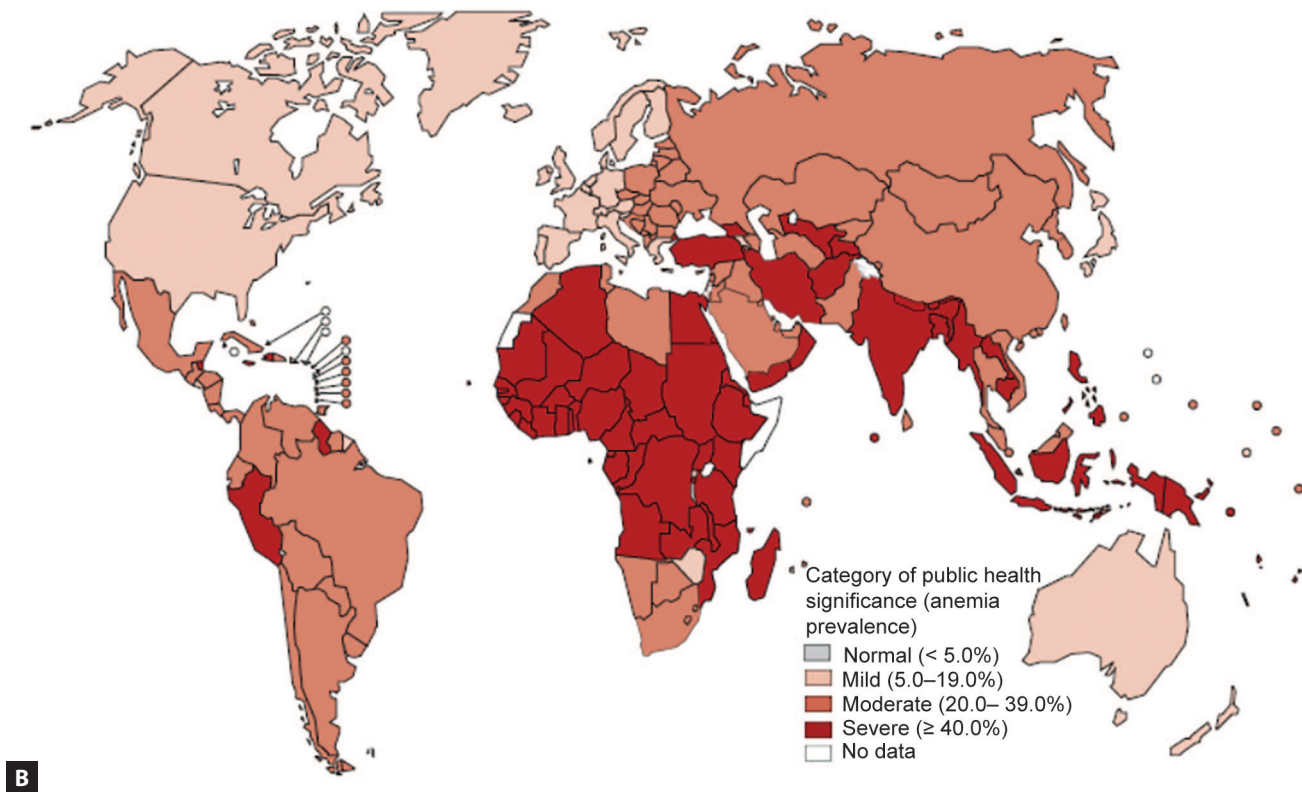
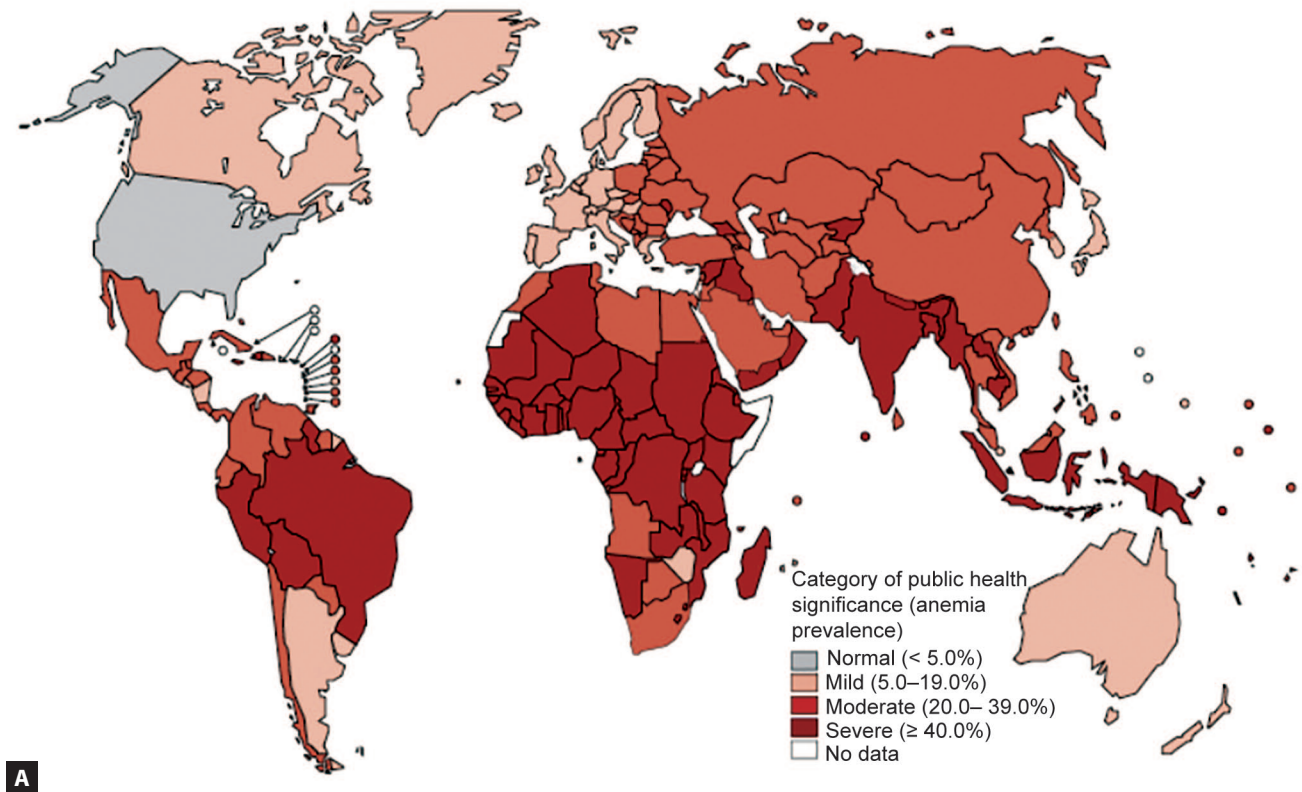
Iodine deficiency disorders (IDD) are connected to iodine deficient soil. Due to flooding, deforestation, glaciations, and changing rivers course the iodine present in top soil is drained constantly. This results in deficiency of iodine in crops grown on iodine deficient soil which in turn leads to low iodine in the diet. Pregnant women have increased requirement of iodine and if mothers do not have adequate iodine intake, babies may develop cretinism. Moreover, iodized salt coverage is still not complete and uniform across the country.

## FOOD SECURITY

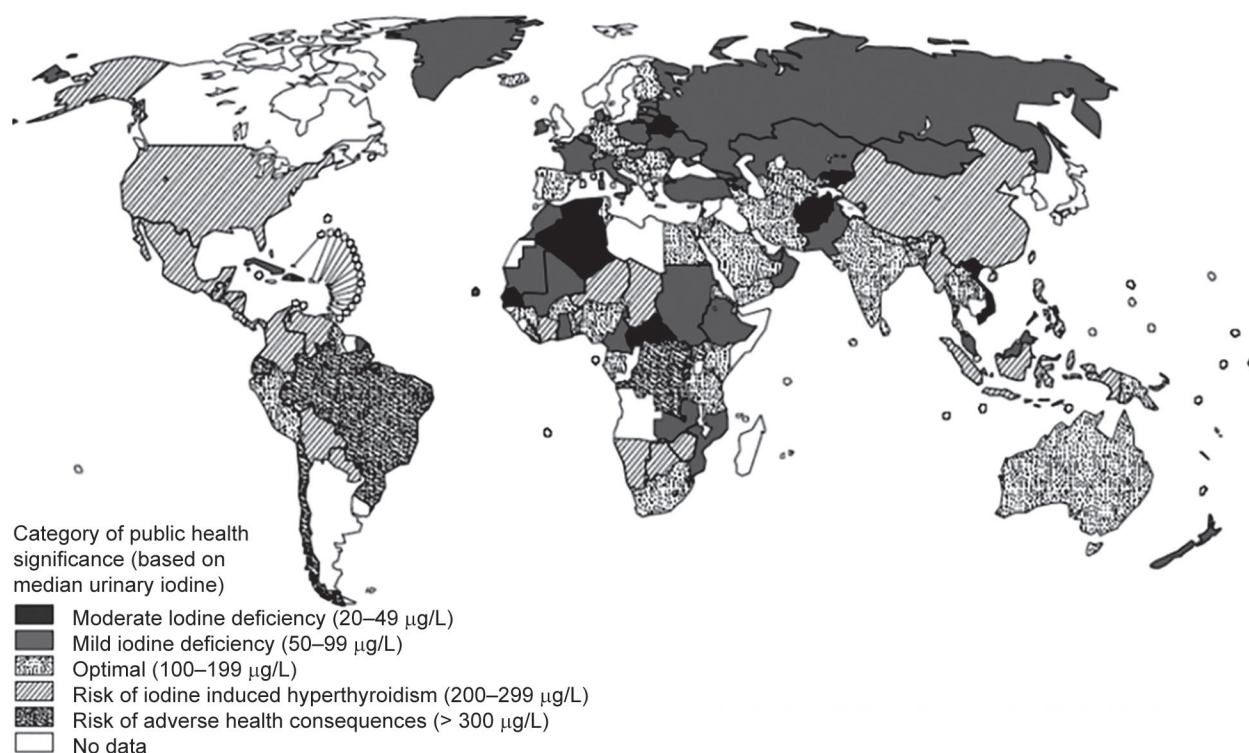
Nutrition security implies *physical, economic and social access to balanced diet, clean drinking water, safe environment, and health care*. The notion of food security rests on three distinct pillars, i.e., access, production and decision about food. Access to food implies physical and economic access to sufficient amounts of nutritious, safe and culturally appropriate foods. Production of food denotes the production methods that are economically viable, socially responsible and environmentally sustainable. Here what needs to be underlined is that while the producers should be able to generate a decent income, the consumers should have a sizeable disposable income to afford appropriate food. And the third pillar, i.e., decision ensures that people are capable of making informed choices about what they eat.

It is worthwhile to note that food security is not just a matter of food or hunger, but it encompasses several other dominant area of human development such as health, education and jobs. The government of India has introduced a Food Security Act (2013) that specifically includes provisions for prevention and management of child malnutrition, nutritional support to children, pregnant women and lactating mothers. The Act stated *to provide for food*





**Figures 5A and B** Anemia as a public health problem in (A) preschool children; (B) pregnant women  
Reproduced with permission, WHO, 2008.



**Figure 6** Degree of public health significance of iodine nutrition based on median urinary iodine  
Reproduced with permission, WHO.

Source: de Benoist B, et al. Iodine deficiency in 2007: Global progress since 1993. Food and nutrition bulletin. 2008;29(3):195-202.

*and nutritional security in human life cycle approach, by ensuring access to adequate quantity of quality food at affordable prices to people to live a life with dignity.*

### MORE ON THIS TOPIC

- Andersson M, Karumbunathan V, Zimmermann MB. Global iodine status in 2011 and trends over the past decade. J Nutr. 2012;142:744-50.
- Micronutrient security for India—Priorities for Research and Action. New Delhi: Indian National Science Academy; 2011.
- Micronutrient Initiative. Investing in the future—a united call to action on vitamin and mineral deficiencies. Global report, 2009. New Delhi: Micronutrient Initiative; 2009. From: [http://www.unitedcalltoaction.org/documents/Investing\\_in\\_the\\_future.pdf](http://www.unitedcalltoaction.org/documents/Investing_in_the_future.pdf). Accessed on April 1, 2014.
- Ministry of Law and Justice. The National Food Security Act, September 2013.
- National Nutrition Monitoring Bureau (NNMB). Prevalence of micronutrient deficiencies. Technical Report No. 22. Hyderabad: National Institute of Nutrition, ICMR; 2003.
- Pandav CS, Yadav K, Srivastava R, et al. Iodine deficiency disorders (IDD) control in India. Indian J Med Res. 2013;138:418–33.

### IN A NUTSHELL

1. Undernutrition can be categorized as macronutrient (protein, fat, and carbohydrates) and micronutrient (vitamins and minerals) deficiency.
2. Macronutrient deficiency results in various syndromes of undernutrition including protein-energy malnutrition (PEM), underweight, stunting, and wasting.
3. Severe acute malnutrition is the most severe form of macronutrient deficiency. It is almost always associated with multiple micronutrient deficiencies.
4. The most important micronutrient deficiencies are those of iron, iodine and vitamin A, resulting in nutritional iron deficiency anemia (IDA), iodine deficiency disorders (IDD), and xerophthalmia, respectively.
5. Food security implies provision for food and nutritional security in human life cycle approach, by ensuring access to adequate quantity of quality food at affordable prices to people to live a life with dignity.

## Chapter 22.6

# Pathophysiology of Undernutrition

OP Mishra

Undernutrition in children occurs due to an imbalance between nutrient requirement and intake leading to deficits of energy, protein, or micronutrients that may negatively affect growth and development. Imbalance between nutritional intake and requirement leading to calorie and/or protein deficiency is coupled with micronutrient deficiencies. As a result there is decrease in lean body mass, muscle weakness, development of edema, immune dysfunction and the risk of recurrent infections. Generalized changes in different organs can cause decreased intake of foods, anorexia, malabsorption, nutrient loss in chronic or recurrent diarrhea and increased energy requirement resulting into undernutrition. The condition is further aggravated by poverty, illiteracy, unhygienic feedings, prolonged starvation during illness and chronic systemic disorders. High prevalence of low birthweight babies and lack of exclusive breastfeeding are the two important factors which lead to high incidence of undernutrition in the developing countries. The two severe forms of undernutrition such as marasmus and kwashiorkor are the result of these physiological alterations.

### THEORY OF ADAPTATION (GOPALAN, 1967)

Gopalan proposed that marasmus represents the extreme form of adaptation to chronic calorie deficiency, while edematous kwashiorkor is the reflection of failure of adaptation to protein deficiency. The adrenocortical response to stress due to protein and calorie deficiency determines the development of these two forms of undernutrition. Detailed pathogenesis is described in **Flow chart 1**.

### THEORY OF FREE RADICAL INJURY (GOLDEN, 1987)

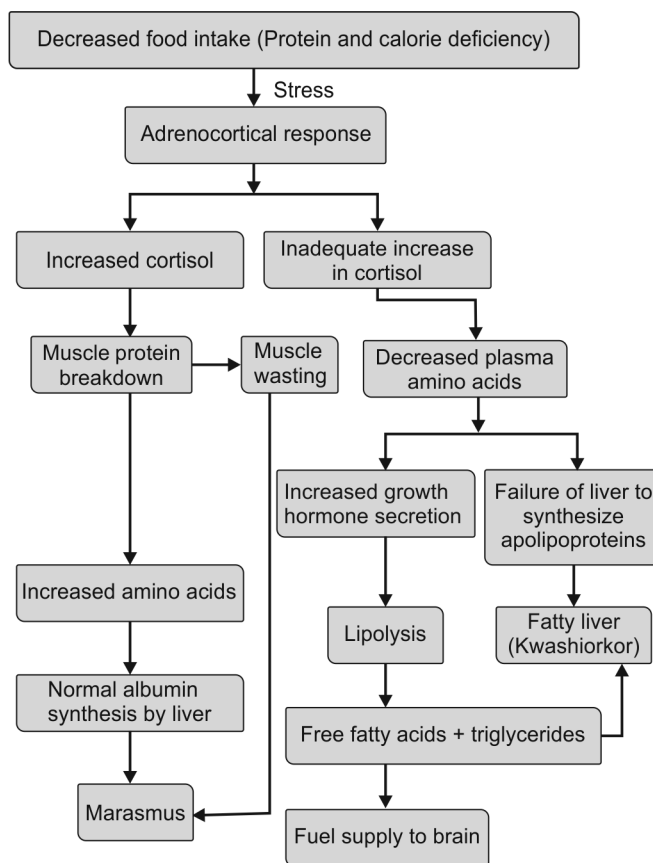
Several etiological factors such as dietary protein deficiency, aflatoxins in food and decreased protein deficiency compounded by infection have been proposed for causation of kwashiorkor. Golden proposed the theory of free radical injury causing cellular damage and exceeding the antioxidant defense mechanism in these patients. Subsequently various studies have demonstrated that children with kwashiorkor had higher concentrations of biomarkers of oxidative stress and lower levels of antioxidants than marasmus and normal healthy controls. The levels of oxidative stress showed normalization after recovery from kwashiorkor. Later, it was shown that antioxidants have no protective effect in the development of kwashiorkor tested in an endemic zone of Malawi. However, it is premature to conclude that oxidants have no role in kwashiorkor as antioxidants consumption may have been in inadequate amount in comparison to oxidative stress in these children. Thus, etiopathogenesis of kwashiorkor could be multifactorial in origin and single factor may not be responsible for the causation of disease.

### CHANGES IN BODY COMPOSITION AND FUNCTION

#### Water and Electrolytes

The total body water is increased in these children. There is more extracellular fluid than intracellular fluid and is found especially

**Flow chart 1** Adrenocortical response and biochemical changes in undernutrition



in edematous children. Marasmic children have the highest total body water and reduced adipose and lean body mass. Body fluid compartments are affected by many factors including nutritional and disease states such as dehydration or fluid overload. Total body sodium is increased. Potassium is low. Dilutional hyponatremia can occur in children with fluid retention or acute kidney injury following acute gastroenteritis. While treating diarrheal dehydration in children with severe malnutrition, it is important not to overload them with fluid or sodium.

#### Plasma Proteins

Hypoproteinemia is commonly found in protein energy malnutrition. Plasma levels of albumin and some fractions of glycoproteins are decreased. Protein binding of some of the drugs is decreased and as a result there can be free drug levels in plasma. Low plasma albumin level is partly responsible for edema in kwashiorkor. Inadequate production of beta-lipoproteins results in an impaired transport of fat from liver leading to fat accumulation in liver and fatty liver. Development of edema in kwashiorkor is multifactorial in origin and is due to low albumin level, free radical injury and inadequate inactivation of antidiuretic hormone by liver leading to water retention.

#### Coexisting Nutrient Deficiencies

Multiple coexisting nutrient deficiencies can be present due to decreased intake, malabsorption and losses in recurrent or persistent diarrhea. Malabsorption occurs due to villus atrophy and secondary enzyme deficiencies. The most common being lactase deficiency leading to lactose intolerance. Nutrients like iron, zinc



and vitamins such as riboflavin, folic acid, vitamin B<sub>12</sub>, C and A can be affected in severe undernutrition and can show their clinical signs and symptoms of deficiencies. As such overt features of rickets are not seen in undernutrition, but become evident during nutritional rehabilitation if vitamin D supplementation is not given.

### Immunity

Overall there is generalized depression in immunity. Lymphoid organs such as lymph nodes, tonsils and thymus are atrophied. There is low complement levels and decreased synthesis of secretory IgA. Cell-mediated immunity is impaired and there is an inadequate response to vaccine antigens. Delayed hypersensitivity reaction to purified protein derivative is impaired in severe undernutrition. There is defective phagocytosis and the typical features of infection such as leukocytosis and fever are absent. Humoral immunity is less affected. Physical barrier such as skin is compromised as it is thin and broken and makes easy entry to microorganisms.

### Gastrointestinal Tract

Gastric acid production is reduced. There is atrophy of pancreas and small intestinal mucosa and overall digestive enzymes are decreased. Malabsorption of nutrients occurs and there is recovery after nutritional rehabilitation. Villus atrophy of jejunal mucosa not only affects the nutrients but also drug absorption. Synthesis of proteins by liver is decreased. The capacity of liver to metabolize and inactivate toxins is severely affected. Liver biopsy shows fatty changes, abnormal rough endoplasmic reticulum and mitochondria and decreased peroxisomes. There is decreased gluconeogenesis resulting in to high incidence of hypoglycemia especially during stress such as infection.

### Central Nervous System

The undernutrition at an early age has important impact on the developing brain. The dendritic arborization and morphology of the dendritic spines as well as myelination are affected. Computerized tomography and magnetic resonance imaging of brain have shown features of cerebral atrophy in children suffering from undernutrition. This affects the higher brain functions and may lead to permanent neuropsychological damage. Cognitive function and learning abilities remain affected even after nutritional rehabilitation.

### Circulatory System

The blood pressure is low due to decreased cardiac output and stroke volume. They have small and thinner heart. Plasma volume is normal, but higher chance of decreased tissue perfusion in state of dehydration. Children with edematous undernutrition have greater chance of development of congestive cardiac failure if any fluid is rapidly infused as circulation overload occurs more easily than normal children due to more sodium and water retention. The basal metabolic rate is reduced to about one-third. Heat generating capacity and protection are reduced as a result there is a greater chance of hypothermia.

### Renal System

The capacity of kidney to excrete excess water or acid is reduced. There is decreased sodium and phosphate excretion. These children have higher incidence of urinary tract infection due to changes in urinary tract epithelium. The serum urea and creatinine levels are normal except in state of dehydration, and it improves following fluid resuscitation. There is no established renal damage in these children, but edema seen in kwashiorkor and marasmic kwashiorkor has been attributed to impaired fluid and sodium excretion in addition to contribution by hypoproteinemia.

## Endocrine System

Endocrine glands play a major role in the process of adaptation in response to stress to protein and calorie deficiency. Almost most of the major hormones are affected in children suffering from chronic undernutrition.

### Cortisol

Cortisol is the major glucocorticoid produced by adrenal cortex. This hormone plays a major role in adaptation to protein and calorie deficiency in these children. Although there is atrophy of adrenal cortex and medulla, good functional reserve is seen in response to corticotropin. When these children are not having any acute stress over their undernutrition, their plasma cortisol level remains normal. But its level is found to be increased when complicated by infection, acidosis, hypoglycemia and hypothermia. The adrenocorticotropin (ACTH) levels are normal despite increase in cortisol levels. Plasma aldosterone level is normal but rate of secretion is increased in marasmus. In contrast, its level is increased in kwashiorkor in spite of normal secretion rate and this is due to decreased metabolism by liver. Further, these abnormalities normalize after nutritional rehabilitation.

### Insulin

There are changes in islets of Langerhans cells of pancreas in chronic undernutrition. Insulin level is low in kwashiorkor and decreased response to intravenous glucose or glucagon is found. Glucose tolerance is impaired in kwashiorkor while it is normal in marasmus. The impaired glucose tolerance may be due to poor insulin release in response to stimulus, insufficient utilization by peripheral tissues, decreased potassium and deficient diet in chromium. The defect in insulin release might be due to either structural damage to beta cell by undernutrition or defective stimulation of insulin release. Glucagon levels have been found to be variable depending upon the involvement of alpha cells.

### Growth Hormone

The response of pituitary gland to secrete growth hormone (GH) mainly depends upon the type of malnutrition. Plasma GH levels are high in kwashiorkor, while reported to be normal, decreased or increased in marasmus. The high GH in kwashiorkor does not respond further to arginine stimulation and falls only when protein is added in the diet. Low fasting levels of insulin and negligible response to hyperglycemia is an adaptive response to fuel supply to brain. Thus, low insulin level acts as a primary regulator of peripheral fuel release and high GH is to provide substrate in response to malnutrition. Somatomedin A and insulin-like growth factors are decreased in kwashiorkor in comparison to marasmus.

### Thyroid Hormones

It has been demonstrated that there is hypofunction of thyroid gland as there is decreased basal metabolic rate, decreased protein-bound iodine, decreased I<sup>131</sup> uptake and low plasma T4 level. The decreased levels of thyroxine-binding prealbumin and globulins are due to decreased synthesis by liver. The low T3 level found in kwashiorkor is due to impaired deiodination in liver. The thyroid-stimulating hormone (TSH) levels are normal and its response to thyrotropin-releasing hormone (TRH) is sustained; indicating good pituitary reserve. There is dramatic catch-up growth following nutritional rehabilitation.

### Gonadotropins

The negative influences of undernutrition and persistent deprivation cause delayed puberty in these children. Menarche in girls is delayed. Failure of maturation of reproductive organs and delay in appearance of secondary sexual characteristics have been observed.



### IN A NUTSHELL

1. Undernutrition is a common public health problem in under-5 children and of multifactorial in origin.
2. Theories of adaptation and free radical injury have been proposed for its pathogenesis.
3. Total body water and sodium are increased; and potassium is decreased in severe malnutrition. Overzealous therapy of dehydration may lead to fluid overload or congestive heart failure.
4. Generalized changes in different systems occur in severe undernutrition and responsible for systemic manifestations.
5. Adrenocortical response to stress of protein and calorie deficiency plays key role in the development of marasmus and kwashiorkor.

### MORE ON THIS TOPIC

- Ahmed A, Rahman S, Cravioto A. Oedematous malnutrition. *Indian J Med Res.* 2009;130:651-4.
- Cornelio-Nieto JO. The effects of protein-energy malnutrition on the central nervous system in children. *Rev Neurol.* 2007;44 Suppl 2:S71-4.
- Elizabeth KE. Triple burden of malnutrition. In: *Nutrition and Child Development.* 4<sup>th</sup> ed. Hyderabad: Paras Medical Publisher; 2010.
- Fuchs GJ. Antioxidants for children with kwashiorkor. *BMJ.* 2005;330:1095-6.
- Mehta NM, Corkins MR, Lyman B, et al. Defining pediatric malnutrition: a paradigm shift toward etiology related definitions. *JPEN J Parenter Enteral Nutr.* 2013;37:460-81.
- Oshikoya KA, Senbanjo IO. Pathophysiological changes that affect drug disposition in protein-energy malnourished children. *Nutr Metabol (Lond).* 2009;6:50.

## Chapter 22.7

# Protein Energy Malnutrition

KE Elizabeth

In 1959, Jelliffe coined the term protein calorie malnutrition (PCM) to include all clinical types of malnutrition. The International System of Units proposed the replacement of the term *calorie* by *Joule* (1 cal = 4.184 J) as a unit and the term *energy* for general use. This has resulted in the term protein energy malnutrition (PEM) instead of PCM. World Health Organization (WHO) defined the term PEM as a range of pathological conditions arising from coincident lack, in varying proportions of protein and calories, occurring most frequently in infants and young children and commonly associated with infections. The term is preferably used for infants and young children.

## SPECTRUM OF PROTEIN ENERGY MALNUTRITION

### Kwashiorkor

Professor Cicely Williams in 1933 from Gold Coast described kwashiorkor. She observed that this was the disease of the first child when the second was on the way displacing the first child from the breast. She named it kwashiorkor. Later on, the term was interpreted as the disease of the *deposed child*. Workers from West Indies identified a syndrome similar to kwashiorkor with prominent cheeks and edema and suggested the term *sugar baby* to stress the dietary origin of the disease. A classic case of kwashiorkor is apathetic, miserable, stunted in growth and has edema, hepatomegaly, anemia and hair and skin changes (**Fig. 1**). The skin changes are collectively referred to as *nutritional dermatosis*. Cutaneous manifestations also include flaky paint dermatitis and crazy pavement dermatosis. The triad of essential features of kwashiorkor consists of growth retardation, edema, and mental changes. A grading of kwashiorkor has been proposed as: Grade I, pedal edema; Grade II, pedal and facial edema; Grade III, pedal, facial, paraspinal, and chest edema; Grade IV, generalized edema with ascites.



**Figure 1** Skin changes, hair changes and edema in an infant with kwashiorkor

### Marasmus

The word marasmus is derived from the Greek word *marasmos*, which means *wasting*. Affected children exhibit extreme wasting and have an *old man appearance* with just skin and bones (**Fig. 2**). The wasting of the brown fat occurs first because it is metabolically more active and is important in thermogenesis. Children with marasmus are generally alert and have good appetite. Later on they become irritable. When marasmic children develop edema, it is termed marasmic kwashiorkor. A grading of marasmus has been proposed as: Grade I, loose skin folds in axilla and groin; Grade II, loose skin folds in thighs and buttocks; Grade III, wasting of chest and abdomen; and Grade IV, wasting of buccal pad of fat.



**Figure 2** A marasmic infant with irritability, loose skin folds in the axilla, thigh, buttocks, chest and face

**Nutritional dwarfing** Prolonged nutritional insult starting early in life and going on chronic without developing kwashiorkor or marasmus results in nutritional dwarfing.

**Underweight** The child is malnourished, but does not have any features of marasmus or kwashiorkor. The weight-for-age (WFA) is between 60% and 80% of the expected.

## ASSESSMENT OF MALNUTRITION

Assessment of nutritional status can be done by evaluating the following ABCDEF:

- Anthropometric assessment
- Biochemical assessment
- Clinical assessment
- Dietary assessment including feeding practices
- Epidemiological and ecological assessment
- Functional assessment for organ function and morphology

### Anthropometric Assessment

Anthropometry is a simple valuable tool and the gold standard for evaluating the nutritional status, but it has many limitations. Adequate precautions are to be taken during measurement and the procedures utilized are to be standardized and checked frequently for accuracy. Intraobserver and interobserver reliability should be established first, measurements must be taken according to the standardized techniques and the equipment should be checked periodically for accuracy. Anthropometric criteria can be categorized as *age-dependent* and *age-independent*.

### Age-dependent Anthropometric Measurements

These include weight, length or height, head circumference noted against the exact age in years and months. These measurements are then compared with median, other percentiles, or Z-score in the reference standards like regional or WHO growth charts.

**Weight-for-age** It indicates the appropriateness of weight for that particular age, in the given child, on the basis of which the child can be labeled as being normal or underweight. WFA less than expected may be due to undernutrition, intrauterine growth retardation, low birthweight, endocrine causes, genetic or chromosomal conditions, syndromic conditions and systemic illness. WFA can be represented as percentage of the expected assuming 50th centile as 100% as per Gomez or Indian Academy of Pediatrics (IAP) Classification (**Table 1**); or as percentile like 50th, 25th, 10th, 5th, 3rd percentile; or as between  $-1Z$  and  $+1Z$  (normal), between  $-1Z$  and  $-2Z$  (mild), between  $-2Z$  and  $-3Z$  (moderate) and more than  $-3Z$  (severe) grades of underweight. The recent general agreement is to use WHO Z-scores for ease of interpretation into mild to moderate or severe underweight. The Gomez classification (1956) and the IAP classification (1972) are based on percentage of the present weight as against the expected weight. The disadvantage of WFA is that it may not be the true reflection of undernutrition, and low weight may also be due to short stature, intrauterine growth restriction, syndromic conditions and endocrine or metabolic causes.

**Length or height-for-age** It indicates grade of stunting in a child, which may be due to chronic malnutrition, short stature, skeletal dysplasia, endocrine causes, genetic or chromosomal conditions, syndromic conditions and chronic systemic diseases. It can also be represented or interpreted as percentage of the expected assuming 50th centile as 100% as per Waterlow or McLaren classification; or as percentile like 50th, 25th, 10th, 5th, 3rd centile; and or as between  $-1Z$  and  $+1Z$  (normal), between  $-1Z$  and  $-2Z$  (mild), between  $-2Z$  and  $-3Z$  (moderate) and less than  $-3Z$  (severe) stunting (**Table 2**).

**Table 1** Classification according to weight-for-age (underweight)

Classification Weight-for-age (% of expected)	Mild Grade I	Moderate Grade II	Severe Grade III	Severe Grade IV
Gomez	75–90%	60–75%	< 60%	-
Indian Academy of Pediatrics (IAP)*	71–80%	61–70%	51–60%*	< 50%
<b>Wellcome Trust Classification</b>				
with no Edema	Underweight 60–80%		Marasmus < 60%	-
with edema	Kwashiorkor 60–80%		Marasmic Kwashiorkor < 60%	-

\*IAP Classification: If the patient has edema of nutritional origin, the letter K is placed along with the grade of malnutrition in order to denote kwashiorkor

**Table 2** Classification according to height-for-age (stunting)

Height-for-age (% of expected)	Waterlow's classification	McLaren's classification
Normal	> 95	> 93
First degree stunting/Short*	90–95	80–93
Second degree stunting	85–90	-----
Third degree stunting/Dwarf*	< 85	< 80

\*Terminology used in McLaren's classification

The present consensus is in favor of using WHO Z-score charts for interpretation of HFA.

**Weight-for-height** It indicates the degree of wasting, which is due to acute malnutrition. It can also be represented or interpreted as percentage of the expected assuming 50th percentile of the WHO WFH growth charts as the expected length or height. Wasting can also be classified as per Waterlow/McLaren/WHO classification (**Table 3**); and/or as percentile like 50th, 25th, 10th, 5th, 3rd percentile and or as between  $-1Z$  and  $+1Z$  (normal), between  $-1Z$  and  $-2Z$  (mild), between  $-2Z$  and  $-3Z$  (moderate) and less than  $-3Z$  (severe) wasting (**Table 3**). WHO has suggested a comprehensive classification of malnutrition based on HFA, WFH, and presence of edema (**Table 4**).

**Head circumference and chest circumference** At birth, the head circumference is more than the chest circumference and both equalize by 1 year. Thereafter, the chest circumference is more than the head circumference. In malnutrition, chest circumference will remain less than head circumference after infancy.

**Skinfold thickness (SFT)** The skinfold thickness at triceps is measured to the nearest 0.1 cm by means of the *Harpender calipers*. This gives an indication of the subcutaneous fat and indirectly the calorie reserve in the body. Subscapular SFT can also be measured under the scapula. This is currently used for research purpose only.

### Age-independent Anthropometric Measurements

**Mid-upper arm circumference (MUAC)** Between 6 months and 60 months of age, MUAC can be used to classify malnutrition (**Table 5**). *Shakir shape* is a colored tape indicating normal

**Table 3** Classification according to weight-for-height (wasting)

Weight-for-height (% of expected)	Waterlow's classification	McLaren's classification	WHO classification
Normal	> 90%	> 90%	
First degree wasting/mild wasting*	80–90%	85–90%	
Second degree wasting/moderate wasting*	70–80%	75–85%	Between $-2Z$ to $-3Z$ score or 70–79% of expected (median)
Third degree wasting/severe wasting*	< 70	< 75	< $-3Z$ score or less than 70% of expected (median)

\*Terminology used in McLaren's classification

**Table 4** WHO classification for assessment of malnutrition

	Moderate undernutrition	Severe undernutrition
Symmetrical edema	No	Yes <sup>a</sup> Edematous malnutrition
Weight-for-height (measure of wasting)	Z score <sup>b</sup> $-2$ to $-3$ (70–79% of expected <sup>c</sup> ) Wasting	Z score $< -3$ ( $< 70\%$ of expected) Severe wasting
Height-for-age (measure of stunting)	Z-score <sup>b</sup> $-2$ to $-3$ (85–89% of expected <sup>c</sup> ) Stunting	Z-score $< -3$ ( $< 85\%$ of expected) Severe stunting

a. This includes kwashiorkor and marasmic kwashiorkor

b. Z (SD) score =  $\frac{\text{Observed value} - \text{expected value}}{\text{Standard deviation of reference population}}$

c. Median (50th percentile of WHO standards)

**Table 5** Classification according to mid-upper arm circumference (MUAC) (6–60 months)

MUAC (cm)	Interpretation
> 13.5	Normal
12.5–13.5	Mild to moderate malnutrition
11.5–13.5	Severe malnutrition
< 11.5	Severe acute malnutrition (SAM)*

\*If length < 66 cm, MUAC < 11 cm

nutritional status (green), mild to moderate malnutrition (MAM) (yellow) and severe malnutrition (red) instead of numbers used in MUAC. *Bangle test* is applied by slipping a bangle of internal diameter of 4 cm, if it slips into the axilla in an under-5 child, it indicates undernutrition.

### Biochemical Assessment

Biochemical changes include lowering of serum protein, especially the albumin fraction, enzymes like esterase, amylase, lipase, cholinesterase, alkaline phosphatase and lactic dehydrogenase, carrier proteins like transferrin, ceruloplasmin and beta-lipoprotein, essential amino acids, essential fatty acids, serum calcium, phosphorus, potassium, iron, and magnesium. Serum protein electrophoresis may show low albumin band and low alpha-2 beta-globulin bands. Alpha-2 globulin and beta-globulin bands represent the carrier proteins. The alpha-1 globulin band that represents acute phase reactants and gamma-globulin band that represents antibodies produced against infection may be raised. Reduction in carrier proteins is an early indicator of PEM. The synthesis of acute phase reactants is given more priority in protein deficiency states than the synthesis of carrier proteins. Urinary creatinine, an indirect evidence of muscle mass may be low.

### Clinical Assessment

The clinical signs vary based on the spectrum of the disease, namely underweight, marasmus, and kwashiorkor. Almost all organs in the body can be affected.

**Growth retardation** This is the most important feature of PEM, evidenced by weight loss, wasting and stunting. Growth retardation is present in both kwashiorkor and marasmus.

**Edema** It is seen in kwashiorkor and marasmic kwashiorkor. Mooning of face is often noted in kwashiorkor. Effusion into the serous cavities may occur in severe edema. Isolated ascites may be due to associated liver disease or intestinal tuberculosis.

**Mental changes** Irritability and apathy are the common changes noted in PEM. They are multifactorial in origin. Affected children fail to interact with the environment and also with the mother. Social smile regresses. Brain edema, electrolyte imbalances, hypokalemia and hypomagnesemia are suggested to be the causes. Alteration in neurotransmitter synthesis and release is found to be another major cause. PEM reduces playful exploratory activity, motivation and arousal.

**Hepatomegaly** This is due to fatty infiltration, which starts in the periphery of the lobule and gradually extends to the center. Histologic evidence will be present, even when fatty liver is not clinically evident.

**Hair changes** The changes are more evident at the root of the hair in acute PEM. The hair becomes sparse, easily pluckable and hypopigmented (hypochromotrichia). In some children, the hair becomes red and this led to the term red boy to denote

kwashiorkor. When the nutritional status is regained, the root becomes pigmented and the tip is seen hypopigmented (*flag sign*). There may also be straightening of curly hair and change in texture.

**Skin changes** These indicate severe degree of malnutrition and may occur rapidly in fatal cases. The skin becomes hypopigmented or hyperpigmented, erythematous or jet black in color. This *flaky paint dermatosis* is pathognomonic. It occurs more often in the extremities than trunk and the hyperpigmented patches peel off to expose raw or hypopigmented areas. The cracked lesion in the flexures, groin and buttocks which is infected and ulcerated is called crazy pavement dermatosis. Deficiencies of tyrosine, niacin, zinc and vitamins are attributed in the pathogenesis of these skin changes. Secondary infection with fungi and bacteria may occur. The term *nutritional dermatosis* is also applicable.

**Mucosal changes** Glossitis, stomatitis, and cheilosis are due to various vitamin deficiencies. Secondary infection may occur as candidiasis.

**Purpura or bleeding** It may be seen in those with gram-negative septicemia, disseminated intravascular coagulation and vitamin C and K deficiency.

**Tremors** These are characteristically seen during treatment. Deficiency of vitamin B factors due to increased demand, electrolyte imbalance, imbalance in the production of inhibitory substances like gamma-aminobutyric acid and demyelination are thought to be the causes. Frequent blinking, tremulous cry due to vocal cord tremor and tremors of the body designated *kwashi shake* are rarely noted. The tremors generally subside after some time.

Clinical signs of malnutrition, as identified by Jelliffe, are listed in **Table 6**.

### Dietary Assessment

A history is obtained regarding breastfeeding, complementary feeding, and family pot feeding. Feeding practices are also ascertained. An overall assessment of average food intake (prior to the illness) is possible by a *24-hour recall method*. Average of a 3-day recall during the mid-week (and not including a festival day) is recommended. A food frequency table to record the frequency of intake of each food item is also desirable, i.e., thrice a day, once a day, twice a week, etc. The standard serve for each item has to be defined prior to this. Weighting the uncooked as well as the cooked food and then assessing the nutritive value of food eaten are the other methods, but often not practical. The service of a dietitian is ideal for accurate assessment. The calculated intake should be finally compared with the recommended dietary allowances for the age. A rough idea about the adequacy of micronutrients like vitamins and minerals in the diet should also be obtained. Diet during illness also should be evaluated including any exclusion diets. Maternal beliefs regarding diet during common childhood illnesses are often wrong and unscientific. It is not uncommon to starve the child during diarrhea, measles, respiratory infection, etc. Mothers must be taught to continue feeding during illness and to select easily digestible food items during illness.

### Epidemiological and Ecological Assessment

Socioeconomic assessment, vital statistics like infant mortality, neonatal mortality, perinatal mortality, still birth and under-5 mortality rate (U5MR) are the usual indicators selected to evaluate the nutritional status of a community. When the nutritional status improves, morbidity and mortality will come down. In an individual child also, the socioeconomic status, morbidity, etc. can be evaluated.

### Functional Assessment

Organ dysfunction, delayed developmental milestones, vision and hearing impairment attributable to deficiencies should



**Table 6** Clinical signs of malnutrition (Jelliffe)

<i>Organ</i>	<i>Signs</i>	<i>Cause</i>
Hair	Lack of luster Thinness and sparseness Straightness Dyspigmentation Flag sign Easy pluckability	Protein and micronutrient deficiency
Face	Diffuse depigmentation Nasolabial dyssebacia Moon face	Riboflavin/multiple deficiency
Eyes	Pale conjunctiva Bitot's spots Conjunctival xerosis Corneal xerosis Keratomalacia Angular palpebritis	Iron, Folate/ B <sub>12</sub> deficiency Vitamin A deficiency
Lips	Angular stomatitis Angular scars Cheilosis	Riboflavin, iron deficiency
Tongue	Edema Scarlet and raw tongue Atrophic papillae	Riboflavin, iron deficiency
Teeth	Mottled enamel	Calcium, vitamin D deficiency
Gums	Spongy, bleeding gums	Vitamin C deficiency
Glands	Thyroid enlargement Parotid enlargement	Iodine deficiency
Skin	Xerosis Follicular hyperkeratosis Petechiae Pellagrous dermatosis Flaky paint dermatosis Scrotal and vulval dermatosis	Vitamin A, essential fatty acid deficiency  Vitamin C deficiency Thiamine deficiency Multiple deficiency
Nails	Koilonychia	
Subcutaneous tissue	Edema Amount of subcutaneous fat reduced	Protein, vanadium deficiency
Muscular and skeletal systems	Muscle wasting Craniotabes Frontal and parietal bossing Epiphyseal enlargement Beading of ribs (tender/nontender) Wide open anterior fontanel Knock-knees or bow legs Diffuse or local skeletal deformities Deformities of thorax Musculoskeletal hemorrhages	Protein deficiency Vitamin D deficiency  Vitamin D, vitamin C deficiency  Vitamin C, K deficiency
Gastrointestinal tract	Hepatomegaly	Lipoprotein deficiency
Nervous system	Psychomotor change Mental confusion Sensory loss Motor weakness Loss of position sense Loss of ankle and knee jerks Calf tenderness	Iron, multiple deficiency  Vitamin B <sub>6</sub> , B <sub>12</sub> deficiency Protein, potassium, vitamin D deficiency Vitamin B <sub>6</sub> , B <sub>12</sub> deficiency Vitamin B <sub>6</sub> , B <sub>12</sub> deficiency Vitamin B, E deficiency
Cardiovascular system	Cardiomegaly Microcardia Tachycardia	Thiamine, selenium deficiency  Iron deficiency

be evaluated and documented. Morphological assessment of changes that occur in the buccal mucosa and hair shaft may be noted. In the buccal smear, above 70% of cells may be seen mutilated as against less than 10% in normal children. The hair shaft size is reduced and most of the cells in the growing end are noted to be in the resting phase of telogen and only very few in the growing phase of anagen. The mineral content of the hair root may also be reduced. Curly hair may straighten up in PEM. Difference in texture of hair is an early sign. X-ray of bones may be evaluated to look for rickets, and delayed bone age. The bone age usually corresponds to the height age rather than the chronological age. Transverse lines that represent periods of arrested growth at the growing end of long bones may be noted prior to the onset of frank PEM.

## INVESTIGATIONS

**Blood** Hemoglobin, complete blood counts, peripheral smear, blood sugar, urea, serum electrolytes, serum protein, albumin, serum calcium, phosphorus, alkaline phosphatase, blood culture; Mantoux test; X-ray chest; urine routine examination and culture; stool for ova and cyst, are usually needed for management. Liver function test, renal function test and lumbar puncture may be done whenever indicated.

## MANAGEMENT

Care of children with severe PEM is quite a challenging task as they often present with life-threatening medical emergencies. The various steps involved are treatment of life-threatening medical complications; restoration of WFH; and rehabilitation and prevention. These steps are detailed in the next chapter on management of severe acute malnutrition. Micronutrients also need to be supplemented. Cautious feeding is the rule starting with 75–100 kcal and 1 g protein/kg/day and slowly increasing, and reaching a goal of 150–220 kcal and 4–6 g protein/kg/day. MAM without medical complications can be treated at home under supervision on an ambulatory basis.

## PREVENTION

Ten key interventions are proposed by UNICEF for prevention of malnutrition (**Box 1**). These are particularly important during the first 1,000 days of life including 9 months (270 days) in utero plus first 24 months (730 days) after birth. The period of the first 1,000 days lays the foundation for growth, development, immunity, etc. By 2 years of age, weight becomes 20%, length becomes 50% and brain attains almost 80% of growth. Myelination is almost complete.

### BOX 1 Ten key interventions to prevent malnutrition

1. Timely initiation of breastfeeding within 1 hour of birth.
2. Exclusive breastfeeding during the first 6 months of life.
3. Timely introduction of complementary foods at 6 months.
4. Age-appropriate foods for children 6 months to 2 years.
5. Hygienic complementary feeding practices.
6. Immunization and biannual vitamin A supplementation with deworming.
7. Appropriate feeding for children during and after illness.
8. Therapeutic feeding for children with severe acute malnutrition.
9. Adequate nutrition and support for adolescent girls to prevent anemia.
10. Adequate nutrition and support for pregnant and breastfeeding mothers.

## IN A NUTSHELL

1. The spectrum of malnutrition extends from mild underweight to severe acute malnutrition and includes wasting, stunting, and severe forms such as marasmus and kwashiorkor.
2. Nutritional status can be assessed by anthropometric, biochemical, clinical, dietary, epidemiological and functional criteria.
3. Weight-for-age (WFA), height-for-age (HFA) and weight-for-height are useful indicators to assess presence of underweight, stunting, and wasting, respectively.
4. Wasting is an indicator of acute malnutrition while stunting indicates chronic nutritional deficit.
5. Z-scores as used in WHO growth charts provide an easier way for anthropometric assessment and interpretation.
6. Mild to moderate cases can be managed in home-based programs, while severely malnourished children need hospitalization.

## MORE ON THIS TOPIC

- Baker SS, Baker RD, Davis A. Pediatric Nutrition Support. Sudbury, MA: Jones and Bartlett Publishers; Inc. 2007
- Elizabeth KE. Nutrition and Child Development. 4<sup>th</sup> ed. Hyderabad: Paras Medical Publishing; 2010.
- Elizabeth K E. Nutrition and Child Development. 5<sup>th</sup> ed. Hyderabad, Paras, 2015.
- Gupte S. Textbook of Pediatric Nutrition. New Delhi: Peepee Publishers; New Delhi. 2006. pp. 351–7.
- Leonberg B. ADA Pocket Guide to Pediatric Nutrition Assessment. USA: American Dietetic Association; 2008.
- Parthasarthy A, Menon PSN, Gupta P. IAP Textbook of Pediatrics. 5<sup>th</sup> ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2013.

## Chapter 22.8

# Severe Acute Malnutrition

Praveen Kumar, Preeti Singh

A child is said to be *underweight* if his or her weight-for-age (WFA) is low as compared to the standard for his or her age and sex [Z-score is less than two standard deviation below the median ( $< -2$  SD)] for the age and sex as per the accepted growth standard. Underweight can result from either acute or chronic malnutrition or both and it is thus a composite measure of stunting and wasting. *Wasting* indicates current or acute malnutrition resulting from failure to gain weight or actual weight loss, represented by low weight-for-height (WFH). *Stunting* is an indicator of linear growth retardation that results from failure to receive adequate nutrition over a long period or due to recurrent infections. Stunting is defined as height-for-age (HFA) less than  $-2$  Z-score. It is an indicator of past growth failure. **Table 1** provides a classification of nutritional status based on assessment of WFA, WFH and HFA. As stated in earlier chapter, mid-upper arm circumference (MUAC) is another indicator of malnutrition, independent of age. Nutritional status of a child can be assessed objectively against standard cut-offs for MUAC (**Table 2**).

Wasting or acute malnutrition is further graded into severe acute malnutrition (SAM) and moderate acute malnutrition (MAM) in children. It has been found that lower the Z-score or MUAC (mm), higher the risk of death. For children in whom WFH Z-score is less than  $-3Z$  and MUAC less than 11.5 cm, risk of mortality increases dramatically. However, in edematous children with SAM, accumulation of fluid may lead to W/H more than  $-3$  SD and even MUAC more than 11.5 cm but risk of mortality is even more than nonedematous SAM children. Hence, edema is included as independent criteria for identifying children with SAM (**Table 3**).

**Severe acute malnutrition** It is defined by presence of very low weight-for-height/length (SD score below  $-3Z$  of the median for WHO child growth standards), and/or mid-upper arm circumference less than 11.5 cm, and/or by the presence of bilateral pitting edema.

**Table 1** Classification of nutritional status

SD score	Indicators		
	Weight-for-age	Height-for-age	Weight-for-length/height
Median or below $-1$ SD	Normal	Normal	Normal
Below $-2$ SD	Moderately underweight	Stunted	Wasted/Moderate acute malnutrition
Below $-3$ SD	Severely underweight	Severely stunted	Severely wasted/Severe acute malnutrition

**Table 2** Classification of nutritional status based on mid upper-arm circumference (MUAC) for children aged 6 months to 5 years

MUAC in cm	Nutritional status
12.5 cm or more	Normal
11.5–12.4 cm	Moderate acute malnutrition or Wasted
Less than 11.5 cm	Severe acute malnutrition or Severely wasted

**Table 3** Recommended criteria for identification of severe acute malnutrition (SAM)

Age	Criteria
6 months to 5 years <sup>#</sup>	<ul style="list-style-type: none"> <li>Weight-for-height/length is less than <math>-3</math> SD and/or</li> <li>Mid-upper arm circumference (MUAC) <math>&lt; 11.5</math> cm and/or</li> <li>Bilateral pitting edema of both feet*</li> </ul>
Less than 6 months**	<ul style="list-style-type: none"> <li>Weight-for-height/length is less than <math>-3</math> SD and/or</li> <li>Bilateral pitting edema of both feet*</li> </ul>

<sup>#</sup>IAP guideline included *severe wasting* as one of the criteria; however, this may be subjective and should be used only when mid-upper arm circumference or weight/height/length measurement is not feasible.

\*Unilateral edema is not an indicator of SAM and there should not be a known cause of edema like nephrotic syndrome, congestive heart failure, etc.

\*\*For children with length less than 49 cm, visible severe wasting is used to identify.

**Moderate acute malnutrition** A child who has WFH SD score between  $-3Z$  and  $-2Z$ , or mid-upper arm circumference of 11.5–12.4 cm and has no bilateral pitting edema is classified as having moderate acute malnutrition.

## How Common is Severe Acute Malnutrition?

Severe acute malnutrition is an important cause of morbidity and death in children. The absolute number of children with SAM is much higher in Asia (13.3 million) than in Africa (5.6 million), although the overall prevalence of SAM in Africa is slightly higher than in Asia. The prevalence of SAM in Asia ranges from 0.8% in Bhutan to 7.7% in Laos (**Fig. 1**). As shown in **Figure 2**, NFHS 2006 data has shown high prevalence of wasting in Madhya Pradesh, Chhattisgarh, Jharkhand, Rajasthan, Bihar, Meghalaya and Odisha.

## Why Acute Malnourished Children Need Early Identification and Treatment?

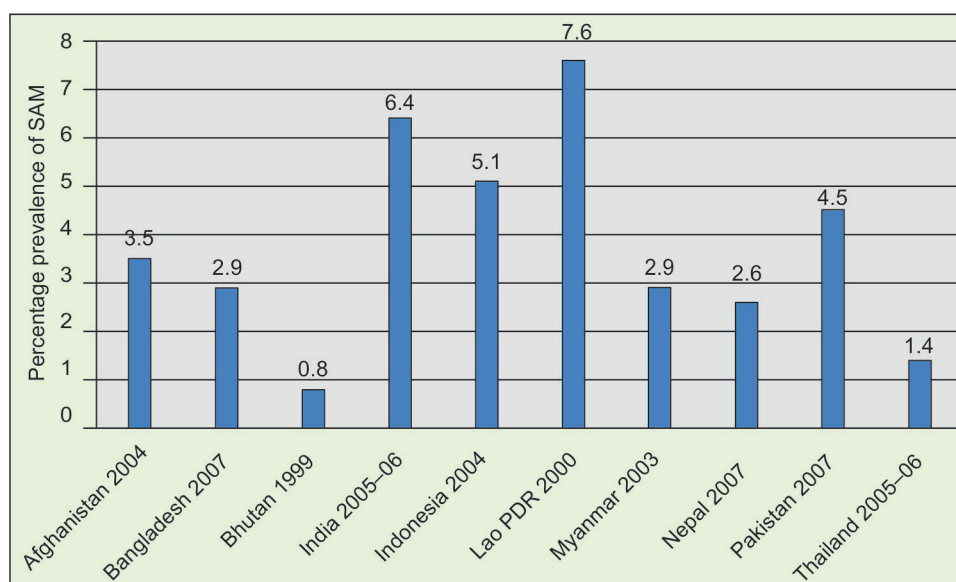
Malnutrition contributes significantly to under-5 mortality as undernourished children have increased susceptibility to infections and, hence, frequent episodes of illness and longer recovery period. Malnutrition lowers the immunity of the child and increases the risk of infection. At the same time, infection results in loss of appetite, increased nutrient requirements and/or decreased absorption of nutrients consumed, which can further cause malnutrition, leading to a vicious cycle. These frequent illness episodes cause economic loss to the family and nation. Moreover, malnourished children have approximately nine times higher risk of mortality due to common illness like diarrhea, etc. pneumonia as compared to children with normal nutritional status.

## Why Children with Severe Acute Malnutrition Need to be Treated Differently?

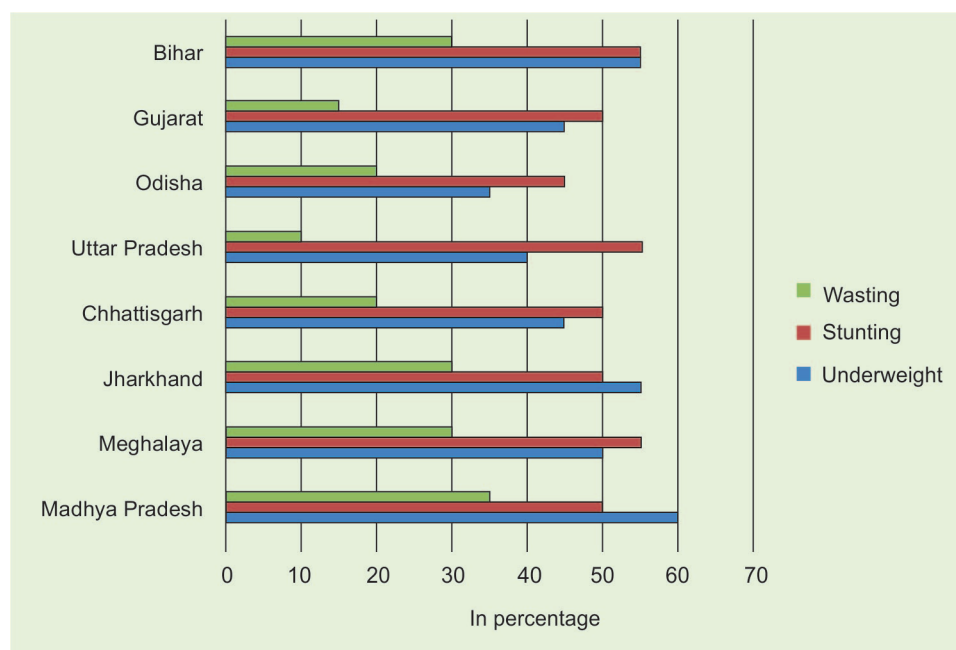
A child with SAM has higher risk of mortality due to several physiological changes occurring in these children, which is known as reductive adaptation.

## What is Reductive Adaptation?

The systems slow down and do less work in order to allow survival on limited calories. When a child's carbohydrate intake is insufficient, fat stores are utilized to provide energy. Later protein is mobilized from muscles, skin and gut. Physiological and metabolic changes also take place to conserve energy. These changes take place in an orderly progression, which is



**Figure 1** Reported prevalence of SAM in under-five children in different countries between 1999 and 2007  
Abbreviation: SAM, severe acute malnutrition.



**Figure 2** Nutritional status of under-five children (NFHS-3, 2006)

called reductive adaptation. A child with SAM conserves energy mainly by reducing physical activity and growth; reducing basal metabolism by slowing protein turnover; reducing the functional reserve of organs; slowing the sodium and potassium pumps in cell membranes and reducing their number; and reducing inflammatory and immune responses.

### Consequences of Reductive Adaptation

The functioning of every cell, organ and system is affected and this puts the child in a very fragile state. Following is a brief description of the effects on different organs:

- The liver is less able to make glucose; so there is increased risk of hypoglycemia and hypothermia. In addition, liver is

less able to excrete excess dietary protein and toxins. These changes have implications for feeding. First, long gaps without food must be avoided. This means giving frequent feeds day and night, which is a ready source of glucose. Second, we must limit protein intake to avoid stressing the liver.

- The kidneys are less able to excrete excess fluid and sodium. So, excess fluid and sodium (from feeds or rehydration fluid) can lead to fluid overload.
- The heart is smaller and weaker and has a reduced output. Any excess fluid in the circulation stresses the heart and can lead to death from heart failure. This means that fluid intake must be carefully controlled initially. Also, feeds and rehydration fluid must be low in sodium.



- The gut produces less acid and smaller amounts of enzymes. The intestinal villi are flattened, motility is reduced. These changes cause bacterial colonization of the small bowel, damage of the mucosa and deconjugation of bile acids. So, initially, feeds must be small to avoid exceeding the gut's functional capacity, and the composition of feeds should be such that it can easily be absorbed. Feeds should be *enteral*, *never parenteral*, to reduce the risk of fluid overload. Repair of the gut is also quicker if nutrients are physically present in the lumen.
- During reductive adaptation, sodium leaks into cells due to fewer and slower pumps, leading to excess body sodium. Potassium leaks out of cells and is lost in urine, contributing to electrolyte imbalance, anorexia, fluid retention and heart failure. So, we need to restrict sodium and provide potassium. We must also provide magnesium to help the potassium get into cells.
- Reduction in muscle mass is accompanied by loss of intracellular nutrients and smaller reserves of muscle glycogen.
- Red cell mass is also reduced, liberating iron. Conversion of harmful *free-iron* to ferritin needs glucose and amino acids, and there may not be enough glucose available to put all the iron into safe storage. Free iron promotes the growth of pathogens and the production of free radicals which damage cell membranes. So, during initial feeding, we need to withhold iron, and provide vitamins and minerals to help mop up free radicals.

Median case fatality rate in children with SAM is very high, i.e., approximately 23.5% if these changes are not kept in mind. Reasons for high case fatality are listed in **Box 1**. The case fatality can be brought down to approximately 7–10% by standard case management protocol.

#### BOX 1 Ten reasons for high mortality in severe acute malnutrition

1. Inability to distinguish between acute and rehabilitation phases
2. Excessive use of intravenous fluids
3. Fluid overload due to lack of monitoring during rehydration
4. Use of diuretics for edema
5. Use of albumin for edema
6. Not keeping the child warm and euglycemic
7. Low index of suspicion for infection
8. Early use of diets high in protein and sodium
9. Failure to monitor food intake
10. Early treatment of anemia with oral iron.

### Initial Work-up

Before taking detailed history in a child with SAM, it is important to look for emergency signs. In presence of any of the following emergency signs, immediate emergency treatment should be provided to child before further evaluation.

1. Not breathing/severe respiratory distress
2. Coma/convulsion
3. Shock
4. Severe dehydration.

If there are no emergency signs, obtain history and examination as described in **Table 4** to find out causes (food scarcity, secondary causes), medical complications, and deciding level of treatment. Laboratory tests that should be routinely done on admission include: blood glucose, serum electrolytes, hemoglobin, PCV in children with severe palmar pallor, and screening for infections. Investigations to identify presence of infections include total and differential leukocyte count; urine routine and microscopic examination; chest X-ray; blood culture and urine culture; Mantoux test; and peripheral smear for malarial parasite. Investigations for secondary causes such as HIV, celiac disease, etc., are undertaken as per clinical suspicion.

**Table 4** History and examination of a child with severe or moderate acute malnutrition

History	Examination
<ul style="list-style-type: none"> <li>• Total duration of sickness</li> <li>• Dietary intake of food and fluids</li> <li>• Breastfeeding</li> <li>• Complementary feeds—introduction time, quality, quantity</li> <li>• Loss of appetite</li> <li>• Any contact with tuberculosis</li> <li>• History of measles in the last 3 months</li> <li>• Known HIV infection</li> <li>• Health of parents</li> <li>• Immunization</li> </ul>	<ul style="list-style-type: none"> <li>• Anthropometric measurements (weight, height/length, MUAC)</li> <li>• Temperature</li> <li>• Pulse rate/heart rate</li> <li>• Respiratory rate</li> <li>• Sensorium</li> <li>• Edema</li> <li>• Lymphadenopathy</li> <li>• Signs of dehydration if history of diarrhea</li> <li>• Capillary refill time</li> <li>• Palmar pallor</li> <li>• Eye signs for vitamin A deficiency*</li> <li>• Localized signs of infections (ear, throat, skin, lungs)</li> <li>• Mouth ulcers/oral thrush</li> <li>• Skin changes for dermatosis</li> </ul>
<ul style="list-style-type: none"> <li>• Duration and frequency of common complaints               <ul style="list-style-type: none"> <li>– Diarrhea (watery/bloody),</li> <li>– Vomiting</li> <li>– Fever</li> <li>– Cough</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Systemic examination—look for hepatosplenomegaly, any murmur or deformities, hypertonia (cerebral palsy) or signs of meningeal irritation</li> </ul>

\*One should be very gentle and careful during examination of the eye to prevent the risk of rupture and blindness particularly if the child resists opening of eyes. Abbreviation: MUAC, mid-upper arm circumference.

## MANAGEMENT OF SEVERE ACUTE MALNUTRITION

Two levels of therapeutic treatment are provided, depending on the presence or absence of appetite (as judged by the appetite test) (**Box 2**) and/or medical complications. In the presence of good community-based management, the vast majority (85–90%) of children with SAM may be managed in the community while only a minority, those with poor appetite and/or with medical complications (10–15%) will need facility-based care in a health facility or nutritional rehabilitation centers (NRCs).

### Community Level

Children with SAM, who have good appetite and are free of medical complications, can be managed at home. These children should receive appropriate therapeutic food and routine medicines from a nearby health facility. Mothers give these therapeutic food and medicines at home and attend health facility or nutritional centers weekly for checkups and to receive supplies of therapeutic food.

#### BOX 2 Appetite test

- The test should be conducted in a separate quiet area
- Explain to the mother the purpose of the test and how it will be carried out
- Ask the mother to wash her hands with soap
- The mother should sit comfortably with the child on her lap
- She should offer therapeutic food gently
- She should encourage the child for feeds
- The child must not be forced to take the therapeutic food
- The child should have free access to water to drink while taking therapeutic foods

#### How to interpret the result?

**Pass:** Child eats eagerly;

**Fail:** Child refuses therapeutic food even after persistent encouragement.

**BOX 3** Indications for hospital management in severe acute malnutrition

- Age less than 6 months
- Presence of any emergency signs
- Hypothermia (axillary temperature < 35°C)
- Edema
- Persistent vomiting
- Very weak, apathetic
- Fever (axillary temperature > 39°C)
- Fast breathing, chest in-drawing
- Extensive skin lesions, eye lesions
- Diarrhea with dehydration
- Severe anemia
- Purpura or bleeding tendency
- Evidence of systemic infections or complications.

**Facility Level**

Children with SAM, who have poor appetite and/or medical complications and/or edema are managed in a health facility as inpatients until they fulfill criteria to be shifted to community management program. Children with medical complications (**Box 3**) require facility based management, preferably at a NRC. In addition to these indications, the child whose mother or caregiver is not able to manage at home, or the child who is not improving, or has weight loss while enrolled in community-based program, should also be admitted in a health facility.

World Health Organization (WHO) has recommended 10 steps of management for SAM children with medical complications (**Fig. 3**).

**Step 1: Treat or Prevent Hypoglycemia**

The blood sugar level is considered low when it is less than 3 mmol/L (< 54 mg/dL). The hypoglycemic child is usually hypothermic also. If hypoglycemia is not prevented or detected early they become lethargic, limp and become unconscious. Sweating and pallor may not occur in children with SAM in presence of hypoglycemia. Treatment is as follows:

**Conscious child** If child is asymptomatic and conscious, give 10% glucose or sucrose 50 mL oral by nasogastric (NG) tube

immediately. This should be followed by starter diet (F-75) every 30 min for first 2 hours and thereafter at 2-hourly intervals.

**Unconsciousness, lethargy, convulsions** Give 10% glucose 5 mL/kg intravenously followed by 10% glucose/sucrose 50 mL orally. Start feeding F-75 diet half an hour after giving glucose and then give it every half an hour during the first 2 hours. Blood sugar should be repeated after 30 min. In case it is still low, repeat 10% glucose bolus.

**Step 2: Treat or Prevent Hypothermia**

Hypothermia is low body temperature defined as axillary temperature below 35°C or rectal temperature below 35.5°C. In children with SAM, less heat is generated due to low basal metabolic rate and inactivity and they are at high risk of losing heat due to lack of insulating fat and higher surface area per kg body weight. Both hypothermia and hypoglycemia are signs that the child has a serious systemic infection and so all children with hypothermia should be treated for hypoglycemia and infection also. If the child is hypothermic, active rewarming is required to raise temperature. Use one of the following rewarming techniques:

- Have the mother hold the child with skin to skin contact (kangaroo technique), and cover both of them. Keep the child's head covered.
- Provide heat with an overhead warmer or radiant heater. Do not point the heater directly at the child and avoid contact with hot water bottles, so as to prevent burns.

In case of severe hypothermia (rectal temperature < 32°C), give warm humidified oxygen and 10% glucose bolus. Use radiant warmer and do slow rewarming to avoid disequilibrium.

**Step 3: Treat or Prevent Dehydration**

Misdiagnosis and inappropriate treatment for dehydration is the commonest cause of death in a child with SAM. Malnutrition results in slowing down of sodium-potassium pump which makes children sensitive to sodium overload. At the same time, total sodium is high in malnourished children. Once excess sodium has been given, either because of a mistaken diagnosis or overenthusiastic rehydration in the emergency department, it is very difficult to get the sodium out of the child. When the starter

	Steps	Stabilization		Phase
		Days 1–2	Days 3–7	Rehabilitation week 2–6
1	Treat/Prevent hypoglycemia	=====		
2	Treat/Prevent hypothermia	=====		
3	Treat/Prevent dehydration	=====		
4	Correct electrolyte imbalance	=====		
5	Treat/Prevent infection	=====		
6	Correct micronutrient deficiencies	=====	No iron =====	With iron =====
7	Start cautious feeding	=====		
8	Achieve catch-up growth			=====
9	Provide sensory stimulation and emotional support	=====		
10	Prepare for discharge and follow-up			=====

**Figure 3** Ten steps for management of children with severe acute malnutrition (SAM)

(F-75) diet is given and cell membrane function starts returning to normal, large amounts of sodium come out of the cells (and potassium enters the cells). So, deterioration in general condition may occur on day 2–3.

It is difficult to determine dehydration status in a child with SAM correctly, as the usual signs of dehydration (such as lethargy, sunken eyes) may be present in these children all of the time, whether dehydrated or not. For diagnosis of dehydration, there should be definite history of diarrhea and history of a recent change in the child's eyes. Even very experienced clinicians may misdiagnose dehydration. For this reason, one should closely monitor and always be prepared to revise the diagnosis of dehydration. Treatment of dehydration in children with SAM without shock consists of fluid administration orally or through NG tube. Every 30 min, 5 mL/kg body weight of rehydration solution should be given during first 2 hours and then 5–10 mL/kg every alternate hour for up to 10 hours. The amount offered in this range should be based on the child's willingness to drink and the amount of ongoing losses in the stool. Starter (F-75) diet is given every hour during this period until the child is rehydrated. All children during rehydration should be closely monitored with weight, pulse rate, respiratory rate and signs of overhydration (**Flow chart 1**).

WHO recommended rehydration solution for malnourished children (ReSoMal) is not available commercially. ReSoMal may be prepared from low osmolarity ORS as described in **Table 5**. However if preparation is not possible, rehydrate with low osmolarity ORS and additional potassium supplements. Intravenous fluids should not be used to treat dehydration except in case of shock with lethargy or unconsciousness. Since the degree of dehydration cannot be determined by clinical signs and too much fluid can cause heart failure, it is very important that fluids are not

**Table 5** Composition of ReSoMAL (Rehydration solution for malnourished children)

Component	Amount (mmol/L)
Glucose	125
Sodium	45
Potassium	40
Chloride	70
Citrate	7
Magnesium	3
Zinc	0.3
Copper	0.045
Osmolarity	300

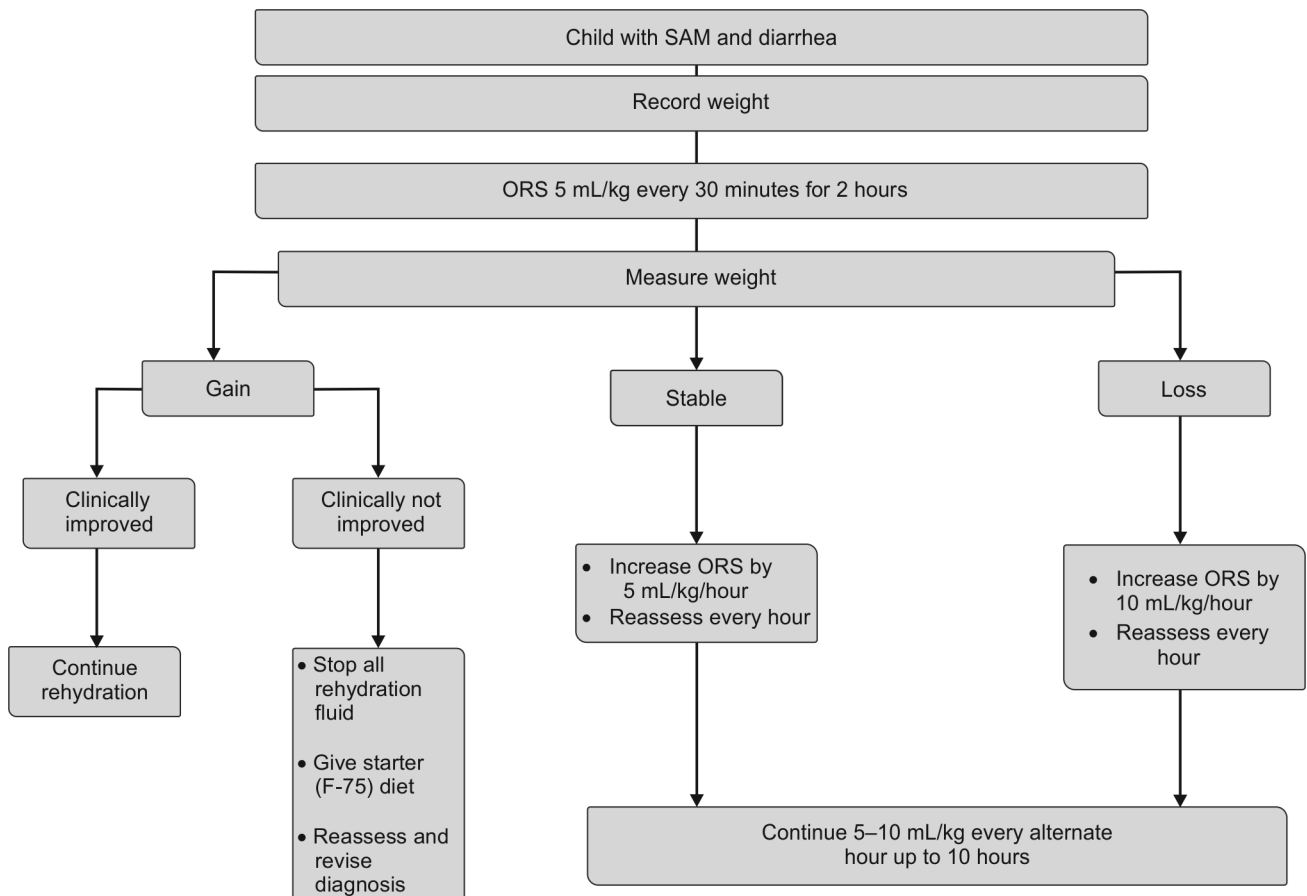
ReSoMAL may be prepared with low osmolarity ORS by dissolving one packet (1L) in 2,000 mL and addition of 50 g of sugar and 40 mL of mineral mix solution.

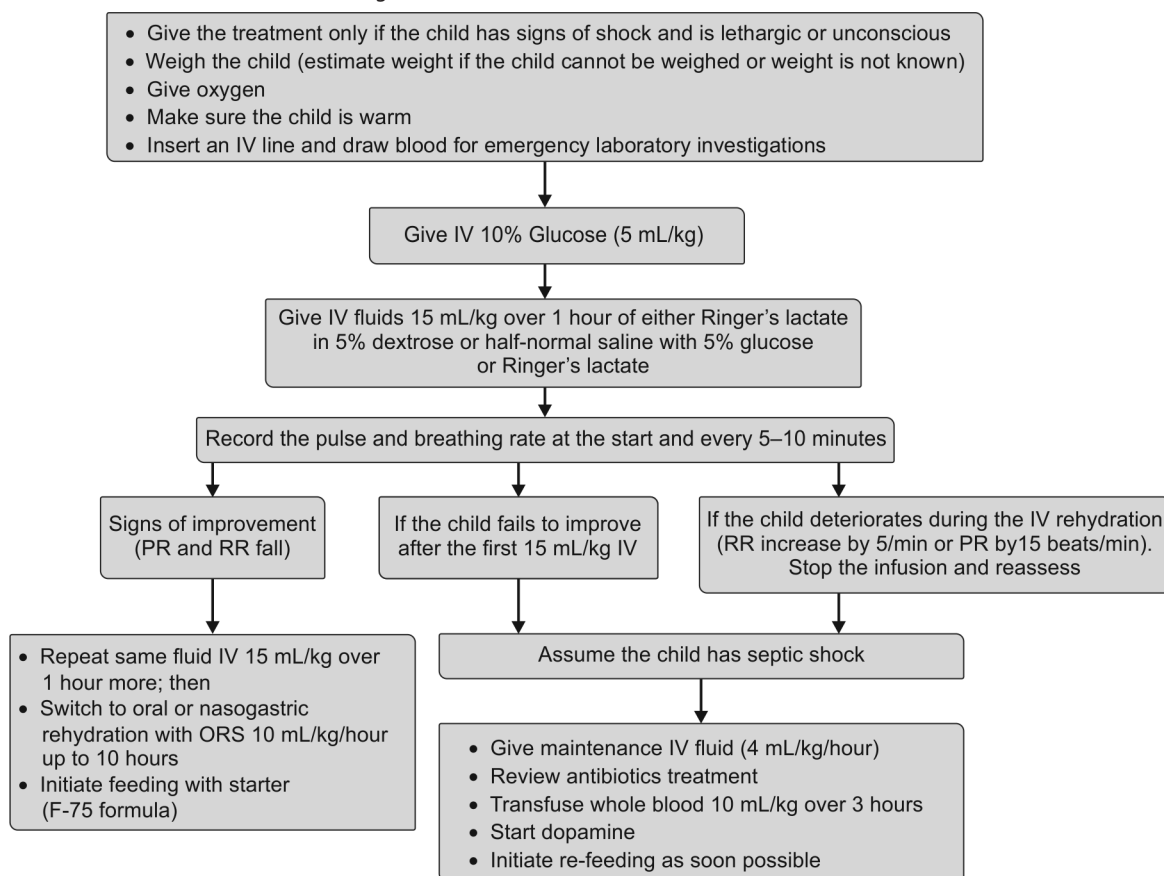
to forced on the child. The child with SAM is considered to be in shock if he or she has cold hands with slow capillary refill (longer than 3 sec) and weak and fast pulse (for a child between 2 months and 12 months of age, a fast pulse is 160 beats or more per minute.; between 12 months and 5 years of age, a fast pulse is 140 beats or more per minute). The management of shock in children with SAM who are lethargic or unconscious is summarized in **Flow chart 2**.

#### Step 4: Correct Electrolyte Imbalance

All children with SAM should be given potassium (3–4 mEq/kg/day). Also give magnesium sulfate 50% once (0.3 mL/kg) up to a maximum of 2 mL on day 1; thereafter, give magnesium sulfate

**Flow chart 1** Management of dehydration in children with severe acute malnutrition (SAM)



**Flow chart 2** Management of shock in children with severe acute malnutrition (SAM)

Abbreviations: PR, pulse rate; RR, respiratory rate.

0.2–0.3 mL/kg/day orally with feeds. Magnesium is essential for potassium to enter the cells and be retained. Children with SAM already have excess sodium in their cells; so sodium intake should be restricted. Both potassium and magnesium supplementation should be continued for at least 2 weeks.

### Step 5: Give Antibiotics

Majority of SAM children have hidden infection. In spite of infection, the usual signs of infection, such as fever, are often absent. Hence, all children with SAM should be given broad spectrum antibiotics. Give the first dose of antibiotics as soon as possible while other initial treatments are going on. Uncomplicated children should receive oral amoxicillin while admitted children should receive combination of ampicillin or third generation cephalosporin with aminoglycosides.

### Step 6: Give Micronutrients

Give oral vitamin A in a single dose to all children with SAM unless there is evidence of receiving vitamin A dose in the last 1 month. Children with clinical signs should be given 3 doses on days 1, 2 and 14. Give other micronutrient supplements daily for at least 2 weeks unless the child is receiving therapeutic food containing these micronutrients: multivitamin supplement (should contain vitamins A, C, D, E and B<sub>12</sub>) twice RDA; folic acid: 5 mg on day 1, then 1 mg/day; elemental zinc: 2 mg/kg/day; and copper: 0.3 mg/kg/day.

### Step 7: Start Cautious Feeding

Children with SAM cannot tolerate usual amounts of protein, sodium or high amounts of fat initially. They may die if given too much protein or sodium. But they need glucose, so they must

be given a diet that is low in protein and sodium and high in carbohydrates. The starter (F-75) diet is designed to fulfill these requirements (**Table 6**).

Give starter (F-75) diet 130 mL/kg (100 mL/kg in case of edema) divided in 12 feeds, i.e., every 2 hours including night. If the child is hypoglycemic, one-fourth of the 2-hourly feed should be given every half hour for the first 2 hours until the child's blood glucose is normal. After the first day, increase the volume per feed gradually so that the child's system is not overloaded. The child will gradually be able to take larger, less frequent feeds (every 3 hours or every 4 hours). If commercially prepared F-75 is not available, starter (F-75) diet may be prepared locally as described in **Table 7**. Most of the children with SAM are able to accept oral feeding. However,

**Table 6** Composition of WHO recommended F-75 and F-100 diets

Constituents	Amount per 100 mL	
	F-75	F-100
Energy (calories)	75	100
Protein (g)	0.9	2.9
Lactose (g)	1.3	3.0
Potassium (mmol)	3.6	5.9
Sodium (mmol)	0.6	1.9
Magnesium (mmol)	0.43	0.73
Zinc (mg)	2.0	2.3
Copper (mg)	0.25	0.25
Osmolality (mOsmol/L)	333	419



**Table 7** Preparation of Starter/Catch up diet locally for treatment of severe acute malnutrition

S. No.	Contents	Starter (F-75 diet) (cereal-based)	Starter (F-75 diet) (noncereal-based)	Catch-up (F-100) diet (cereal-based) Amount for 100 mL	Catch-up (F-100) diet (noncereal-based) Amount for 100 mL
1.	Cow's milk/full cream dairy milk	30 mL	30 mL	75 mL	90 mL
2.	Sugar	7 g	10 g	2.5 g	7.5 g
3.	Vegetable oil	3.5 g	-	2 g	2 g
4.	Puffed rice	2 g	2 g	7 g	-
5.	Water to make	100 mL	100 mL	100 mL	100 mL
	<i>Composition</i>	<i>Amount</i>	<i>Amount</i>	<i>Amount</i>	<i>Amount</i>
1.	Energy (kcal/100 mL)	75	77	100	100
2.	Protein (g/100 mL)	1.1	0.9	2.9	2.9
3.	Lactose (g/100 mL)	1.2	1.2	3	4.2

remember that they have weak muscles and swallow slowly. Encourage breastfeeding on demand between therapeutic feeds. It may be necessary to use an NG tube if the child is very weak; has mouth ulcers that prevent drinking; or cannot take enough F-75 diet by mouth (is not able to finish 80% of the amount offered on 2–3 consecutive feeds).

### Step 8: Achieve Catch-up Growth

F-100 diet is used to rebuild wasted tissues after stabilization which provides 100 kcal energy and 2.9 g protein per 100 mL. Following signs indicate readiness to move from F-75 to F-100:

- Return of appetite (easily finishes 4-hourly F-75 diet)
- No episodes of hypoglycemia or hypothermia
- Edema starts disappearing.

Transition usually takes 3 days, during which catch-up (F-100) diet should be given according to the schedule given in **Box 4**. The goal is to achieve a calorie intake of 150–220 kcal/kg/d and protein of 4–6 g/kg/day.

#### BOX 4 Schedule of transition from F-75 to F-100

*First 48 hours (2 days):* Give Catch-up (F-100) diet every 4 hours in the same amount as you last gave starter (F-75) diet.

*On the 3rd day:* Increase each feed by 10 mL as long as the child is finishing feeds up to a maximum of 220 mL/kg. If the child does not finish a feed, offer the same amount at the next feed. If the child is breastfeeding, encourage the mother to breastfeed between feeds of F-100 diets. Remember F-100 diet is given in the range of 150–220 mL/kg according to current weight of the child.

**Monitoring** Weight is recorded daily to monitor the progress:

- Good weight gain: 10 g/kg/day or more
- Moderate weight gain: 5–10 g/kg/day
- Poor weight gain: less than 5 g/kg/day

A child is failing to respond if he or she does not improve initially; or gains weight but then levels off or deteriorates. Child is also said to fail treatment if there is: (a) failure to regain appetite by day 4; (b) failure to lose edema by day 4; or (c) edema still present on day 10. Failure to gain at least 5 g/kg/day for 3 successive days after feeding freely on catch-up (F-100) diet is a matter of concern and needs evaluation.

### Step 9: Sensory Stimulation

Due to lack of interaction and play, children with SAM have delayed mental and behavioral development. Play therapy is intended to develop language and motor skills aided by simple, inexpensive toys. It should take place in a loving, relaxed and

stimulating environment. Physical activity should be stimulated as soon as the child is well. Mothers should be taught to play with their children using simple, homemade toys. It is important to play with each child individually for at least 15–30 min/day, in addition to informal group play.

### Step 10: Prepare for Discharge and Follow-up

WHO (2009) guidelines had recommended 15% weight gain as one of the criteria for discharge but the current evidence fails to support it as it results in the more severely malnourished children getting the shortest duration of treatment and being discharged when still malnourished. According to recent (2013) WHO recommendation, children with SAM should be discharged when either weight-for-height or length is more than or equal to –2 Z-score or mid-upper arm circumference is more than or equal to 125 mm (depending upon admission criteria) criteria and they have had no edema for at least 2 weeks.

Whenever there is community-based program available, children may be shifted after stabilization at the facility, i.e., fulfilling following criteria:

- Appetite returned to normal (eats at least 75% of therapeutic food)
- Medical complications resolved
- No edema
- Satisfactory weight gain (at least 5 g/kg/day) for 3 consecutive days.

The decision to transfer children from inpatient to outpatient care should be determined by their clinical condition and not on the basis of specific anthropometric outcomes, such as a specific mid-upper arm circumference or weight-for-height/length Z-score. Before discharge from facility immunization should be updated and treatment for helminthic infections should be given as 200 mg albendazole for children aged 12–23 months; and 400 mg for older children.

### Criteria Related to Mother or Caregiver

- Knows how to prepare appropriate foods and feed the child
- Knows how to make toys and play with the child
- Knows how to give treatment at home for diarrhea, fever and acute respiratory infection
- Knows how to recognize danger signs for which they should seek medical assistance
- Follow-up plan has been explained to them.

**Follow-up plan** Before discharge, the need to follow-up and the plan should be explained to the mother and family. They should be followed every 15 days, up to 2 months (four follow-up visits)

and then monthly until WFH SD score reaches  $-1$  SD or above. At each follow-up visit, the child should be examined for any medical complications; the child should be weighed. In case there is no weight gain or weight loss, look for the cause; and the mother should be asked about the child's recent health, feeding practices and play activities.

### Ready-to-Use Therapeutic Food

Based on experiences from several countries; WHO and UNICEF have recommended use of ready-to-use therapeutic food (RUTF) for management of children with SAM without complications. These children are managed under an outpatient therapeutic program where they are provided with a high energy *therapeutic food*. RUTF is a kind of therapeutic food which is energy dense and at least 50% proteins obtained from milk products. Conventionally, the ingredients used in the production of RUTF are milk powder, vegetable oil, peanuts, sugar, minerals and vitamins. Shelled and roasted groundnuts are broken to smaller particle size in a grinder. Skimmed milk powder, the ground peanuts, vegetable oil, powdered sugar and the minerals and vitamins are then amalgamated in a mixer and the paste is further homogenized to reduce particle size ( $< 200 \mu\text{m}$ ). They can be easily and safely administered to children with SAM of more than 6 months of age by the caregiver. The absence of water in RUTF gives them protection against bacterial contamination and the ease of storage at home even without refrigeration. RUTF is consumed with plenty of water every 2–3 hourly in an amount described in **Table 8**. While the child is on therapeutic food, breastfeeding should be continued. If the child desires and there is no diarrhea, then even other home-cooked foods may be given.

**Table 8** Amount of ready-to-use therapeutic food (RUTF)

Weight (kg)	Amount of RUTF (g/day)
3–4.9	105–130
5–6.9	200–260
7–9.9	260–400
10–14.9	400–460

Although the efficacy of RUTF has been shown in several African countries and other regions, there are concerns regarding its misuse. Since the administrative system is porous and there is a chance of commercial exploitation and misuse of RUTF, so it is essential to ensure the availability and utilization of RUTF to the target population only. At present, RUTF is not approved for its use in SAM children by the Government of India.

### MORE ON THIS TOPIC

- Bhatnagar S, Lodha R, Choudhury P, et al. IAP guidelines 2006 on hospital based management of severely malnourished children. *Indian Pediatr.* 2007;44:443–61.
- Community based management of severe acute malnutrition. A joint statement by the World Health Organization, World Food Programme, United Nations Standing Committee on Nutrition, United Nations Children's Fund. Geneva: World Health Organization/World Food Programme, United Nations Standing Committee on Nutrition/United Nations Children's Fund; 2007.
- Dalwai S, Choudhury P, Bavdekar SB, et al. Consensus Statement of the Indian Academy of Pediatrics on integrated management of severe acute malnutrition. *Indian Pediatr.* 2013;50:399–404.
- Management of severe malnutrition: a manual for physician and other senior health workers. Geneva: World Health Organization; 1999.
- Ministry of Health and Family Welfare, Government of India. Operational guidelines on facility based management of children with severe acute malnutrition. National Rural Health Mission. New Delhi, India: Ministry of Health and Family Welfare; 2011.
- WHO child growth standards and identification of severe acute malnutrition in infants and children. A joint statement by the World Health Organization and the United Nations Children's Fund. Geneva: World Health Organization; 2009.
- WHO Guidelines Approved by the Guidelines Review Committee. Guideline: Updates on the Management of Severe Acute Malnutrition in Infants and Children. Geneva: World Health Organization; 2013.

### IN A NUTSHELL

1. Presence of severe acute malnutrition (SAM) increases risk of mortality in common illnesses like diarrhea, pneumonia by approximately 8–9 times as compared to children without malnutrition.
2. Due to reductive adaptation, children with SAM are at high risk of hypoglycemia, hypothermia, electrolyte imbalance, infections and heart failure.
3. All SAM children with loss of appetite and medical complications should be treated in a health facility while those without complications may be treated in community.
4. WHO has recommended 10 steps of management for children with SAM. Early identification, special therapeutic diet (F-75/F-100), broad-spectrum antibiotic, sodium restriction and supplementation of potassium and magnesium are integral parts of management.
5. In children with SAM, all the signs of dehydration are unreliable. So rehydration should be slow under close monitoring. IV fluids should not be used to treat dehydration in children with SAM (except in case of shock).
6. Structured play therapy improves outcome in children with SAM.

## Chapter 22.9

### Vitamin A

Neetu Sharma, Piyush Gupta

Vitamin A is a subgroup of retinoids exhibiting the biological activity of retinol. Naturally occurring retinoids include retinol (vitamin A alcohol), retinyl palmitate (vitamin A ester), retinal (vitamin A aldehyde) and retinoic acid (vitamin A acid). Retinoic acid is the most active form of vitamin. Vitamin A from the diet is ingested as carotene (from plant sources) and retinyl esters (from animal sources). Beta-carotene (provitamin A) yields the highest amount of retinol. The absorption of dietary beta-carotenes varies according to the source, and is generally assumed to be 50%. Absorbed vitamin A is stored in liver as retinyl palmitate. Zinc is required for mobilization of retinyl palmitate to free retinol. The general term vitamin A is usually used for retinol.

#### PHYSIOLOGY

Body obtains vitamin A in two forms, i.e., preformed vitamin A (ester) and provitamin A (carotenoids). Retinyl esters are hydrolyzed to retinol by pancreatic triglyceride lipase and the intestinal brush border enzyme phospholipase before being taken in by the enterocytes by a saturable carrier-mediated process. Carotenoids are disintegrated into retinol by carotene cleavage enzyme dioxxygenase in the small intestinal lumen before being taken up in the enterocytes by passive diffusion. Retinol is then re-esterified with long chain fatty acids (mainly palmitate) in the enterocytes after absorption. In enterocytes, retinol is bound to cellular retinol-binding protein type II (CRBP-II) that facilitates retinol esterification by the enzyme lecithin: retinol acyltransferase (LRAT). Most of the retinyl palmitate (esters) thus produced are incorporated into chylomicrons, and secreted from the enterocytes into the intestinal lymph and moved to liver and other tissues for storage. A sizeable chunk of absorbed vitamin A is secreted into portal circulation as unesterified retinol. This pathway holds importance in situations where secretion of chylomicrons is affected, as in abetalipoproteinemia. Extra-hepatic uptake is also important to make retinyl esters and carotenoids available to tissues, such as mammary tissue, bone marrow, adipose tissue, and spleen bone marrow, peripheral blood cells, spleen, skeletal muscle and kidney. After hydrolysis of retinyl esters in hepatocytes, unesterified retinol binds to retinol-binding protein (RBP), and is sent from the liver to tissues as the *holo*-RBP complex. Most of the plasma RBP is affiliated with transthyretin (TTR) and this complex provides the retinol as well as thyroid hormones to the tissue. RBP is crucial for mobilization of hepatic retinol into plasma, and for cellular uptake of retinol in the retina. In addition, about 50–80% of unesterified retinol in hepatocytes is transferred to perisinusoidal stellate cell for storage where it is packed in cytoplasmic lipid droplets. This huge storage of retinyl esters in stellate cells acts as a reserve of vitamin A for few weeks or months, ensures a steady blood plasma retinol level despite fluctuations in daily intake of vitamin A.

#### FUNCTION

Vitamin A and its metabolites play several critical roles in body physiology. These effects are mediated via retinoic acid which is an important signaling molecule acting as a ligand for specific nuclear transcription factors. Vitamin A is vital for vision. Apart from its role in vision, vitamin A is necessary for regulation of many genes involved in cell division and differentiation. Many

physiologic processes involving the fetal growth and development, reproduction, gastrointestinal and respiratory function and immunity are dependent on vitamin A. Carotenoids, precursors of vitamin A are also important antioxidant defenses.

#### Vision

Vitamin A works in the retina, through its aldehyde (retinal) form which is the prosthetic group on visual proteins rhodopsin and iodopsin. During low-intensity light, 11-cis-retinal in rhodopsin is converted to all-transretinal which generates an electrical signal transmitted via the optic nerve to brain, resulting in night (low-intensity light) vision. Thus, deficiency of vitamin A results in night blindness. Secondly, vitamin A is also essential to maintain the conjunctival mucosa and the corneal stroma via conjunctival epithelial cell ribonucleic acid (RNA) and glycoprotein synthesis.

#### Resistance to Infections

Vitamin A is commonly known as the anti-infective vitamin. The two prime functions responsible for the prevention of diseases are the effect on the immune system and on epithelial integrity. Both humoral immunity and cell-mediated immunity are depressed by deficiency of vitamin A. The principal effects seem to be a consequence of impaired growth and differentiation of myeloid tissues as retinoic acid is essential for development and differentiation of white blood cells, especially activation of T-lymphocytes. Vitamin A deficiency (VAD) has been shown to increase the frequency and severity of many infectious diseases. Vitamin A supplementation has been found to reduce mortality from measles and diarrhea.

#### Epithelial Cell Integrity

Vitamin A is essential for the integrity and function of skin and mucosal cells of the respiratory airways, digestive tract and urinary tract that acts as a barrier and builds the body's first line of defense against infection. In hypovitaminosis A, mucus secretion decreases, mucosa atrophies goblet cells are lost, and keratinization of skin occurs. Destruction of this first line defense leads to the invasion by microorganism and increased severity of infection.

#### Growth and Development

In fetal development, retinoic acid is required for the development and formation of the heart, limb, eyes and ears. It may have a role in regulation of expression of the gene for growth hormone. Retinoic acid is present in abundance in the developing brain and found to be associated with synaptic plasticity of the hippocampus. Thus, it has a role in the spatial and relational memory and maturation of learned behaviors.

#### Antineoplastic Activity

Vitamin A has a role in cancers of mouth, skin, bladder, lung, prostate and breast. It is used as a therapeutic agent in certain premalignant lesions, such as oral leukoplakia, xeroderma pigmentosum and cervical dysplasia.

#### Others

Vitamin A is required for normal functioning of osteoblasts and osteoclasts. Sperm production requires normal level of vitamin. Vitamin A helps in normal stem cell differentiation as well as in mobilization of iron from storage sites to the developing red blood cell. Change in retinoic acid level results in several abnormalities, like absence of posterior hindbrain, abnormal dorsoventral patterning of the spinal cord, and is found to be involved in CNS disorders like Alzheimer's disease, schizophrenia, depression and sleep disorders.

## SOURCES

Breastmilk fulfills the needs of vitamin A entirely for the first 6 months of life. It continues to be an important source (38–75% of requirement) depending on mother's vitamin A status and volume of the breastmilk consumed, up to 2 years of age. Preformed vitamin A (retinol) is abundant in fish liver oils, liver, dairy products and egg yolk. Vegetarian sources of vitamin A include green leafy vegetables, and yellow fruits and vegetables, such as carrots, papaya, tomatoes, sweet potatoes, mango, broccoli and spinach. Liver is the richest dietary source. Some processed foods and infant formulas are now fortified with preformed vitamin A. Dehydroretinol (vitamin A<sub>2</sub>), with 40% biological activity of retinol, is found only in freshwater fish.

## RECOMMENDED DAILY ALLOWANCE

Infants (0–12 months): 350 µg; children (1–6 years): 400 µg; children (7–9 years): 600 µg; adolescents and adults: 600 µg; pregnant women: 800 µg; lactating women: 950 µg. All these values are in terms of retinol equivalents (RE) (ICMR, 2011). If carotenes are the sources, the RDA in terms of RE is multiplied by 8 assuming a 1:8 conversion efficiency. It is recommended that minimum 50% of RE should be derived from animal sources to ensure adequacy in vulnerable groups.

1 µg of retinol = 3.33 international units (IU) of vitamin A

1 IU = 0.3 µg of retinol = 0.6 µg of β-carotene = 1.2 µg of other carotenes.

60 g of retinol = 110 mg of retinyl palmitate = 69 mg retinyl acetate = 2 lac IU of vitamin A.

## VITAMIN A DEFICIENCY

Vitamin A deficiency of sufficient duration or severity can lead to xerophthalmia, childhood blindness, anemia, decrease host resistance to infection and increased risk of mortality in under-five children. Subclinical VAD is a severely significant problem in preschool children, while overt VAD is rampant in pregnant women in India.

### Indicators of VAD

Clinically, presence of night blindness is used as the best indicator for VAD. Serum retinol of less than 0.70 µmol/L is used to identify those at risk for biochemical VAD. However, the deficiency problem is overestimated if we do not consider coexisting deficiency of iron, zinc and protein; or take infections into account. Iron deficiency reduces serum retinol levels. Zinc affects metabolism by influencing absorption, transport and utilization. Protein is needed to mobilize liver reserves into blood. A child with severe acute malnutrition will thus have lower serum retinol level. Serum retinol concentrations can be lowered up to 25% by infections, so C-reactive protein should be estimated while assessing serum retinol levels. Serum retinol can be measured by high-pressure liquid chromatography (HPLC), fluorescence or ultraviolet (UV) spectrophotometry in dried blood spots. HPLC is the method of choice, due to its high sensitivity and specificity. Prevalence cut-offs to define significance of VAD in a given population are already detailed in Chapter 22.5.

### Causes of Deficiency

Vitamin A is not synthesized within the body, and needs to be supplied by external sources. Deficiency can occur secondary to defective absorption, altered metabolism, decreased ingestion or increased requirement. While a child's liver can store vitamin A for only few weeks, the same can be stored in adult liver for a year or so. VAD may begin in early neonatal period with discarding of colostrums which is rich in vitamin A. Inadequate breastfeeding adds further to the deficiency. Vegetarians run the risk of having

deficiency as fruits and vegetables, compared with animal sources and fortified foods, provide proportionately insufficient amount of vitamin A. As the beta-carotene : retinol ratio for fruits and vegetables is 12:1 and 26:1, respectively, only 20% of RDA in 4–8 year-old is provided by a 70 g serving of dark-green leafy vegetables. Thus, one has to eat 350 g of leafy vegetables per day to fulfill the RDA requirement, which is difficult in practice. Severe malnutrition is an important cause of deficiency as it leads to impaired synthesis of retinol transport protein. The requirement of vitamin A is increased in preterms, and during infections (measles, respiratory tract infections). Coexisting infection and VAD result in decreased appetite, reduced absorption, excessive metabolism and increased excretion of vitamin A. Moreover, provitamin A is fat-soluble and its absorption depends on the presence of adequate lipid and protein in the diet. Chronic diarrhea, malabsorptive states and chronic liver disease, therefore, cause significant VAD. Zinc deficiency may also increase the risk of VAD.

## Clinical Features

### Subclinical Deficiency

Respiratory system, urinary tract, intestinal epithelium and immune system are affected before the deficiency manifests clinically. Subclinical VAD contributes to an increased severity of certain infections and an increased risk of infection-related mortality. Long-standing deficiency causes several changes and eye tends to be the main victim.

### Xerophthalmia

Defective dark adaptation is the most characteristic early clinical feature, resulting in night blindness. Children in 6–36 months of age are mostly affected.

*Xerosis of the conjunctiva* is usually the first clinical sign. Palpebral conjunctiva loses its sheen and wetness. Wrinkling appears in the conjunctiva which can be appreciated as conjunctival folds when the child moves the eye ball towards the opposite side. It is because the normal lacrimal and mucus-secreting epithelium are replaced by a keratinized epithelium (**Fig. 1**).

*Bitot's spots* are the most characteristic feature of xerophthalmia and appear next as triangular areas on the temporal aspects of junction of cornea with sclera. The spots are made up of heaped up dry masses of conjunctival epithelium. There may be more than one spot measuring from 1 mm to 5 mm. The spots are whitish grey, look dry, non-reflective, and may have embedded wrinkles (**Fig. 2**). These are present bilaterally and associated with a muddy conjunctiva. The spots may be stained black, if the mother has applied kohl (kajal) in the eyes of the infant.

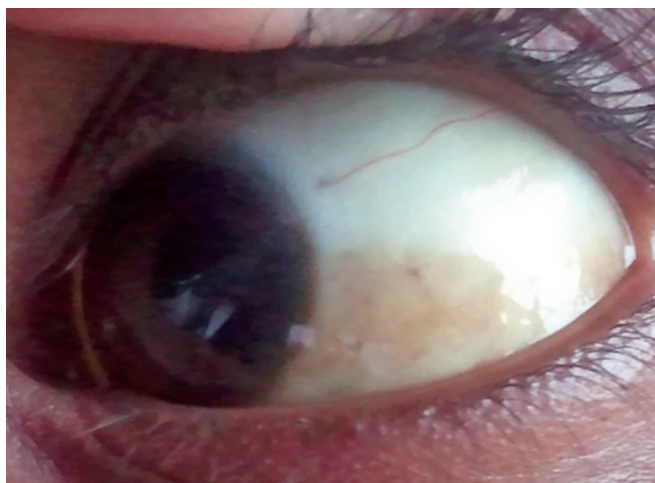
*Corneal xerosis* cornea dries up as the next step. A dry cornea is susceptible to exposure injury and can get ulcerated easily. Ulcers are pinpoint initially and later coalesce. The ulceration spreads to involve most of the cornea. This stage is known as *keratomalacia* and is a forerunner to corneal perforation (**Fig. 3**).

*Blindness* Aqueous humor and iris prolapse out, that ultimately results in corneal blindness. Corneal xerosis is reversible while keratomalacia is irreversible. It results in corneal scarring (**Fig. 4**). On funduscopy, pale yellow spots can be visualized near the course of retinal vessels and also in the periphery.

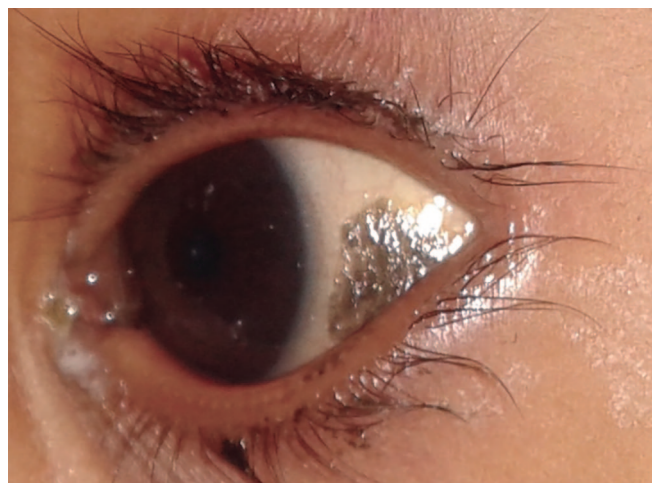
The sequence of changes described above remains the same, though the rate of progression may be acute, subacute or chronic. WHO classification for ophthalmic manifestations of VAD is tabulated in **Table 1**.

Besides ophthalmic changes, other signs that may appear are excessive deposition of periosteal bone secondary to reduced osteoclastic activity, anemia, recurrent infections as diarrhea, pneumonia, dry skin, dry hair, pruritus and broken fingernails.

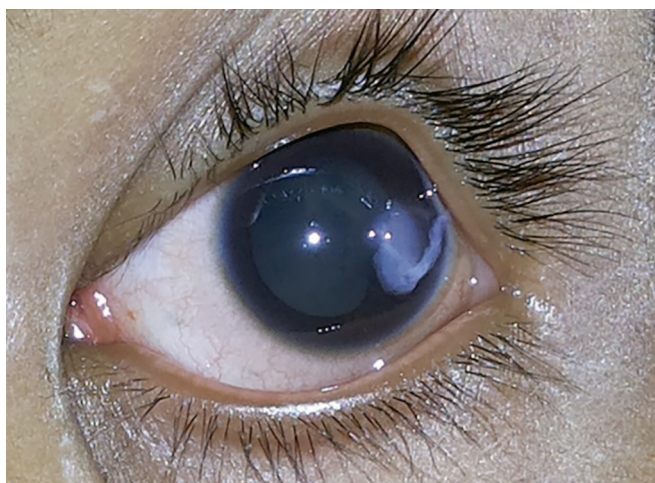




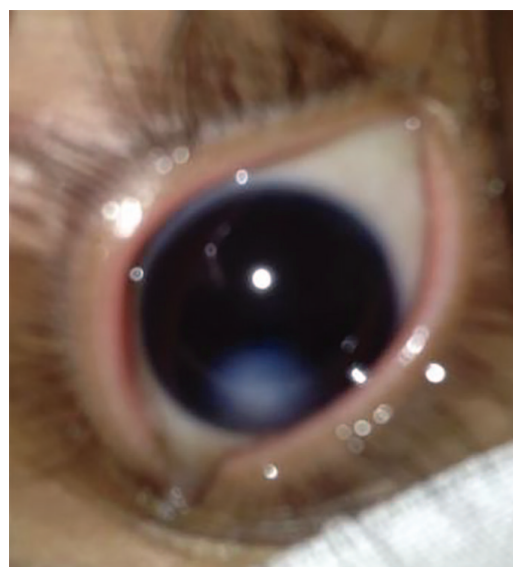
**Figure 1** Conjunctival xerosis



**Figure 2** Bitot's spots



**Figure 3** Corneal ulceration



**Figure 4** Corneal scarring

**Table 1** WHO classification of xerophthalmia

<i>Primary signs</i>		<i>Secondary signs</i>	
X1A	Conjunctival xerosis	XN	Night blindness
X1B	Bitot's spots	XF	Fundal changes
X2	Corneal xerosis	XS	Corneal scarring
X3A	Corneal ulceration (< 1/3 of cornea)		
X3B	Corneal ulceration (> 1/3 of cornea)		

## VITAMIN A SUPPLEMENTATION AND CHILD MORTALITY

Vitamin A supplementation has been linked with 23% reduction in child mortality in several trials in developing nations. However, these claims have been challenged. In north India, VAD (retinol < 0.70  $\mu\text{mol/L}$ ) is common in preschool children and 2–3% die at ages 1.0–6.0 years. A large [DEVTA (Deworming and Enhanced

Vitamin A)] trial in preschool children from 8,338 villages from north India contradicts the expectation from other trials that vitamin A supplementation would reduce child mortality by 20–30%, but cannot rule out some modest effect. Meta-analysis of DEVTA plus eight previous randomized trials of supplementation (in various different populations) yielded a weighted average mortality reduction of 11% (95% CI 5–16).

## TREATMENT OF VITAMIN A DEFICIENCY

Xerophthalmia can progress from conjunctival xerosis to perforation very rapidly, resulting in blindness. Thus, any evidence of VAD should be treated on priority and emergency basis.

### Specific Therapy

Treat all children with clinical signs of VAD as early as possible. Immediately on diagnosis, oral vitamin A is administered in a dose of 50,000, 1 lac and 2 lac international units in children aged less than 6 months, 6–12 months and more than 1 year, respectively. The same dose is repeated the next day and 2 weeks later. Parenteral

water-soluble vitamin A administration is recommended (in half the doses suggested above) in children with impaired oral intake, persistent vomiting and severe malabsorption. Oil-based injections should not be used to treat xerophthalmia. Administer vitamin A immediately as per schedule (**Box 1**).

#### BOX 1 Treatment schedule for xerophthalmia

Three doses of vitamin A are given as follows: first dose immediately on diagnosis, second dose 24 hours later and the third dose 1–4 weeks later in an age-specific schedule as shown below:

< 6 months	50,000 units
6–12 months	1 lac units
> 12 months	2 lac units

Vitamin A is available in the form of a syrup (one lac units per mL) or capsule (one lac units per capsule).

Source: Vitamin A supplements. WHO/UNICEF/IVACG task force, WHO, 1997.

### Local Treatment

Antibiotics drops or ointment should be instilled three times a day to prevent secondary infection in the event of presence of corneal ulcer. Padding the eye in such cases prevents dehydration and further corneal exposure. Padding also enhances epithelial healing and reduces pain and photophobia. Mydriatics are necessary; usually atropine drops 1% or ointment is applied once a day.

### PREVENTION AND CONTROL

Vitamin A deficiency in affected populations can be curtailed via three types of community interventions: (a) improving the availability and consumption of vitamin A by dietary diversification and to strengthen the general nutritional standing of the population; (b) food fortification; and (c) periodic mega-dose vitamin A supplementation to preschool children and during pregnancy. These approaches should be seen as complementary to each other.

#### Promoting Consumption of Vitamin A Rich Food

- Encourage regular intake of vitamin A-rich foods by pregnant and lactating mothers and by under-5 children.
- Education to be imparted to mothers attending the antenatal clinic, immunization clinic and Integrated Child Development Services (ICDS) about the importance of preventing VAD.
- Encourage breastfeeding. In particular, rectify the malpractice of discarding colostrums.
- Promote intake of locally available carotene rich foods, i.e., green leafy vegetables and yellow and orange vegetables and fruits like pumpkins, carrots, papayas, mangoes and oranges, along with cereals and pulses. Consumption of milk and milk products, egg and liver must be promoted.
- During economic instabilities, homestead food production can diversify the diet and enhance income. Horticultural interventions including home gardening. Growing of vitamin A-rich foods in the home and in gardens should be promoted to increase the availability of vitamin A-rich foods.
- Nutrition education for dietary diversification. And awareness about consumption of vitamin A-rich foods should be created.
- Nutritional supplementation.
- Provision of safe drinking water and sanitation.

#### Selective Fortification for Risk Areas and Special Groups

In cases where dietary quality cannot be enhanced by food variety, fortification of staple food with vitamin A is a viable and cost-effective intervention. What matters significantly in the fortification process is the compatibility of the food, stability of

vitamin A in the food all through the marketing process and the cost of fortification for each food. Needless to mention that the choice of suitable food for fortification differs from country to country, and can range from refined sugar to edible vegetable oils and fats, from grains like wheat and rice to maize flours, from condiments and seasonings to powdered and liquid milk. Two other issues that need extra attention are packaging and cooking. Since sunlight is harmful for vitamin A, tin containers can ensure preserving maximum of vitamin A. Compared to frying or boiling, pressure cooking preserves more vitamin A nonetheless, in general 65–85% vitamins are preserved irrespective of cooking method.

#### Administering Massive Doses of Vitamin A

A periodic delivery of high-potency supplements, i.e., 2 lac IU of vitamin A to the children up to 5 years of age and half of this dose to infants of 6–11 months of age is the most prevalent practice in most high risk countries to control VAD. In many of these high risk countries, as per the WHO policy, mothers are given this vitamin A supplement as 2 lac IU orally within 6 weeks post-delivery in order to enhance the breastmilk content of vitamin A.

*Prophylactic vitamin A to healthy children* Prophylactic vitamin A (one dose of 1 lac units of vitamin A along with measles vaccine at 9 months followed by four more doses of 2 lac IU each at 18, 24, 30 and 36 months) may be administered in areas with high prevalence of VAD. This practice has been shown to reduce the risks of xerophthalmia by 90% and mortality by 23–30% in young children, however, the effect on increasing the serum retinol concentration is modest. Prophylactic mega dose administration of vitamin A is primarily advocated because of the claim of 23% reduction in childhood mortality. However, benefits on this scale have been found only in areas with rudimentary health care facilities where clinical deficiency is common, and there is substantial heterogeneity, especially with inclusion of all trials. There is an urgent need for adopting a targeted rather than universal prophylactic mega dose vitamin A supplementation in preschool children. This approach is justified on the basis of currently available evidence documenting a substantial decline in VAD prevalence, substantial heterogeneity and uncertainty about mortality effects in present era with improved health-care, and resource constraints with competing priorities.

*Prophylactic vitamin A to sick children* Infants and young children suffering from diarrhea, measles or ARI should be encouraged to consume vitamin A-rich foods and administered an additional dose of vitamin A (**Table 2**). Children suffering from measles and severe malnutrition should be administered oral vitamin A (1 and 2 lac IU each for < 1 year > 1 year olds respectively), on two consecutive days. Those with persistent diarrhea and other prolonged febrile conditions are given one dose in each episode.

*Vitamin A during pregnancy and in neonates* Relatively small increased needs for vitamin A during pregnancy should be met through diet or through a supplement not exceeding 10,000 IU daily throughout pregnancy. Where VAD is endemic in under-fives and maternal diets are low in vitamin A content, administer either a daily 10,000 IU daily supplement at any time during pregnancy, or weekly supplementation 25,000 IU. A single dose more than 25,000 IU is not advisable between day 15 and day 60 following conception.

Breastfed neonates do not need vitamin A supplement in the first 6 months.

The above-mentioned three strategies are considered complementary: hence need to be combined. Besides, other approaches that can also play a vital role in curtailing VAD include strategies for advocating breastfeeding, enhanced vaccine coverage particularly against measles, family planning measure for birth gaps and oral rehydration therapy to cure diarrhea.



**Table 2** Case management schedule for areas with endemic vitamin A deficiency

Disease	Dosage by mouth	Timing
Measles		
< 12 months	1 lac units	On diagnosis and the next day
> 12 months	2 lac units	On diagnosis and the next day
Severe PEM	Same as above	Second dose only if the condition worsens
Persistent diarrhea	Same as above	One dose for each episode with at least a month interval between doses
Other prolonged febrile conditions	Same as above	One dose for each episode with at least a month interval between doses

Abbreviation: PEM, protein-energy malnutrition.

Source: Strategies for prevention of blindness, WHO, 1997.

## HYPERVITAMINOSIS A

Several factors can lead to toxicity from preformed vitamin A such as diets with rich sources of vitamin A (liver of certain animals), supplements like cod liver oil, and medicinal form prescribed in various conditions. Levels increase either due to enhanced intestinal absorption of vitamin A or diminished chylomicron clearance. As compared the oil-based retinol preparations, aqueous preparations are 10 times toxic. Since the conversion to the active form of vitamin A is significantly regulated, increased intake of provitamin does not lead to hypervitaminosis. Nonetheless, overconsumption of beta-carotene may result in carotenemia (presenting with yellowish discoloration of skin).

### Clinical Features

Clinical manifestations vary, and so does the dose required for toxicity. Acute toxicity occurs at doses of 25,000 IU/kg of body weight or when adults and children ingest more than 100× and more than 20× the RDA, respectively, over a period of hours or a few days. For liver toxicity, the levels as low as 15,000 IU/day and in renal failure, 4,000 IU/day are reported to be toxic. It gets further sensitive where the body mass is smaller, like in children, where daily intakes of 1,500 IU/kg body weight may cause toxicity.

### Acute Hypervitaminosis A

Acute hypervitaminosis A causes pseudotumor cerebri manifesting as bulging fontanel, vomiting, and irritability in young infants. Older children may complain of diplopia and headache. Papilledema and cranial nerve palsies are rare. Symptoms and signs improve rapidly on withdrawing vitamin A. Acetazolamide, mannitol, or a therapeutic lumbar tap may be needed in severe cases. Other symptoms include nausea, headache, fatigue, loss of appetite, dry skin, desquamation and redness, cerebral edema, drowsiness, dizziness and delirium.

### Chronic Toxicity

Chronic toxicity usually results from intake of medicinal vitamin A over a period of several weeks, where the lowest intake capable of eliciting toxicity differs from person to person. Intake of 4,000 IU/kg of body weight daily for 6–15 months is considered toxic. Chronic hypervitaminosis A results in skin desquamation, alopecia, hepatosplenomegaly, bone swellings and increased intracranial tension. The shaft of long bones may show hyperostosis as synthetic

retinoids are known to change bone metabolism, and an increase in turnover leading to spontaneous bone fracture, osteoporosis, premature epiphyseal closure, hypercalcemia, bone and joints pain, and elevated alkaline phosphatase. Other symptoms of chronic toxicity are hepatosplenomegaly, chronic inflammation of the liver, cirrhosis, dry lips, anorexia, headache, psychiatric changes, conjunctivitis, irritability, mouth ulcers, abnormal softening of the skull bone, changes in consciousness, poor weight gain and hair loss.

Excessive intake of vitamin A is teratogenic during first trimester of pregnancy, and has been linked with central nervous system malformations, other birth defects and spontaneous abortions. An area of emerging concern is the subtoxicity *sans* any clinical signs of toxicity as intake of preformed sources of vitamin A usually tends to exceed the RDA for adults notably in developed nations. Only double the RDA intake of preformed vitamin A has been linked with osteoporosis and hip fracture.

### Management

Diagnosis of toxicity is difficult since serum retinol is not sensitive to toxic level of vitamin A. Even with inconsistent dietary intake of vitamin A, the serum retinol concentrations is maintained within normal range of 1–3 mol/L by homeostatic regulation. Instead fasting retinyl ester concentrations more than 10% of total circulating vitamin A could indicate the toxic level. This occurs as a result of overflowing of extra esters into the blood from already saturated hepatic stellate cells and decreased hepatic uptake of vitamin A. Discontinuation of excessive intakes usually results in complete recovery. Prevention is possible by restricting the intake as per RDA. Caution should be exercised while administering massive doses for prophylaxis and in conditions like pregnancy and liver disease.

### IN A NUTSHELL

1. Vitamin A and its metabolites play critical role in vision, fetal growth and development, reproduction, gastrointestinal and respiratory function and immunity. It is part of antioxidant defenses.
2. Preformed vitamin A (retinol) is abundant in fish liver oils, liver, dairy products and egg yolk. Vegetarian sources of vitamin A include green leafy vegetables, and yellow fruits and vegetables such as carrots, papaya, tomatoes, sweet potatoes, mango, broccoli and spinach.
3. Vitamin A deficiency (VAD) of sufficient duration or severity can lead to xerophthalmia, childhood blindness, anemia, decrease host resistance to infection, and increased risk of mortality in under-5 children.
4. Prevalence of night blindness and Bitot's spots, and serum retinol of less than 0.70 µmol/L are used as the indicators for VAD in a community.
5. Treat all children with clinical signs of VAD as early as possible with massive doses of vitamin A.
6. Vitamin A deficiency in the community can be prevented by improving the availability and consumption of vitamin A by dietary diversification and to strengthen the general nutritional standing of the population; food fortification; and targeted mega-dose vitamin A supplementation to preschool children and during pregnancy.

### MORE ON THIS TOPIC

Awasthi S, Peto R, Read S, et al. Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial. *Lancet*. 2013;381:1469-77.

- Blomhoff R, Blomhoff HK. Overview of retinoid metabolism and function. *J Neurobiol.* 2006;66:606-30.
- Kapil U, Sachdev HP. Massive dose vitamin A programme in India--need for a targeted approach. *Indian J Med Res.* 2013;138:411-7.
- Murray F. Vitamin A and Beta-Carotene are Miracle Workers. New Delhi: Gyan Publishing House; 2012.
- Serum retinol concentrations for determining the prevalence of vitamin A deficiency in populations. *Vitamin and Mineral Nutrition Information System.* Geneva: World Health Organization; 2011.
- WHO, UNICEF, IVACG Task Force. Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia, 2nd ed. Geneva, World Health Organization, 1997.
- WHO. From: <http://whqlibdoc.who.int/publications/1997/9241545062.pdf>. Accessed 20 May, 2014.
- XXII IVACG meeting 2005 Labadarios D, Randal P: Presentation highlights: vitamin A and the common agenda for micronutrients. XXII IVACG meeting, 15–17 November 2004, Lima, Peru. *Sight Life.* 2005;1:9-17.



## Chapter 22.10

# Vitamin B Complex Deficiency

Vineeta Gupta

Vitamin B complex includes thiamine (B<sub>1</sub>), riboflavin (B<sub>2</sub>), niacin (B<sub>3</sub>), pyridoxine (B<sub>6</sub>), cobalamin (B<sub>12</sub>), biotin and pantothenic acid, all of which are water-soluble vitamins. Two other nutrients choline and inositol are also considered part of the vitamin B complex group. Specific signs and symptoms related to deficiency of these two compounds have not been described.

B-complex vitamins function as coenzymes in several enzymatic reactions. Lack of any one of the vitamins can interrupt many closely related reactions and lead to diverse clinical manifestations. Poor diet can result in deficiency of one or more B vitamins; therefore, it is usual practice to supplement all the B-complex group of vitamins in a deficient person.

### THIAMINE (VITAMIN B<sub>1</sub>)

Thiamine is composed of two rings thiazole and pyrimidine linked together by a methylene ring. Thiamine diphosphate and thiamine pyrophosphate are two phosphate derivatives of thiamine, which function as cofactors for many enzymes involved in carbohydrate metabolism. Synthesis of neurotransmitters, such as acetylcholine and gamma-aminobutyric acid (GABA) also requires thiamine, both of which are important for nerve conduction. Thiamine requirements are increased during periods of increased metabolism, like fever, pregnancy, lactation and hyperthyroidism. Alcohol interferes with the uptake and transport of thiamine, which can lead to deficiency in chronic alcoholics.

### Dietary Sources

Thiamine is widely distributed in both nonvegetarian and vegetarian foods, such as fish, poultry, pork, yeast, legumes and cereals. It is both heat-labile and water-soluble and also sensitive to pasteurization. As the vitamin is present in the outer layers of the grain, repeated washing of rice may cause loss of the vitamin.

### Absorption

Thiamine is absorbed in the jejunum and ileum. The absorption is inhibited by alcohol consumption and folic acid deficiency. It may also be decreased in patients with gastrointestinal disease. At low concentrations, the absorption is carrier mediated but at high concentrations, the process occurs by passive diffusion.

### Recommended Daily Allowance (ICMR, 2011)

0–6 mo: 0.2 mg; 7–12 mo: 0.3 mg; 1–3 years: 0.5 mg; 4–6 years: 0.7 mg; 7–9 years: 0.8 mg; 10–12 years: male 1.1 mg, female 1.0 mg; 13–15 years: male 1.4 mg, female 1.2 mg; 16–17 years: male 1.5 mg, female 1.0 mg.

### Thiamine Deficiency

Thiamine deficiency can affect many organ systems, particularly the nervous system. Deficiency can occur with malnutrition and consumption of a diet which has high content of thiaminase-rich foods (raw fresh-water fish) or foods rich in antithiamine factors, such as tea and coffee. It has also been seen when polished rice is the staple diet as may occur in periods of food shortage and in refugee camps. Several chronic diseases, such as HIV-AIDS, gastrointestinal diseases and alcoholism may also be associated with thiamine deficiency.

Thiamine deficiency can present with nonspecific signs and symptoms in the early stages, which include anorexia, nausea,

fatigue, irritability and apathy. As the condition progresses, it presents with more definite features. The well-known syndromes associated with thiamine deficiency are beriberi and Wernicke-Korsakoff syndrome.

### Beriberi

Beriberi can affect either nervous system (dry beriberi); or cardiovascular system (wet beriberi). Infantile form occurs in breastfed infants of mothers with thiamine deficiency.

*Dry beriberi* Peripheral neuropathy is a characteristic feature of dry beriberi. There is symmetric impairment of sensory and motor functions. Distal limb segments are affected more than the proximal. Signs and symptoms include tingling, burning, tenderness, decreased tendon reflexes and loss of vibration sense. They can also have ptosis of eye lids and psychic disturbances.

*Wet beriberi* This condition is characterized by edema, tachycardia, cardiomegaly and congestive heart failure. The exact cause of edema is not clear but may be due to cardiac or renal dysfunction. Fatty degeneration of the myocardium has also been described. Untreated condition can rapidly progress leading to fatal outcome. The changes are quickly reversed on thiamine supplementation.

*Infantile beriberi* This can present with either cardiac or neurologic forms of the disease. Infants with cardiac form have tachycardia, dyspnea, cyanosis and cardiomegaly. Neurologic form can present with seizures. Untreated disease can result in death if thiamine is not supplemented rapidly.

### Wernicke Encephalopathy

Wernicke encephalopathy is characterized by the triad of ophthalmoplegia, ataxia, and mental changes. Classically thought to be a disease of chronic alcoholics, but may be seen in severely undernourished infants and children also. It has also been reported post bariatric surgery.

*Treatment* Diagnosis can be confirmed by demonstration of decreased levels of RBC transketolase. Oral administration of thiamine may be adequate in the absence of gastrointestinal disturbances. Children with cardiac failure and neurological features require 10 mg thiamine intramuscular or intravenous for 1 week followed by 3–5 mg per day for 6 weeks. Several weeks of treatment is needed for complete cure.

### RIBOFLAVIN (VITAMIN B<sub>2</sub>)

Riboflavin acts as coenzyme in many metabolic pathways and mitochondrial respiratory chain.

### Dietary Sources

Riboflavin is distributed in meats, eggs, milk, legumes, mushrooms and vegetables such as broccoli and spinach. It is resistant to heat and pasteurization but destroyed by light.

### Recommended Daily Allowance

0–6 mo: 0.3 mg; 7–12 mo: 0.4 mg; 1–3 years: 0.6 mg; 4–6 years: 0.8 mg; 7–9 years: 1.0 mg; 10–12 years: male 1.3 mg, female 1.2 mg; 13–15 years: male 1.6 mg, female 1.4 mg; 16–17 years: male 1.8 mg, female 1.2 mg.

### Deficiency

Riboflavin deficiency is observed in malnutrition and malabsorption disorders. Prolonged gastrointestinal infections and diarrhea are other causes. Phenothiazines, probenecid and oral contraceptives can also cause riboflavin deficiency.

## Clinical Features

Riboflavin deficiency presents with cheilosis (**Fig. 1**), glossitis, keratitis, conjunctivitis, photophobia, lacrimation and seborrheic dermatitis. Cheilosis is observed at the angle of the mouth which starts as pallor and progresses to maceration and fissuring. Fissures extend radially from the angle of mouth. Loss of papillae causes a smooth tongue. Impaired erythropoiesis may lead to normochromic, normocytic anemia. Eye manifestations also include circumcorneal vascularization.



**Figure 1** Angular cheilosis in a child with vitamin B complex deficiency

## Treatment

A well-balanced diet which includes milk and milk products provides adequate amounts of riboflavin. Oral administration of 3–10 mg/day of riboflavin corrects the deficiency. It can be given as part of the vitamin B complex mix.

## NIACIN (VITAMIN B<sub>3</sub>)

Niacin (nicotinamide or nicotinic acid) is a constituent of two cofactors, nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate involved in vital oxidation-reduction reactions. These compounds are important coenzymes for glycolysis, pyruvate metabolism, protein and amino acid metabolism, pentose biosynthesis and fatty acid metabolism. Niacin is essential for functioning of skin, intestinal tract, and nervous system. It is rapidly absorbed from stomach and intestine.

## Dietary Sources

Niacin is widely distributed in both vegetarian and nonvegetarian food sources such as meat, fish, poultry, cereals, legumes and green leafy vegetables. It can also be synthesized from tryptophan in eggs and milk. It is heat stable.

## Recommended Daily Allowance

0–6 mo: 710 µg/kg; 7–12 mo: 650 µg/kg; 1–3 years: 8 mg; 4–6 years: 11 mg; 7–9 years: 13 mg; 10–12 years: male 15 mg, female 13 mg; 13–15 years: male 16 mg, female 14 mg; 16–17 years: male 17 mg, female 14 mg. These intakes are expressed in terms of niacin equivalents (1 mg niacin equivalent = 1 mg niacin = 60 mg tryptophan).

## Deficiency

Niacin deficiency initially presents with nonspecific signs and symptoms such as anorexia, weakness, numbness and dizziness. Chronic and severe niacin deficiency results in classic triad of dermatitis, diarrhea and dementia referred to as *pellagra*. Primary deficiency results from inadequate niacin and/or tryptophan in the diet as occurs in those whose staple diet is maize. It can also occur with prolonged parenteral nutrition without appropriate niacin supplementation, anorexia nervosa and chronic alcoholism. Secondary deficiency can also occur when disease conditions (prolonged diarrhea, ulcerative colitis, tuberculosis of the gastrointestinal tract) interfere with niacin absorption. HIV infection induces pellagra like state which is reversible with nicotinamide treatment.

In the initial stages, cutaneous lesions of pellagra resemble sunburn. Skin becomes red and large blisters or blebs may develop which leave a dusky brown-red coloration on healing. In late stages, the skin is dry, scaly and hyperkeratotic with yellowish brown hue. Later on, it becomes darkly pigmented. The lesions are frequently seen on the dorsal surfaces of the hands, face, neck, arms and feet. In the neck it may be seen in a characteristic necklace like distribution (*Casal necklace*). Lesions may be exacerbated by exposure to sun, heat or friction.

Gastrointestinal tract disturbances include nausea, vomiting, abdominal pain and epigastric discomfort. Diarrhea may occur due to diffuse involvement of the gut. Loss of appetite and malabsorption cause malnutrition and severe weight loss.

Mental disturbances may be unnoticed in the initial stages when patient may be only apathetic and slightly depressed. Later on, neuropsychiatric manifestations may be seen as headache, irritability, fatigue, anxiety, confusion, delusions, hallucinations, tremor and disorientation. With progressive deficiency, patients may become comatosed.

## Treatment

Supplementation of 50–300 mg/day of niacin with a balanced diet rapidly corrects the deficiency. Severe cases or those with poor intestinal absorption may require intravenous niacin. Sun exposure should be avoided for skin lesions and emollients can be applied on the affected areas.

## VITAMIN B<sub>6</sub> (PYRIDOXINE)

Vitamin B<sub>6</sub> acts as a cofactor in many enzymatic reactions related to amino acid biosynthesis and carbohydrate and fatty acid metabolism. It comprises of three pyridine derivatives called pyridoxine, pyridoxal and pyridoxamine. Pyridoxal 5-phosphate is the biologically active form which is involved in the metabolism of many neurotransmitters such as dopamine, serotonin, adrenaline, and GABA. Vitamin B<sub>6</sub> is mainly absorbed in the jejunum.

## Dietary Source

Vitamin B<sub>6</sub> is widely distributed in many kinds of food including meats, pulses, cereals, vegetables and fruits. A small proportion of vitamin B<sub>6</sub> is derived from intestinal bacterial flora. The vitamin is heat-labile and may be lost during high temperature processing of cereals.

## Recommended Daily Allowance

0–6 mo: 0.1 mg; 7–12 mo: 0.4 mg; 1–6 years: 0.9 mg; 7–12 years: 1.6 mg; 13–17 years: 2 mg.

## Deficiency

Infants with vitamin B<sub>6</sub> deficiency present with irritability, apathy, seizures, vomiting and failure to thrive. Electroencephalogram

abnormalities have also been reported. Peripheral neuropathy may be seen in adults. Skin lesions can be seen in form of cheilosis, glossitis and seborrheic dermatitis. Other features associated with vitamin B<sub>6</sub> deficiency include lymphopenia, hyperglycemia, infections and microcytic anemia.

Several vitamin B<sub>6</sub> dependency syndromes due to defects in enzyme structure or function have been described which include vitamin B<sub>6</sub>-dependent seizures, vitamin B<sub>6</sub>-responsive anemia, homocystinuria and cystathioninuria. These syndromes respond to large doses of vitamin B<sub>6</sub>. During treatment of tuberculosis with isonicotinic acid hydrazide (INH), peripheral neuropathy may develop which responds to vitamin B<sub>6</sub>.

### Treatment

Child should consume a balanced diet which includes a variety of foods to meet the normal requirements. Seizures due to vitamin B<sub>6</sub> deficiency respond to 100 mg of pyridoxine. Further doses are not required with good dietary intake. 2–10 mg intramuscular or 10–100 mg oral pyridoxine daily is needed for pyridoxine dependent children.

### FOLIC ACID

Folic acid is composed of a pterin ring connected to para-aminobenzoic acid which is conjugated to one or more glutamate residues. Many naturally occurring and structurally related compounds are collectively known as folates. Folic acid (pteroylglutamic acid) is the synthetic form which is used in food fortification. Pteroylpolylglutamate is the naturally occurring folate in foods. Tetrahydrofolate is the biologically active form.

Folate coenzymes participate in many important reactions, including synthesis of deoxyribonucleic acid and purine and amino acid interconversion. It also converts homocysteine to methionine in conjunction with vitamin B<sub>12</sub> and lowers the risk of cardiovascular diseases. It is also involved in the synthesis of neurotransmitters, such as serotonin which plays important role in the regulation of mood and sleep. Folate deficiency also leads to impaired methylation reactions involved in the regulation of gene expression leading to increased neoplastic risk.

### Dietary Sources

Leafy vegetables such as spinach, turnips, lettuce, dried beans and peas; and sunflower seeds are rich sources of folates cereals, nuts and fruits are also good sources.

### Recommended Daily Intake

Infants (0–12 mo): 25 µg; 1–3 years: 80 µg; 4–6 years: 100 µg; 7–9 years: 120 µg; 10–12 years: 140 µg; 13–15 years: 150 µg; 16–17 years: 200 µg.

### Absorption

Folates are present as polyglutamates in natural foods and tissues. In the plasma, they are found as monoglutamates, the form in which they can be transported across cell membranes. Polyglutamates are converted to monoglutamates by the enzymes in the lumen of the small intestine which are absorbed in the proximal jejunum via both active and passive transport.

### Deficiency

Risk of folate deficiency is increased during periods of rapid growth as in infancy. It can also result from poor nutritional intake, malabsorption (celiac disease, inflammatory bowel disease), increased cell turnover (chronic hemolytic anemia), prolonged drug treatment (methotrexate, 6-mercaptopurine, azathioprine, phenytoin, etc.) and some inborn errors of folate metabolism (methylene tetrahydrofolate reductase deficiency).

### Clinical Features

Folate deficiency causes anemia which typically consists of macrocytosis and hypersegmented polymorphonuclear leukocytes. Anemia progresses slowly and symptoms may not be evident till hematocrit falls to very low levels. Folate deficiency leads to accumulation of homocysteine and high levels of homocysteine are associated with atherosclerotic diseases such as coronary artery disease and stroke.

Maternal folate status has been linked to spontaneous abortion, abruptio placentae and neural tube defects). Folic acid supplementation (400 µg) is recommended in the periconceptional period (1 month before and at least 3 months after) for women of child bearing age to decrease the risk. In several countries like USA and Canada, mandatory fortification of cereal grains has proved effective in reducing the incidence of neural tube defects significantly.

### Treatment

Recommended dietary allowance of folate is 100–300 µg/day. In case of deficiency states such as megaloblastic anemia, therapeutic doses of 1–5 mg/day of folate are needed along with vitamin B<sub>12</sub> for 3–4 weeks. Folate deficiency due to anti-folate medication requires elimination of the offending drug.

### VITAMIN B<sub>12</sub> (COBALAMIN)

Vitamin B<sub>12</sub> is composed of four linked pyrrole rings which surround a cobalt moiety. Methylcobalamin and 5-deoxyadenosyl are the active forms in tissues whereas cyanocobalamin is the commercially available form of B<sub>12</sub>. Vitamin B<sub>12</sub> acts as cofactor for the enzyme involved in conversion of methylmalonyl coenzyme A to succinyl coenzyme A which is an important reaction in the lipid and carbohydrate metabolism. Vitamin B<sub>12</sub> in conjunction with folate participates in conversion of homocysteine to methionine, synthesis of purines and pyrimidines, protein biosynthesis and methylation reactions. It also plays an essential role in the folate metabolism to maintain its cellular levels.

### Dietary Sources

Vitamin B<sub>12</sub> is obtained only from animal sources like muscle meat, eggs, clams, oysters and dairy products. Organs such as liver, heart and kidney have high concentrations of the vitamin.

### Recommended Daily Allowance

0.2 µg for infants and 0.2–1.0 µg for older children and adolescents.

### Absorption

Vitamin B<sub>12</sub> requires *intrinsic factor* for its absorption in the ileum. Intrinsic factor is a glycoprotein which is produced in the stomach. Its absence causes pernicious anemia where there is an inability to absorb ingested vitamin B<sub>12</sub>. A very small fraction of the vitamin is absorbed through passive diffusion. Vitamin B<sub>12</sub> is largely stored in the liver and can take years to deplete before deficiency develops.

### Deficiency

Insufficient dietary intake as in strict vegans who do not consume any animal products and impaired absorption either due to deficiency of intrinsic factor or intestinal or liver disease are common causes of vitamin B<sub>12</sub> deficiency in adults. Some drugs such as anticonvulsants, aspirin, oral contraceptives and alcoholism can also interfere with the absorption of vitamin B<sub>12</sub>. Gastrectomy, gastric bypass and medications suppressing stomach acid production are other causes of vitamin deficiency. As the deficiency takes a long time to manifest, young infants usually

do not present with clinical features unless they are exclusively breastfed by deficient mothers.

### Clinical Features

Manifestations of vitamin B<sub>12</sub> deficiency include glossitis and nonspecific gastrointestinal symptoms like nausea, vomiting and anorexia. Dermatologic signs include hyperpigmentation of the skin (**Fig. 2**), especially noticed on the knuckles and abnormal pigmentation of hair due to increased melanin synthesis. Hematologic manifestations include megaloblastic anemia which has been discussed separately. Subacute combined degeneration of the cord is a specific neurologic manifestation which presents with diffuse and progressive demyelination of the peripheral nerves, spinal cord and central nervous system.

### Treatment

Several protocols are available for treatment of vitamin B<sub>12</sub> deficiency, which will be discussed in the chapter on megaloblastic anemia.



**Figure 2** Hyperpigmentation in a child with vitamin B<sub>12</sub> deficiency

## BIOTIN

Biotin acts as a cofactor in carboxylation reactions which are involved in gluconeogenesis, fatty acid metabolism and amino acid catabolism. Biotin is widely distributed in food stuffs and deficiency is uncommon. Infants and children receiving total parenteral nutrition without biotin supplementation may develop deficiency. It may also occur in persons consuming large quantities of raw egg white which contains avidin, a biotin antagonist. Clinical features of deficiency include dermatitis, conjunctivitis, alopecia and central nervous system abnormalities. Oral administration of 2–5 mg biotin daily for 2–3 weeks corrects the deficiency.

### IN A NUTSHELL

- Vitamin B complex includes thiamine (B<sub>1</sub>), riboflavin (B<sub>2</sub>), niacin (B<sub>3</sub>), pyridoxine (B<sub>6</sub>), cobalamin (B<sub>12</sub>), biotin and pantothenic acid, all of which are water soluble.
- B-complex vitamins function as coenzymes in several enzymatic reactions.
- Poor diet can result in deficiency of one or more B complex vitamins, leading to beriberi (B<sub>1</sub> deficiency), pellagra (niacin deficiency); or megaloblastic anemia (B<sub>12</sub> deficiency).
- Malabsorption syndromes and drugs can cause secondary deficiency of vitamin B complex.
- All the B complex vitamins are supplemented together in a deficient person.
- Folate deficiency has been linked to increased incidence of neural tube defect.
- Folate supplementation is recommended in periconceptual period in women of child bearing age.

### MORE ON THIS TOPIC

- Bender DA. Vitamin B6 requirements and recommendations. *Eur J Clin Nutr.* 1989;43:289-309.
- Lee LW, Yan AC. Skin manifestations of nutritional deficiency disease in children: modern day context. *Int J Dermatol.* 2012;51:1407-18.
- Pawlak R, Parrott SJ, Raj S, et al. How prevalent is vitamin B<sub>12</sub> deficiency among vegetarians? *Nutr Rev.* 2013;71:110-7.
- Sriram K, Manzanara W, Joseph K. Thiamine in nutrition therapy. *Nutr Clin Pract.* 2012;27:41-50.
- Wan P, Moat S, Anstey A. Pellagra: a review with emphasis on photosensitivity. *Br J Dermatol.* 2011;164:1188-200.



## Chapter 22.11

# Vitamin C and Scurvy

Tejinder Singh, Shaveta Kundra

Vitamin C or ascorbic acid is a six carbon compound, structurally related to its precursor, D-glucose. It is a white crystalline, odorless, water-soluble substance with very high melting point (192°C) and a strong reducing agent. The crystalline form remains stable in dark and in dried form while in aqueous form it is attacked by high pH and temperature, atmospheric oxygen and other oxidizing agents. Pure ascorbic acid is synthesized from D-sorbitol (30 g of ascorbic acid/100 g of sugar). L-ascorbic acid and dehydroascorbic (formed from reversible conversion of ascorbic acid) acid are the active forms of vitamin C. The absorption of vitamin C occurs from the gastrointestinal tract in a dose-dependent manner. At lower intakes almost complete absorption occurs by active transport mechanism while at higher intake absorption is reduced and occurs mainly by passive diffusion. The unabsorbed ascorbic acid in the bowel lumen can cause osmotic diarrhea. Gastrointestinal disorders causing its destruction or damage can impair the ascorbic acid absorption. Excretion of ascorbic acid occurs rapidly in urine and to some extent in sweat and feces.

## PHYSIOLOGICAL FUNCTIONS

Vitamin C primarily maintains collagen formation. It acts as a coenzyme in various hydroxylation reactions; e.g., proline to hydroxyproline, an important step in collagen synthesis. It is required for tyrosine metabolism in both children and adults. For example, transient hypertyrosinemia of the newborn, which is relatively common among low-birthweight infants and to a lesser extent in term infants fed high-protein diets, can be corrected by administering ascorbic acid. Vitamin C is effective in wound healing. Deficiency of ascorbic acid leads to impaired collagen formation in the healing wounds. Ascorbic acid also is necessary for conversion of folic acid or other conjugates; deficiency may lead to megaloblastic anemia. Consumption of vitamin C along with iron increases its absorption from the gut by approximately 200–600%. When consumed with food vitamin C increases the bioavailability of both heme and non-heme iron. Vitamin C acts as a reducing agent and lowers the toxicity of several elements, e.g., selenium, nickel, lead and cadmium. The reduced forms of these elements are either poorly absorbed or excreted rapidly. Vitamin C also stimulates the production of interferon and thereby affects immune function. Vitamin C acts as an antioxidant, and plays a role in prevention of infections, protection against the effects of stress and detoxifying chemicals; and as a necessary substance in the regulation of cholesterol.

## SOURCES OF VITAMIN C

Marine fish, fresh fruits, especially citrus fruit, and vegetables (cauliflower, broccoli and cabbage) are good sources of vitamin C. Vitamin C is lost in cooking as a result of heat and oxidation. Vitamin C content of common food item is summarized in **Table 1**. Breastmilk contains adequate vitamin C provided the mother is not deficient in vitamin C. The vitamin C content of cord blood plasma is usually two to four times that of maternal plasma. Bovine milk contains very little vitamin C; thus, infants fed bovine milk formulas must receive vitamin C supplements. The requirement increases in children with febrile illness, particularly infectious and diarrheal diseases; severe malnutrition, children

**Table 1** Vitamin C content of common food items

Food group	Food items	Vitamin C content (mg/100 mg)
Green leafy vegetables	Agathi, cabbage, coriander leaves, drumstick leaves,	120–220
Other vegetables	Capsicum	137
	Green chillies	117
	Tomato	24
Fruits	Amla	600
	Guava	212
	Lemon, orange	50

with prolonged illness or hospitalization on parenteral nutrition. Iron deficiency, cold exposure and protein depletion also increase the need for vitamin C.

## RECOMMENDED DAILY ALLOWANCE (RDA)

The RDA for vitamin C is 25 mg/day for infants and 40 mg/day for older children. The requirement increases to 60–80 mg/day during pregnancy and lactation.

## VITAMIN C DEFICIENCY

Clinical manifestations of deficiency usually develop after several months of inadequate intake due to the relatively slow turnover of connective tissues. However, the symptoms can develop much more rapidly in children due to increased demands of growth. Deficiency of vitamin C results in *scurvy*, a condition in which formation of collagen and chondroitin sulfate is impaired. This results in increased tendency to hemorrhage, defective tooth dentin formation and loosening of the teeth. The shafts and epiphysis of the long bones become rarified due to failure of osteoblastic function and disrupted balance of productive and destructive processes in the bone. Number of proliferating cartilage cells is markedly reduced and their mitosis is impaired; resulting in reduced growth. Calcification of cartilaginous matrix remains uninterrupted. As a result the zone of provisional calcification gets thickened but brittle and liable to fissuring and fractures or epiphysal separation and displacement. Hemorrhage can occur under the periosteum due to capillary permeability, and can cause periosteal stripping and pain; the hematoma subsequently becomes calcified (dumbbell-shaped calcification).

## CLINICAL FEATURES

Scurvy can occur at any age. Since prolonged deprivation of vitamin C is required to deplete the tissue stores, deficiency is unusual in infants less than 6 months. Most commonly it occurs in infants between the ages of 6 months and 24 months, who are fed on boiled milk without supplements. Onset is usually abrupt in an infant who has previously appeared well.

The first symptom is pain and tenderness of the limbs, particularly in the legs. The infant screams when picked up or moved or handled during bathing or while changing the diaper. There may be obvious swelling along the shaft of legs in one or more limbs; usually on the thighs. The child is fretful and assumes a froglike position when at rest with the thighs abducted and knees slightly flexed. The swelling may sometime be extensive and involve the whole thigh. The swelling may become hard after some weeks due to deposition of calcium in the subperiosteal hematoma. The displacement of epiphysis or fragmentation of the calcified matrix at the end of the bone may cause severe pain and restriction of limb movement, resulting in pseudoparalysis.

Dental changes are appreciated after eruption of teeth. The mucous membrane becomes bluish purple, swollen and spongy especially over the upper incisors. The gums may become necrotic and the teeth shed. In severe cases, purpuric spots or spontaneous ecchymoses may appear into the skin. Bleeding may occur in brain (subdural hemorrhage), eyes (subconjunctival hemorrhage) or orbits leading to black eye. Rarely internal bleeding like hematemesis, hematuria or melena may occur. Other features include beading at costochondral junction of ribs—scorbutic rosary, depression of the sternum, moderate anemia and often mild fever. Scorbutic rosary should be differentiated from rachitic rosary (described in differential diagnosis). Anemia is normocytic or macrocytic. Fever of scurvy usually subsides with vitamin C therapy.

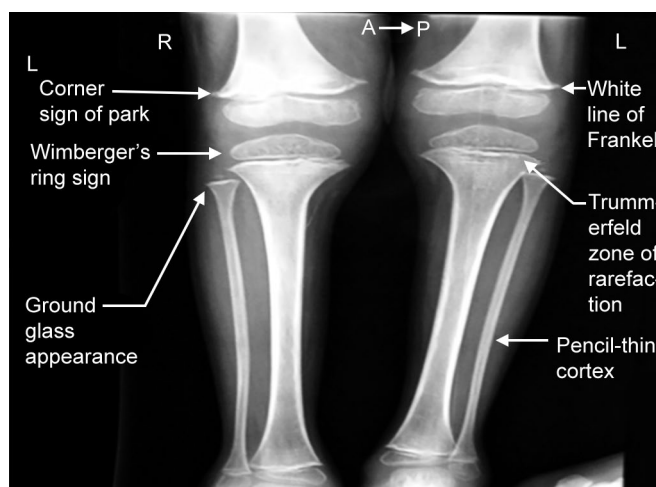
## DIAGNOSIS

The diagnosis is suggested by characteristic clinical manifestations, radiographic appearance of the long bones and history of poor vitamin C intake. Estimation of plasma vitamin C concentration or leukocyte vitamin C concentration can aid in diagnosis. Normal plasma vitamin C levels in persons with adequate consumption are 0.4–1.4 mg/dL. A continuously low plasma vitamin C level (< 0.1 mg/dL) can lead to scurvy. Leukocyte vitamin C concentrations are more useful, as these reflect the tissue levels and are independent of plasma concentration. In addition, ascorbic acid concentration of the white cell or platelet layer of centrifuged oxalated blood can be measured. Tissue saturation of vitamin C can be estimated from urinary excretion of the vitamin after test dose of ascorbic acid. In normal children, 80% of the test dose appears in the urine within 3–5 hours after parenteral administration of the test dose (11 mg/kg of ascorbic acid). There can be generalized nonspecific aminoaciduria with normal plasma amino acid concentration. In deficiency state administration of vitamin C results in tissue storage. Once tissue stores are replete, additional administration results in loss in urine. The amount of vitamin utilized can be estimated from the difference between intake and excretion of the vitamin.

## Radiological Signs of Scurvy

The characteristic changes are seen in rapidly growing bones; at shaft and growth cartilage junction (**Fig. 1**). Common sites of involvement are upper end of humerus, knee joint (lower end of femur and upper end of tibia), and sternal ends of the ribs. These signs are characteristic and depend partly on failure of osteoblastic function and partly on the occurrence of hemorrhages. The changes in the acute phase are as follows:

- Generalized osteoporosis of bone involving both the shaft and epiphysis resulting in *ground glass appearance*. There is thinning of cortex of the shaft. It may become mere pencil streak (*pencil point cortex*) or even vanish next to the epiphysal line.
- The epiphysis seems outlined with the rim of increased density standing out against the rarified bone, so called *penciling*—resembling the *signet rings*. A circular, opaque radiologic shadow surrounding the epiphysal centers of ossification is seen, known as *Wimberger sign*.
- Thickening and widening of zone of provisional calcification occurs, known as *white line of Frankel*.
- A transverse band of radiolucency appears secondary to poorly formed trabeculae in the metaphysis subjacent to the zone of provisional calcification, known as *Trümmerfeld zone* or *scurvy line*.
- The lateral projection of the calcified matrix beyond the usual limits of the shaft forms a spur (*Pelkan spur*). This is also known as *corner sign* and provides one of the most diagnostic features of scurvy. Pelkan spurs are associated with fractures of the Trümmerfeld zone and periosteal elevation.



**Figure 1** Radiological changes in scurvy  
Source: Dr Elizabeth KE, Thiruvananthapuram, Kerala.

- Adjacent to the dense calcified line, atrophy of the sub-epiphysal cortex and spongiosa casts a narrow zone of rarefaction involving the lateral aspects of the white line, which may result in partial separation of the epiphysal plate.
- Fissuring and fractures of the calcified metaphysis are common because in spite of denseness of the shadow, *the plate is brittle*. On the other hand, in spite of the cortical atrophy, diaphysal cortical fractures are rare.
- Displacement of the epiphysis, when it occurs, is indicated by faulty alignment of the epiphysal line in the shaft. Partial separation without displacement, which is more common, shows as a crack extending only part way across.
- Large subperiosteal hematomas produce regional increases in the soft tissue density. Later, calcification occurs in the hematoma, which shows in X-rays as a shell enveloping the shaft.
- In extreme cases, the X-ray skull may show *hair-on-end appearance* due to porotic hyperostosis or secondary to marrow hyperplasia in response to anemia. No changes occur in the sphenoid.

During healing, the cortex becomes thicker, spongiosa more clearly defined and the rarefied transverse areas at the ends regain normal density. Where there has been lateral displacement of the epiphysal cartilage, the new shell of the bone on the cortex aligns itself with the displaced epiphyses on treatment, leaving no permanent deformity. The contour of the shaft will be altered by the surrounding calcification for long after, but ultimately normal contour is re-established without any permanent deformity.

## DIFFERENTIAL DIAGNOSIS

The diagnosis is usually clinical with characteristic clinical features like pain and tenderness in the limbs with or without joint swelling, spongy gums and scorbutic beading of ribs. However, swelling of limb has to be differentiated from traumatic swellings (redness and warmth), osteomyelitis (high fever and leukocytosis) and osteochondritis of congenital syphilis (seen in infants < 6 months).

Pseudoparalysis of scurvy should be differentiated from that in congenital syphilis (occurs in smaller infants) from fracture (palpable fracture or crepitus) and from paralysis of poliomyelitis. In pseudoparalysis, painful stimulation of extremity will indicate that actual paralysis is not there.

In scorbutic beading, there is an abrupt step down from the rib to its cartilage, best appreciated by running a finger run along from

the lateral aspect of the rib towards the sternum. It occurs probably due to backward dislocation of the sternum due to hemorrhage between the end of the rib and the cartilage. In contrast, rickety rosary appears as rounded knobs, formed by enlargement of costochondral junction. Beading in rickets feels as a gradual sloping off to the cartilage.

The classical radiological signs like ground glass appearance, penciling of bones, dense white line at epiphysial ends with adjacent translucency and spurs usually confirm the diagnosis. However, osteoporosis alone is nonspecific. In septic arthritis radiological changes occur in the involved limb. In contrast, X-ray changes in the bones in scurvy are widespread and symmetrical. Even if scorbutic disability is confined to the upper limbs, characteristic changes can be seen in X-ray of lower extremities.

In infantile cortical hyperostosis, X-ray appearance resembles healing scorbutic lesion but absence of other features distinguishes between the two. Radiological features of epiphyseal separation or periosteal reaction can be seen in battered baby or child abuse; changes are generalized associated with multiple fractures.

## MANAGEMENT

Response to vitamin administration is dramatic. The daily therapeutic dose is 100–200 mg, oral or parenteral. Oral route permits slower absorption and is preferable to parenteral route. Intramuscular injections are avoided. Also, large amount of vitamin C is lost in urine if given by IV route. Intake of vitamin C is improved by consumption of fresh citrus fruits, orange or tomato juice. Recovery, including resumption of normal growth, is rapid with proper treatment. However, for complete recovery, prolonged treatment for up to 3 months should be taken. Pain and tenderness disappear within a week. Persistence of tenderness suggests separation of an epiphysis. Radiological improvement can be noted after 1–2 weeks of therapy with 500 mg vitamin C given orally. Even after marked displacement of an epiphysis, the alignment between the shaft and the epiphysial fragment is gradually restored with

laying down of new bone. Local treatment of the extremities is not required. The swelling of subperiosteal hemorrhage may take months to disappear.

## PREVENTION

Scurvy can be prevented by an adequate intake of vitamin C. Exclusive breastfeeding provides protection against vitamin C deficiency throughout infancy. Nonbreastfed babies should receive either vitamin C fortified formulas or adequate vitamin C-rich foods in infancy if consuming heat-treated milk. Increased supplementation is required in malnourished children and during pregnancy and lactation.

### IN A NUTSHELL

- Vitamin C is a water-soluble vitamin, lost in cooking as a result of heat and oxidation.
- Fresh citrus fruit and vegetables (cauliflower, broccoli and cabbage) are good sources of vitamin C.
- Deficiency results in scurvy; manifests as petechial hemorrhages, painful and swollen bones, and poor wound healing.
- Diagnosis is clinically supported by radiological changes.
- Oral supplementation produces dramatic improvement in symptoms.

## MORE ON THIS TOPIC

- Brickley M, Ives R. Skeletal manifestations of infantile scurvy. *Am J Phys Anthropol*. 2006;129:163–72.
- Scurvy and its prevention and control in major emergencies. Geneva: World Health Organization; 1999.
- Shah D. In: Parthasarathy A, Menon PSN, Gupta P, Nair MKC. *IAP Textbook of Pediatrics*. 5<sup>th</sup> ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2013. pp. 146–7.

## Chapter 22.12

## Vitamin D, Nutritional Rickets and Hypervitaminosis D

*S Balasubramanian*

Vitamin D refers to the precursors of the active secosteroid hormone 1,25-dihydroxyvitamin D<sub>3</sub> (1,25-OH<sub>2</sub> D<sub>3</sub>), named as calcitriol. Recognition of rickets as a childhood bone disease led to the discovery of vitamin D, a fat-soluble prohormone. In the beginning of 20th century, the antirachitic effect of cod liver oil was first described. Evidence for the fact that there are benefits extending beyond bones has resulted in renewed interest in this direction. An increasing variety of noncalcemic actions is reported in the recent times, particularly those related to decreasing risk of common cancers, autoimmune diseases, infectious diseases, heart disease, neurocognitive disorders, psychiatric illnesses, allergy, asthma, diabetes mellitus, pain and even mortality.

## EPIDEMIOLOGY OF VITAMIN D DEFICIENCY

Vitamin D deficiency is considered as the most under-diagnosed and under-treated nutritional deficiency in the world and is widely prevalent in all parts of the world irrespective of age, gender, race and geography. The prevalence in India is reported to be as high as 70–100% in the general population. The reasons for this are factors, such as non-fortification of dairy products, socioreligious and cultural practices not facilitating adequate sun exposure. As a consequence, subclinical vitamin D deficiency is prevalent in epidemic proportions in both urban and rural settings, and across all socioeconomic and geographic strata in the society. The other reasons for the high prevalence include vegetarianism, low calcium intake, high phytate diet, lactose intolerance and genetic factors.

## ETIOLOGY OF VITAMIN D DEFICIENCY

Vitamin D deficiency is common in infants who are dark-skinned and exclusively breastfed beyond 3–6 months of age, particularly in the background of maternal vitamin D deficiency during pregnancy or prematurity. Vitamin D deficiency is also common among children who are on vegetarian and unusual diets, use anticonvulsant or antiretroviral medications, or those with malabsorption. Additional risk factors include residence at higher latitudes, winter season, and other causes of low sun exposure (**Box 1**). Genetic pleomorphism predisposing individuals to vitamin D deficiency rickets has been recently reported.

## VITAMIN D METABOLISM

Vitamin D<sub>2</sub> (ergocalciferol) is obtained only from diet, whereas vitamin D<sub>3</sub> (cholecalciferol) is found in cod liver oil and oily fish and is the form synthesized in skin. Sunlight, specifically ultraviolet B rays in the 290–315 nm range, converts 7-dehydrocholesterol (present in skin) to previtamin D<sub>3</sub>. At normal skin temperature, previtamin D<sub>3</sub> thermally isomerizes during a period of hours to vitamin D<sub>3</sub>. It binds to vitamin D-binding protein and is transported to the liver for 25-hydroxylation and then to the kidney. The vitamin D binding protein-25OHD complex is excreted and then reabsorbed in the proximal tubule through the endocytic receptors megalin and cubilin, where it undergoes 1-hydroxylation by CYP27B1 resulting in the active metabolite 1,25-dihydroxyvitamin D [calcitriol, 1,25(OH)<sub>2</sub>D]. 1,25(OH)<sub>2</sub>D binds to the vitamin D receptor, which heterodimerizes with the retinoic acid receptor, to form a ligand-receptor complex that targets specific response elements on the genome (**Fig. 1**).

## BOX 1 Etiology of vitamin D deficiency

## Disorders of vitamin D synthesis

- Increased skin pigmentation
- Topical application of sunscreen agents
- Overclothing preventing sunlight exposure
- High-rise buildings and urbanization

## Geographical location

- Latitude (> 400 north or south)
- Winter season
- Air pollution, cloud cover
- High altitude
- Avoidance of sunlight for cosmetic reasons and fear of skin cancer

## Decreased intake of vitamin D—vegetarianism

## Decreased maternal vitamin D stores and exclusive breastfeeding

## Malabsorption

- Celiac disease
- Pancreatic insufficiency
- Chronic cholestasis

## Decreased synthesis or increased degradation of 25(OH)D

- Chronic liver disease
- Drugs (rifampicin, isoniazid, antifungals, anticonvulsants)
- Genetic factors.

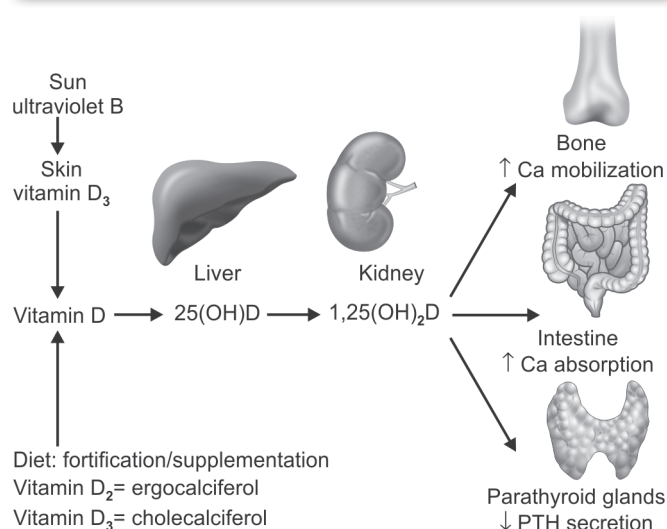


Figure 1 Vitamin D metabolism

## MECHANISM OF ACTION

Maintaining an adequate level of serum calcium and phosphorus is the most important biochemical function of vitamin D without which only 10–15% of dietary calcium and about 60% of phosphorus will be absorbed. Vitamin D receptors exist in a variety of cells responsible for the biological effect on more than mineral metabolism. The primary action of 1,25(OH)<sub>2</sub>D is to stimulate intestinal calcium absorption. Vitamin D sufficiency increases calcium and phosphorus absorption. The interaction of 1,25(OH)<sub>2</sub>D with its receptor in the osteoblast stimulates the expression of receptor activator of a nuclear factor ligand, which interacts with receptor activator of a nuclear factor resulting in induction of immature monocytes to become mature osteoclasts, which in turn results in dissolution of the matrix and mobilization of calcium and other minerals from the skeleton. In addition, 1,25(OH)<sub>2</sub>D also stimulates calcium reabsorption from the glomerular filtrate.

Most tissues and cells in the body contain receptors for 1,25(OH)<sub>2</sub>D which has a wide range of biological actions, including inhibiting cellular proliferation and inducing terminal differentiation, inhibiting angiogenesis, stimulating insulin production, inhibiting renin production, and stimulating macrophage cathelicidin production. In addition, 1,25(OH)<sub>2</sub>D stimulates its own destruction



by enhancing the expression of the 25-hydroxyvitamin D-24-OHase (CYP24R) to metabolize 25(OH)D and 1,25(OH)<sub>2</sub>D into water-soluble inactive forms. Several tissues and cells possess 1-OHase activity. Locally produced 1,25(OH)<sub>2</sub>D in various tissues may be involved in the regulation of up to 200 genes, thereby facilitating many of the pleiotropic health benefits due to vitamin D. Though the conversion to the active 1,25(OH)<sub>2</sub> form is tightly regulated by parathyroid hormone (PTH) and low levels of calcium and phosphorus, the conversion of D to 25(OH)D is not well regulated. PTH is released from the parathyroid gland in response to decreased calcium and/or elevated phosphorus levels. PTH stimulates the kidneys to increase calcium resorption and activate CYP27B1 to synthesize more 1,25(OH)<sub>2</sub>D and activates osteoblasts that facilitate the conversion of preosteoclasts to osteoclasts. Osteoclasts dissolve bone to free up calcium to correct the effects of deficiency that originally activated the parathyroid gland to secrete PTH. Production of excess of active vitamin D is inhibited by a negative feedback loop. 1,25(OH)<sub>2</sub>D inhibits PTH, stimulates the release of fibroblast growth factor 23 (FGF23) from osteoblasts, and also induces the enzyme CYP24A1. FGF23 reduces circulating phosphorus by altering kidney production of a sodium-phosphorus cotransporter and inhibits the vitamin-D-activating enzyme CYP27B1. CYP24A1 enzyme places a hydroxyl group on C-24 of 1,25(OH)<sub>2</sub>D, facilitating its metabolism into calcitriol and subsequent excretion in the bile.

## DAILY REQUIREMENTS AND SOURCES

For most humans, vitamin D comes from exposure of the skin to sunlight. When compared with ingested vitamin D, what is produced in the skin may last at least twice as long in the blood. The recommended dietary allowance of vitamin D for children 1–18 years, pregnant and lactating women is 600 IU (15 mcg) daily. This intake can be provided in the diet or as a vitamin D supplement. The estimated adequate intake for infants up to 12 months is 400 IU (10 mcg) daily. Routine supplementation of vitamin D to exclusively breastfed infants is yet not recommended in India.

The present recommendations for dietary vitamin D intake are primarily based upon the beneficial effects of calcium and vitamin D on skeletal health. The evidence supporting a benefit of vitamin D on extraskeletal outcomes has so far been weak, inconsistent, inconclusive as to causality and insufficient and, therefore, has not been used as a basis for dietary reference intake development.

## RICKETS

The pathological definition of rickets, the failure to mineralize newly formed bone, means that preformed osteoid is unmineralized (osteomalacia) and endochondral calcification at the growth plate is absent or reduced with associated growth-plate deformity. Rickets and osteomalacia are both disorders of deficient mineralization of organic matrix, but with fundamental differences. Rickets is a disease of the physes (growth plates) characterized not only by deficient mineralization of cartilage and osteoid but also by retarded endochondral ossification, which causes excessive accumulation of physal cartilage, growth failure and skeletal deformities. The abnormalities of mineralization and ossification are caused by insufficient circulating levels of calcium and phosphate ions. As rickets is a disorder of open growth plates, it is seen only in children and manifests mostly during infancy (usually less than 18 months of age) and the adolescent growth spurt. In osteomalacia, an insufficient  $\text{Ca} \times \text{P}$  product causes failure of normal mineralization of osteoid, laid down either at sites of bone turnover or by the periosteum in the process of membranous bone formation. These processes occur in both adults and children. Hence, osteomalacia can be present at any age. Abnormalities of mineral ion homeostasis lead to skeletal deformity by disrupting endochondral ossification rather than just causing deficient mineralization of cartilage and osteoid.

## Staging of Rickets

### Stage I

Following vitamin D deficiency, intestinal absorption of calcium declines causing hypocalcemia, which can be clinically silent or lead to seizures or other manifestations. In response, secondary hyperparathyroidism (HPTH) develops, mobilizing calcium and phosphate from bone, increasing renal calcium reabsorption and phosphate excretion, and upregulating renal 25-hydroxyvitamin D-1 $\alpha$ -hydroxylase (1-OHase) to increase calcitriol and, hence, intestinal calcium absorption.

### Stage II

There is normalization of circulating calcium. PTH and alkaline phosphatase (ALP) are elevated and there is hypophosphatemia. Calcitriol levels can be elevated at this time, hence, their measurement is generally not useful in the diagnosis of vitamin D deficiency. At this stage, physal manifestations of rickets become apparent clinically and radiographically.

### Stage III

With worsening vitamin D deficiency, substrate 25-hydroxyvitamin D (25D) levels fall low enough that calcitriol can no longer be maintained despite PTH stimulation of 1-OHase. This leads to decreased intestinal calcium absorption, return of hypocalcemia, worsening of secondary HPTH, and florid clinical and radiographic features of rickets.

## Clinical Features

Florid skeletal features are most prevalent between 3 months and 18 months of age due to development of deformities of weight-bearing limbs. In infants, deformities occur in the forearms, whereas, in toddlers, bow legs (genu varum) (**Fig. 2**) or knock knees (genu valgum) are often seen. Craniotabes, poor growth in height and weight, frontal bossing of the skull, swelling of wrists, knees and ankles and increased sweating are frequently present. *Rachitic rosary* (**Fig. 3**) due to expansion of the costochondral junctions and an inward diaphragmatic pull of the soft rib cage gives rise to Harrison's sulcus (groove). Dentition may be delayed, and development of tooth enamel may be impaired. Irritability, secondary to bone pain, is a common feature in rachitic infants. Muscle weakness leads to hypotonia and delayed motor development, such as late walking. Adolescents with rickets usually present with vague symptoms, such as aches and pains in lower limbs, often with exercise. Muscle weakness and the proximal myopathy may cause difficulty in climbing stairs. Hypocalcemic tetany may occur in adolescents. Florid signs of rickets are rare in adolescents. Pelvic deformities that develop during female adolescence can later lead to obstructed labor due to cephalopelvic disproportion.

## Diagnosis

### Biochemical Changes

Elevated ALP is a reliable marker of disease activity because it participates in the mineralization of bone and growth plate cartilage. ALP levels are normal up to 500 IU/L in neonates and 1,000 IU/L in children up to 9 years of age and decrease after puberty. Serum phosphorus concentrations usually are low in both calcipenic and phosphopenic rickets. Serum calcium levels are usually low in calcipenic rickets, but may be normal in some stages of the disease due to secondary HPTH. The serum concentration of PTH is elevated in calcipenic rickets but is normal in phosphopenic rickets (**Table 1**).

### Radiographic Findings

The following findings may be seen: (a) widening of the epiphyseal plate; (b) cupping and splaying of the epiphyseal end

of metaphysis with stippling and formation of cortical spurs; (c) delay in appearance of the epiphyseal bone centers which are small and osteopenic; (d) osteopenic shafts of the long bones and thin cortices; (e) fuzzy trabecular pattern which is coarse, with a ground-glass appearance; and (f) deformed shafts of the long bones (**Figs 4 and 5**). Extreme deficiency *may lead to* pathological fractures and looser zones (Milkman's fractures). Looser zones are pseudofractures, narrow radiolucent lines, 2–5 mm wide, with sclerotic borders, and are typical findings in osteomalacia and are bilateral and symmetric and lie perpendicular to the cortical margins of bones. *Milkman syndrome* is the combination of multiple, bilateral and symmetric pseudofractures.

### Bone Mineral Density

In those with osteomalacia related to vitamin D deficiency, markedly reduced spine, hip and forearm bone density [as measured by dual-energy X-ray absorptiometry (DXA)] may be observed though bone mineral density (BMD) is not necessarily required for the diagnosis of osteomalacia, and reduced BMD does not distinguish osteoporosis from osteomalacia.

### Vitamin D Levels

Measurement of 25(OH)D levels is the ideal tool to assess vitamin D status. 25(OH)D is the main circulating form of vitamin D and has a half-life of 2–3 weeks in contrast to 1,25(OH)<sub>2</sub>D which has a shorter



**Figure 2** Bowlegs and double malleoli in a child with rickets



**Figure 3** Rachitic rosary



**Figure 4** Skiagram of the chest showing widening of the anterior ends of the ribs and decreased bone density



**Figure 5** Skiagram of the wrist showing cupping, fraying and decreased bone mineral density

**Table 1** Stages of vitamin D deficiency in relation to biochemical markers and radiographic features

Stages	Plasma calcium	Plasma phosphorus	ALP	PTH	25(OH)D	1,25(OH) <sub>2</sub> D3	Radiography
Early	N / ↓	↓	↑	↑	↓	N	Osteopenia
Moderate	N / ↓	↓	↑	↑↑	↓	↑	Rachitic changes 1+
Severe	↓↓	↑↓	↑↑	↑↑	↓↓	↑ / N / ↑	Rachitic changes 2+

half-life of about 4 hours. Measurement of  $1,25(\text{OH})_2\text{D}$  is neither reliable nor recommended for assessment of vitamin D stores. For children with calcipenic rickets, measurement of serum  $25(\text{OH})\text{D}$  helps to distinguish rickets caused by vitamin D deficiency from other causes of calcipenic rickets. Serum concentration of  $25(\text{OH})\text{D}$  accurately reflects the amount of vitamin D stored in the body, and, hence is low in nutritional rickets, whereas it is normal or slightly increased in the other forms of rickets.  $1,25(\text{OH})_2\text{D}$  can be low, normal or increased in calcipenic rickets.  $1,25(\text{OH})_2\text{D}$  levels paradoxically may initially increase in response to rising levels of PTH, but may subsequently decrease because its substrate,  $25(\text{OH})\text{D}$ , is limited but is always increased in VDDR type II and hypophosphatemic rickets.

Majority of children with vitamin D deficiency rickets have serum  $25(\text{OH})\text{D}$  concentrations less than 25 nmol/L (10 ng/mL), and often less than 12.5 nmol/L (5 ng/mL), though serum  $25(\text{OH})\text{D}$  concentrations may not be markedly reduced in overtly rachitic children who have low dietary calcium intake. The most widely accepted standards for defining vitamin D status in children and adolescents are: vitamin D *sufficiency*:  $25(\text{OH})\text{D}$  more than or equal to 20 ng/mL; vitamin D *insufficiency*: 15–20 ng/mL; and vitamin D *deficiency*:  $\leq 15$  ng/mL. A level less than 5 ng/mL has been considered as an indicator of *severe deficiency* (Table 2). Values of more than 100 ng/mL are considered as vitamin D *excess* and above 150 ng/mL as *intoxication*.

## Treatment

The ideal treatment for vitamin D deficiency consists of administration of vitamin  $\text{D}_3$  (cholecalciferol) since ergocalciferol ( $\text{D}_2$ ) is not widely available. The dose recommended for treatment of vitamin D deficient rickets is 1,000 IU daily for newborns less than 1 month, 1,000–5,000 IU daily for infants 1–12 months old, and 5,000–10,000 IU daily for children 1 year and older. Treatment should be continued until there is biochemical evidence of recovery and radiographic evidence of healing which usually occurs by 12 weeks. Thereafter, the dose of vitamin D can be reduced to 400 IU/600 IU daily. Calcium intake should be maintained at 50–75 mg/kg of elemental calcium per day in three divided doses to avoid *hungry bone syndrome*. Skeletal deformities regress completely if appropriate medical therapy is given.

*Stoss therapy* consists of administration of (a) high dose of oral vitamin D (600,000 IU) given on a single day, then maintained at 400–1,000 IU of vitamin D per day; or (b) 50,000 IU of vitamin  $\text{D}_2$  weekly for 8 weeks orally (teenagers) followed by 400 IU/day. This regime however, has a potential for hypercalcemia. Lesser doses of 150,000 or 300,000 IU have been reported to be equally effective with lesser side effects. Since normalization of vitamin D status may not be achieved after 12 weeks even in those given single high

**Table 2** Vitamin D status based on  $25(\text{OH})\text{D}$  levels

Vitamin D status	Levels
<i>US IOM classification</i>	
Severe deficiency	$\leq 12.5$ nmol/L or 5 ng/mL
Deficiency	$\leq 37.5$ nmol/L or 15 ng/mL
Insufficiency	37.5–50 nmol/L or 15–20 ng/mL
Sufficiency	50–200 nmol/L or 20–100 ng/mL
Excess	$> 250$ nmol/L or $> 100$ ng/mL
Intoxication	$> 375$ nmol/L or $> 150$ ng/mL
<i>US Endocrine Society classification</i>	
Deficiency	$< 20$ ng/mL (50 nmol/L)
Insufficiency	21–29 ng/mL (52.5–72.5) nmol/L
Sufficiency	$> 30$ ng/mL
Toxicity	$> 150$ ng/mL

1 mcg = 40 IU; 0.025 mcg is 1 IU

dose stoss therapy, it is necessary to recheck the vitamin D status 12 weeks after initiating therapy (Table 3).

## Prevention

Sun exposure allows for cutaneous vitamin D synthesis. During most seasons, 10–15 min of sun exposure near midday is sufficient for adequate vitamin D synthesis in light-skinned individuals. However, darker skin pigmentation, winter season, or northern latitudes can markedly reduce skin synthesis of vitamin D and increase the need for dietary sources. Studies are necessary to assess the impact of these recommendations in dark-skinned children, and it is possible that relaxation of these measures in dark-skinned children will allow for sufficient cutaneous vitamin D synthesis in the summer months, particularly at lower latitudes.

*American Academy of Pediatrics* recommends that all exclusively breastfed infants should receive 400 IU/day of vitamin D supplements, based on the fact that breastmilk has very low vitamin D content, and that cutaneous vitamin D synthesis from sun exposure is inconsistent and unpredictable. At present, there are no such recommendations for Indian infants. Standards for defining vitamin D sufficiency in healthy children are not well established. In children, radiological changes of rickets and low bone density have been reported at  $25(\text{OH})\text{D}$  levels of less than 16–18 ng/mL (40–45 nmol/L), and ALP levels have been noted to rise at  $25(\text{OH})\text{D}$  levels less than 20 ng/mL (50 nmol/L). At this time, there is little evidence from studies in children to indicate that vitamin D levels above the threshold of 20 ng/mL (50 nmol/L) are necessary to optimize calcium absorption or bone density.

**Table 3** Treatment regimens for vitamin D deficiency

Age group	Daily regimen (8–12 weeks)	Weekly regimen (8–12 weeks)	Stoss therapy	Maintenance dosage
$< 1$ month	1,000 IU	50,000 IU*	Not Recommended	400–1,000 IU/day
1–12 month	1,000–5,000 IU	50,000 IU	1 lakh–6 lakhs units over 1–5 days oral (preferably 3 lakhs)**	400–1,000 IU/day
1–18 years	5,000 IU	50,000 IU	3–6 lakhs units over 1–5 days oral**	600–1,000 IU/day
Any age with obesity, malabsorption syndrome or those on medications affecting vitamin D status	6,000–10,000 IU/day			3,000–6,000 IU/day

\* To convert (IU) to mcg of calciferol, divide by 40.

\*\* Parenteral (intramuscular) therapy—best avoided unless there is severe malabsorption or concern for compliance to oral regimens.



## VITAMIN D TOXICITY

Despite robust skin production, vitamin D toxicity cannot occur from skin production. This is due to the fact that once maximum cutaneous production occurs, additional sun exposure will not result in additional net input to the system. The same ultraviolet B (UVB) that produces vitamin D in the skin also degrades it, causing a steady state that limits cutaneous production to a maximum of ~20,000 IU/day. There have been no reports of vitamin D toxicity from either sun exposure or from exposure to artificial UVB light. The intake at which the dose of vitamin D becomes toxic is not clear. The suggested *tolerable upper intake level* (UL) for vitamin D is 100 micrograms (4,000 IU) daily for healthy adults and children 9–18 years.

Vitamin D intoxication generally occurs after inappropriate use of vitamin D preparations. Symptoms of acute intoxication are due to hypercalcemia and include confusion, polyuria, polydipsia, anorexia, vomiting, and muscle weakness. Long-term intoxication can cause bone demineralization and pain. In children, the hypercalcemia can cause brain injury. Chronic intoxication may cause nephrocalcinosis and bone demineralization (**Box 2**). Diagnosis of vitamin D toxicity is confirmed by high serum calcium, high serum vitamin D 25(OH) and normal PTH.

### Treatment

The main goal of treatment is correction of hypercalcemia. Emergency intervention is necessary when the calcium exceeds 14 mg/dL. Effects of toxicity may last for months because of storage in fatty tissues. Treatment measures include: discontinuation of intake; diet low in calcium and phosphorus. Acute toxicity will require intravenous hydration with saline; and loop diuretics, furosemide. Corticosteroids, calcitonin and bisphosphonates have also been used.

#### BOX 2 Symptoms of vitamin D toxicity

Hypercalcemia  
Hypercalciuria  
Kidney stones  
Hyperphosphatemia  
Polyuria  
Polydipsia  
Ectopic calcification of soft tissues (kidney and lung)  
Nausea/vomiting  
Anorexia  
Constipation  
Headache  
Hypertension

## IN A NUTSHELL

1. There has been increasing interest in the recent times on the role of vitamin D, the sunshine hormone not only in skeletal disorders but also in relation to its benefits on extraskeletal health.
2. There is a high prevalence of vitamin D deficiency in India cutting across age, sex and geographical location.
3. The options available for prevention of vitamin D deficiency include sensible sunlight exposure, changes in dietary habits, routine supplementation and food fortification.
4. Nutritional rickets manifests mostly in infants and toddlers with bony deformities. Vitamin D deficiency in infancy may also present with hypocalcemic seizures.
5. Measurement of 25(OH)D levels is the ideal method to determine and define the vitamin D status. Measurement of alkaline phosphatase levels in plasma is a useful screening test for vitamin D deficiency.
6. Treatment of deficiency with vitamin D<sub>3</sub> with a variety of regimens have been recommended which are equally effective.
7. Hypervitaminosis D manifesting with features of hypercalcemia needs to be recognized early and appropriately treated to prevent serious consequences.

## MORE ON THIS TOPIC

- Balasubramanian S, Dhanalakshmi K, Amperayani S. Vitamin D deficiency in childhood—a review of current guidelines on diagnosis and management. *Indian Pediatr*. 2013;50:669-75.
- Elder CJ, Bishop NJ. Rickets. *Lancet*. 2014;383:1665-76.
- Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911-30.
- Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know? *J Clin Endocrinol Metab*. 2011;96:53-8.
- Sahay M, Sahay R. Rickets-vitamin D deficiency and dependency. *Indian J Endocrinol Metab*. 2012;16:164-76.
- Shaw NJ, Mughal MZ. Vitamin D and child health part 1 (skeletal aspects). *Arch Dis Child*. 2013;98:363-7.
- Shore RM, Chesney RW. Rickets: Part I. *Pediatr Radiol*. 2013;43:140-51.
- Shore RM, Chesney RW. Rickets: Part II. *Pediatr Radiol*. 2013;43:152-72.



## Chapter 22.13

# Iodine Deficiency Disorders

Umesh Kapil, Neha Sareen

Iodine deficiency is the most prevalent and most common preventable cause of mental deficiency in the world today. Iodine-deficiency disorders (IDDs), which may originate before birth, jeopardize children's mental health and often their very survival. Serious iodine deficiency during pregnancy can result in stillbirth, spontaneous abortion and congenital abnormalities, such as cretinism, a grave, irreversible form of mental retardation that affects people living in iodine-deficient areas. IDDs refer to all of the consequences of iodine deficiency in a population that can be prevented by ensuring an adequate intake of iodine.

Iodine is one of the essential elements required for normal human growth and development. Its daily per capita requirement is 150 micrograms. Iodine is also required for the synthesis of the thyroid hormones, thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>). These hormones which are iodinated molecules of the essential amino acid tyrosine regulate cellular oxidation and, hence, affect calorogenesis, thermoregulation and intermediary metabolism. The thyroid hormones are necessary for protein synthesis, and they promote nitrogen retention, glycogenolysis, intestinal absorption of glucose and galactose, lipolysis and uptake of glucose by adipocytes. Synthesis and secretion of T<sub>4</sub> and T<sub>3</sub> are under the control of the thyroid-stimulating hormone (TSH) which is secreted from the anterior lobe of the pituitary gland. TSH stimulates iodide transport from the blood into thyroid cells, oxidation of iodide to iodine, and iodine binding to tyrosine. Synthesis of thyroid hormones is regulated by the levels of circulating free T<sub>4</sub> and T<sub>3</sub> as a negative feedback mechanism.

## RECOMMENDED DAILY INTAKE

- 90 µg for preschool children (0–59 months);
- 120 µg for schoolchildren (6–12 years);
- 150 µg for adolescents (above 12 years) and adults;
- 250 µg for pregnant and lactating women.

Eating seafood does not ensure adequate dietary iodine sufficiency. Iodine deficiency in population residing at sea coast has been documented from pockets of Azores, Bangkok, Manila, Goa, Mumbai, Kerala, Andaman and Nicobar Islands. New areas, which were relatively free of this problem, are now being identified as iodine-deficient possibly because of intensive agricultural technologies and multiple cropping.

Presence of certain substances (goitrogens) which adversely influence the utilization of iodine in staple foods is also recognized as one of the etiological factors for IDD. They are generally present as thioglycosides or glucosinolates, the glucan portion of which is responsible for its goitrogenicity. Other chemical substances, such as thiocyanates, thio-oxazolidinone, flavonoids, disulfides, phenols, phthalates, biphenyls and lithium, found in environment are also included in goitrogens category. These goitrogens are known to interfere with iodine metabolism at various stages or levels. Some of these substances are found in abundance in certain tubers and vegetables, like tapioca, cabbage and cauliflower.

## PATHOPHYSIOLOGY

Iodine is present in the soil and is ingested through foods grown on that soil. Iodine is present in the superficial layers of the soil and absorbed by crops grown on it. Glaciations, heavy snow and heavy rain leach away iodine from the soil. The erosion of soils in

riverine areas due to loss of vegetation for agricultural production, overgrazing by livestock, and tree-cutting for firewood results in a continued and increasing loss of iodine from the soil. Groundwater and food grown locally in these areas lack iodine. Consumption of crops and plants grown on iodine deficient soils leads to iodine deficiency in populations solely dependent on this vegetation for their iodine requirements. Iodine deficiency in food and water leads to less availability of iodine to thyroid gland for synthesis of T<sub>3</sub> and T<sub>4</sub>. As a result, the thyroid gland becomes hyperactive to produce the requisite amounts of T<sub>3</sub> and T<sub>4</sub> thereby enlarging itself by hyperplasia. This enlargement of the thyroid gland is known as goiter.

The healthy human body contains 15–20 mg of iodine, of which about 70–80% is present in the thyroid gland. The thyroid gland which weighs only 15–20 g possesses a remarkable concentrating power for iodine. Thyroid function is essential for normal growth and development. Thyroid hormone deficiency, whether produced by removal or absence of the thyroid due to disease or congenital defects is associated with severe retardation of growth and maturation of almost all organ systems. The most critical period for the brain in human life cycle is from the second trimester of pregnancy to the first year after birth. In areas of iodine deficiency, where thyroid hormone levels are low, brain development is impaired. In its most extreme form, this result in cretinism, but of much greater public health importance are the more subtle degrees of brain damage and reduced cognitive capacity which affects the entire population. As a result, the mental ability of normal children living in areas of iodine deficiency is reduced.

Simple goiter is due to a lack of iodine in diet due to iodine deficiency in soil, ingestion of a goitrogen, or a demonstrable defect in a hormone biosynthetic pathway, leading to impaired thyroid hormone synthesis. It could also be due to when one or more factors impair the capacity of the thyroid to secrete active hormones sufficient to meet the needs of the peripheral tissues. The depletion of glandular organic iodine accompanying impaired hormone synthesis increases the responsiveness of thyroid structure and function to levels of TSH that remain within the normal range. When the underlying disorder is severe, compensatory responses, including hypersecretion of TSH, are inadequate to overcome the impairment, and the patient is both goitrous and hypothyroid. Thus, simple goiter cannot be clearly separated in the pathogenetic sense from goitrous hypothyroidism. Initially, goiter is characterized by diffuse, homogenous enlargement, but over time nodules often develop.

## HEALTH CONSEQUENCES OF IODINE DEFICIENCY

Iodine deficiency affects all the stages of human development starting from the fetal life (**Box 1**). If the diet of a pregnant woman lacks iodine, the fetus is also deprived of adequate iodine and, hence, cannot produce enough thyroxine. This may lead to fetal growth retardation (**Fig. 1**). Hypothyroid fetuses often perish in the womb, and many infants die within few weeks of birth. Those born with hypothyroidism have global developmental delay and remain intellectually subnormal with low IQ. They are often incapable of completing school. In areas with prevalence of mild to moderate iodine deficiency, the school children are on an average 13.5 points of IQ below those living in iodine-sufficient areas.

### BOX 1 Spectrum of iodine deficiency disorders

1. *Fetus*: Abortions, stillbirths, congenital abnormalities, neurological cretinism, mental deficiency, deaf mutism, spastic diplegia, squint myxedematous cretinism and dwarfism
2. *Neonate*: Neonatal hypothyroidism, mental deficiency
3. *Childhood and adolescence*: Goiter, hypothyroidism, dwarfism, impaired mental function, poor school performance



**Figure 1** A 3-months-old infant with hypothyroidism. Note abdominal distension, large tongue, umbilical hernia and dry skin.  
Source: PSN Menon, Anurag Bajpai.

### Effects on Growing Brain

Severe iodine deficiency during pregnancy increases risk of stillbirths, abortions and congenital abnormalities. Iodine supplementation to pregnant women in regions of severe deficiency reduces fetal and perinatal mortality and improves motor and cognitive performance of the offspring. Maternal thyroxine crosses the placenta before onset of fetal thyroid function at 10–12 weeks. The most serious adverse affect of iodine deficiency is brain damage to the fetus. The critical period for maximal brain growth and maturation comprises the last 6 months of gestation and the first year of life. Iodine is required for the synthesis of thyroid hormones, which exert action through binding of triiodothyronine (T<sub>3</sub>) to nuclear receptors. These nuclear receptors regulate the expression of specific sites in different brain regions following a precise developmental schedule. Biochemical data indicates that thyroid hormones also have an effect on RNA polymerase II in assembling messenger RNA, influence tRNA sulfurtransferase, which confers the release of polypeptide chains from ribosomes and play an important role in the timing, rate and quantity of brain cell proliferation. The growth and differentiation of the central nervous system is closely related to iodine and thyroid hormones and impairment of cerebral functions in the fetus is directly related to maternal thyroxinemia. Iodine induced hypothyroidism during the fetal period also leads to a decrease in the proportion and density of radial glial cells fibers of the hippocampal formation of the brain.

Extensive experimental studies have been done on animals to demonstrate effect of severe iodine deficiency on the brain of neonates. Postnatal morphogenesis of the nervous system in animals thyroidectomized at birth showed a decrease in axodendritic connections primarily in the neuropil, small size and abnormally densely packed perikarya and reduced number of axons and dendrites in the interperikaryonal space.

### ASSESSMENT OF IODINE DEFICIENCY

#### Total Goiter Rate

Clinically, presence of goiter (**Fig. 2**) is considered a marker of iodine deficiency. WHO staging of goiter is listed in **Box 2**. The size of the thyroid gland changes inversely in response to alterations in iodine intake, with a lag interval that varies from a few months to several years, depending on many factors. These include the severity and duration of iodine deficiency, the type and effectiveness of iodine supplementation, age, sex, and possible additional goitrogenic factors. According to WHO, total goiter rate (TGR, goiter grades 1 and 2) of 5% or more, in 6–12



**Figure 2** Goiter in a school-age child  
Source: Dr Umesh Kapil.

years school children should be utilized to signal the presence of a public health problem. The cutoff of 5% allows some margin of inaccuracy of goiter assessment and also for goiter which may occur in iodine replete population due to other causes such as goitrogens and autoimmune thyroid diseases. TGR of 5–19.9, 20–29.9, and more than or equal to 30% indicate mild, moderate, and severe endemicity of iodine deficiency.

#### BOX 2 Simplified classification of goiter\* by palpation

Grade 0	No palpable or visible goiter
Grade 1	A goiter that is palpable but not visible when the neck is in the normal position (i.e., the thyroid is not visibly enlarged). Thyroid nodules in a thyroid, which is otherwise not enlarged, fall into this category.
Grade 2	A swelling in the neck that is clearly visible when the neck is in a normal position and is consistent with an enlarged thyroid when the neck is palpated.
*A thyroid gland will be considered goitrous when each lateral lobe has a volume greater than the terminal phalanx of the thumbs of the subject being examined.	

#### 24-hour Urinary Iodine

Excretion in school-age children ( $\geq 6$  years) is considered a good marker of recent dietary iodine intake. Twenty-four-hours urinary iodine more than 100  $\mu\text{g/L}$  is a valid indicator of iodine sufficiency. About 300 casual samples of urine from a given population group provides valid estimates of iodine status in a community. Median urinary iodine less than 20, 20–49, 50–99  $\mu\text{g/L}$  indicate severe, moderate or mild iodine deficiency in a given population.

#### Thyroid-stimulating Hormone

It can serve as another marker for iodine deficiency. TSH in neonates is a valuable indicator for assessing iodine deficiency. The neonatal thyroid has a low iodine content compared to that of the adult, and hence, iodine turnover is much higher. This high turnover, which is exaggerated in iodine deficiency, requires increased stimulation by TSH. Hence, TSH levels are increased in iodine-deficient newborns in the first few weeks of life. The prevalence of neonates with elevated TSH levels is, therefore, a valuable indicator to assess the severity of iodine

deficiency in a population. Methods for determining TSH concentrations are: from either dried whole blood spots on filter paper or from serum. These methods are well established and widely available. The number of neonates with moderately elevated TSH concentrations (above 5 mIU/L whole blood) is proportional to the degree of iodine deficiency during pregnancy. When less than 3% of children show more than 5 mIU/L of TSH, this indicates iodine sufficiency in a population. Thyroglobulin reference interval for iodine-sufficient school children is 40 µg/L.

## PREVENTION

There are several modes of iodine supplementation used for prevention of IDD. These are: iodized salt, iodized oil, iodized capsules, iodized bread and iodized water. Out of these, the most effective method is iodized salt. This is because salt is one food item which is taken in a fixed amount everyday by everybody, whether rich or poor, old or young. Thus, salt is an ideal vehicle for supply of constant amount of iodine to entire population daily. It is also most economical way of supplying iodine. Public health measures to reduce IDD include measures such as universal iodization of salt, and administration of iodized oil in deficient areas. In rare instances, it may happen that salt iodization efforts are unable to meet the requirement of women during pregnancy, exposing the progeny to potential developmental risks. In such situations, while efforts to improve the salt iodization program should be continued, iodine supplementation may be considered for both pregnant women and children less than 2 years of age as a single oral dose of iodized oil every 6 to 12 months. Single oral dose of Lipiodol containing 240 mg iodine for 6-month coverage or 480 mg for 12 months is recommended.

## IN A NUTSHELL

1. Iodine is essential for normal growth and development.
2. Iodine is required in a small amount, i.e., 150 µg/day. There is no natural food item which is rich in iodine.
3. Iodine deficiency disorders include fetal loss, stillbirths, cretinism, dwarfism, intellectual disability, spastic diplegia, neonatal or childhood hypothyroidism, and poor school performance.
4. Iodine deficiency affects all the stages of human development.
5. Iodine deficiency is the world's major cause of preventable mental retardation.
6. The indicators utilized for assessment of iodine deficiency disorders (IDD) are total goiter rate, urinary iodine excretion, and thyroid stimulating hormone (TSH).
7. Iodized salt, iodized oil, iodized capsules and iodized water are common modes of iodine supplementation for prevention of IDD.

## MORE ON THIS TOPIC

- Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers. WHO/UNICEF/ICCIDD. Geneva: World Health Organization; 2007.
- Bernal J, Nunez J. Thyroid hormone action and brain development. *Trends Endocrinol Metab.* 2000;133:390-98.
- Hetzel BS. SOS for a billion—The nature and magnitude of iodine deficiency disorders. In: Hetzel BS, and Pandav CV, eds. *SOS for a billion—The conquest of iodine deficiency disorders*. 2<sup>nd</sup> ed. New Delhi: Oxford University Press; 1997. pp. 1-29.
- MOHFW, GOI. Revised Policy Guidelines on National Iodine Deficiency Disorders Control Programme. New Delhi: IDD and Nutrition Cell; Ministry of Health and Family Welfare; 2006.
- WHO. Iodine deficiency, list of publications. [http://www.who.int/nutrition/publications/micronutrients/iodine\\_deficiency/en/index.html](http://www.who.int/nutrition/publications/micronutrients/iodine_deficiency/en/index.html). Accessed July 1, 2014.

## Chapter 22.14

# Zinc in Child Health

Shashi Ajit Chiplonkar

Zinc is an essential trace mineral and a component of numerous proteins and metalloenzymes in the body which are involved in myriad of biological functions. The first cases of human zinc deficiency were reported in early 1960s in male adolescents from the Middle East as characterized by delayed sexual development and short stature. Later, efficacy of zinc supplementation was confirmed by a significant increase in height, bone development and sexual maturation.

Zinc is omnipresent in cellular metabolism. Therefore, inadequate supply is likely to have multiple biological and clinical effects. A mild to moderate deficiency of zinc may lead to retarded growth, impaired immunity and poor cognition. However, signs and symptoms of zinc deficiency are nonspecific and lack of a sensitive biomarker of zinc presents a challenge to clinicians to identify the need for medical intervention.

## EPIDEMIOLOGY

Adequacy of zinc in diet is essential to maintain a steady state as there are no specific body stores of zinc. Percent population at risk of inadequate zinc intakes is lower (6.4% to 9.6%) in Southern America, China and Europe than in Asia, North Africa, sub-Saharan Africa and west pacific countries (17.1% to 29.6%). Global estimates of zinc deficiency in pediatric population are lacking. Evidence from diet assessment studies in children indicate that the overall prevalence of zinc deficiency as 30% to 57% in children and adolescents from Asian and South African countries.

Zinc deficiency results in a substantial morbidity and mortality predominantly among children under 5 years of age who are most affected by diarrhea, malaria and pneumonia. The five countries with the highest numbers of total deaths attributable to zinc deficiency (India, Nigeria, Democratic Republic of Congo, Ethiopia and Afghanistan) together account for 47% of all attributable deaths. Zinc supplementation as an adjunctive treatment may be the best way to target children at risk of deficiency. In older children (6–16 years), zinc deficiency can lead to low immunity, stunting, impaired taste perception and poor cognitive performance.

## STRUCTURE AND METABOLISM OF ZINC

The total body zinc content is around 2 g which is found in almost all tissues and fluids. Zinc is a component of over 300 enzymes including nicotinamide adenine dinucleotide dehydrogenases, RNA and DNA polymerases, and DNA transcription factors as well as alkaline phosphatase, superoxide dismutase, and carbonic anhydrase. These are used to maintain healthy cell reproduction, growth, and adult fertility, synthesize cholesterol, protein, and fats, enhance immunity and protect the body against harmful free radicals. Zinc is vital for several body functions, such as vision, insulin function, taste perception, thymulin activity and anti-inflammatory activity. In addition, it regulates the release of vitamin A from the liver.

Zinc is important for the cognitive function of children because it is important for myelination and for release of the neurotransmitters gamma-aminobutyric acid and glutamate, which are key modulators of neuronal excitability. Zinc is an intracellular signaling molecule and it plays an important role in cell-mediated immune functions and oxidative stress. Zinc is also an anti-inflammatory agent. Zinc has direct effects on the primary hormonal system [insulin growth factor-I/growth hormone (IGF-I/GH)] that controls growth in the postnatal phase when the majority of stunting occurs.

## ABSORPTION OF ZINC

Dietary zinc is released as free ions during digestion and is actively absorbed from the gut into epithelial cells, where it is stored as mucosal metallothionein or released into the plasma, where 70% is mainly bound to albumin. It is then transported to the liver, where it is stored by hepatocytes in metallothionein. Other specific transporters, such as zinc transporter protein-1 (ZnTP-1) may facilitate passage of zinc across the basolateral membrane of the enterocyte into the portal circulation. Endogenous zinc is reabsorbed in ileum and colon creating enterohepatic circulation of zinc. Regulation of zinc absorption is thought to be controlled by the amount of metal-free albumin. Zinc is primarily stored in RBCs, WBCs, muscle, bone, skin, kidneys, liver, pancreas, retina, prostate, etc.

Increased zinc intake depresses copper absorption and conversely copper absorption is greatly increased in zinc deficiency. Metabolic interactions occur between zinc and cadmium, zinc and iron, and zinc and chromium. Cadmium and iron uptake are depressed by high zinc levels, while chromium and zinc are metabolized by a common pathway in the intestine and are mutually antagonistic.

## DIETARY SOURCES AND DAILY REQUIREMENTS OF ZINC

Animal foods like oysters, lean meat are rich sources of zinc, while plant foods contain relatively low amounts of zinc (**Table 1**). Phytic acid and fiber in these foods reduce the bioavailability of zinc. Dietary nutrients, such as iron, calcium and folic acid also affect bioavailability of zinc. Cooking processes, such as soaking, germination and fermentation of food products can reduce the inhibitory effect of phytic acid, thereby improving zinc bioavailability.

Zinc stored in body tissues does not function as zinc reserves, so the body depends on adequate dietary intake for its daily requirements. Overall, the body absorbs 15–30% of dietary zinc, depending on the body's requirement and source of zinc. Vegetarian foods have poor zinc bioavailability than animal foods. It is therefore postulated that vegetarians may have as much as a 50% higher need for zinc than non-vegetarians. The WHO has provided the recommended dietary intakes for zinc based upon levels of absorbable zinc from diets (**Table 2**).

## CAUSES OF ZINC DEFICIENCY

Inadequate dietary intake is the foremost and major contributor to zinc deficiency. It may result out of consuming foods low in zinc or

**Table 1** Zinc content of selected cooked foods per 100 g weight

Animal foods	Zinc (mg)	Plant foods	Zinc (mg)
Oysters	45.1	Pearl millet unleavened pancake	2.0
Beef lean	6.8	Lentils	1.3
Ground beef	5.8	Dill leaves	1.6
Turkey	4.2	Almonds, dry and unsalted	3.5
Chicken liver	4.0	Peanuts roasted	3.9
Shrimp	1.6	Pumpkin seeds, dry	4.2
Goat meat	5.2	Sunflower seeds, dry	5.0
Bear meat	10.2	Sesame, dry	12.2
Cheese non-fat	3.9	Cashewnuts, dry and unsalted	6.0

Source: Nutrient database for standard reference, USDA (2010), Indian cooked food database (Chiplonkar & Agte, 2007).



high in phytates or due to increased requirements during rapid growth. Malabsorption of zinc may occur in inflammatory bowel disease. Interactions with phenytoin and tetracycline reduce zinc absorption leading to zinc deficiency. Further, increased losses of endogenous zinc may occur in conditions of cystic fibrosis, celiac disease, Crohns disease, or chronic kidney disease. Diarrhea can cause zinc deficiency due to losses of endogenous zinc in diarrheal fluids.

Zinc deficiency can occur because of impaired utilization of zinc due to certain drugs (e.g., ethambutol, halogenated 8-hydroxyquinolines, penicillamine) that chelate zinc systemically and make it less available for use by tissues. Also infections cause sequestration of zinc in the liver, and decreased circulating levels of zinc, which will reduce the availability of zinc to other tissues. Over-supplementation with iron or copper has also been reported to cause zinc deficiency.

## CLINICAL MANIFESTATIONS

Growth retardation or decreased growth velocity is often the first sign of zinc deficiency in infants, children and adolescents. Severe zinc deficiency can be characterized by short stature, hypogonadism, impaired immunity, skin disorders, cognitive dysfunction, and anorexia. Although severe zinc deficiency is rare, mild-to-moderate zinc deficiency is quite common throughout the world. Clinical symptoms of zinc deficiency are illustrated in **Table 3**. Chief clinical conditions associated with increased risk of zinc deficiency are acute diarrhea, celiac disease, cystic fibrosis and Wilson disease.

Acrodermatitis enteropathica is a genetic disorder of zinc metabolism that manifests as severe zinc deficiency, characterized by failure to absorb zinc from diet, abrupt cessation of weight gain, hypogonadism, gastrointestinal disturbances and skin lesions. Skin

lesions of severe acute zinc deficiency syndromes have a characteristic distribution, primarily at the extremities and adjacent to the body orifices (**Fig. 1**). Secondary infection with *Candida* is common.

Abnormalities of immune system occur in less severe zinc deficiency also. Lowered learning abilities, apathy, lethargy, depression and mental retardation are notable features of insufficient body zinc levels.

Chronic zinc deficiency in adolescents may prolong sexual maturation. Some cases of impotence complicating chronic renal



**Figure 1** Acrodermatitis enteropathica: acquired zinc deficiency responded dramatically to zinc supplementation

Source: Dr. Arun Shah, Mujaffarpur, Bihar.

**Table 2** Recommended nutrient intakes (RNIs) for dietary zinc (mg/day) to meet the normative storage requirements from diets differing in zinc bioavailability

Age group	Assumed body weight (kg)	High bioavailability <sup>a</sup>	Moderate bioavailability <sup>b</sup>	Low bioavailability <sup>c</sup>	Indian RDA, 2010
<i>Infants and children</i>					
0–6 months	6	1.1 <sup>d</sup>	2.8 <sup>e</sup>	6.6 <sup>f</sup>	-
7–12 months	9	0.8 <sup>d</sup> , 2.5 <sup>g</sup>	4.1	8.4	-
1–3 years	12	2.4	4.1	8.3	5
4–6 years	17	2.9	4.8	9.6	7
7–9 years	25	3.3	5.6	11.2	8
<i>Adolescents</i>					
Females 10–18 years	47	4.3	7.2	14.4	-
Females 10–12 years					9
Females 13–15 years					11
Females 16–17 years					12
Males 10–18 years	49	5.1	8.6	17.1	-
Males 10–12 years					9
Males 13–15 years					11
Males 16–17 years					12

a. Assumed bioavailability of dietary zinc, 50%. Refined diets mainly having meat, fish.

b. Assumed bioavailability of dietary zinc, 30%. Mixed diets; lacto-ovo, ovo-vegetarian or vegan diets.

c. Assumed bioavailability of dietary zinc, 15%. Plant-based diets high in phytate and fiber.

d. Exclusively human-milk-fed infants.

e. Formula-fed infants with low-phytate feeds.

f. Formula-fed infants, a phytate-rich vegetable protein-based formula

g. Not applicable to infants consuming human milk only.

Source: WHO & FAO (2004, p. 240), Dietary guidelines for Indians, NIN, 2010.

**Table 3** Clinical features of zinc deficiency

System	Signs and symptoms
Gastrointestinal system	Loss of appetite, diarrhea, anorexia, taste and smell dysfunction, eating disorders, glossitis, gingivitis
Hair	Early graying of hair, alopecia, hair loss
Nails	Blackening of nails, nail dystrophy
Eye	Impaired vitamin A metabolism with weakened vision, eye lesions, lack of dark adaptation, photophobia, conjunctivitis, blepharitis
Central nervous system	Behavioral abnormalities, impaired mental function, cognitive dysfunction, and depressed mood
Skin	Skin lesions, acne, delayed healing of wounds, dermatitis
Reproductive system	Problems in the menstrual cycle of women, impaired reproduction, hypogonadism in males, zinc deficiency in the pregnant woman can lead to poor growth in the fetus
Growth and development	Weight loss with increased susceptibility to infections, impaired cell mediated immunity, thyroid dysfunction, growth failure, delayed sexual maturation, impaired immune function
General	Hypozincemia during fever may trigger febrile convulsions Reduced RBC zinc in patients with sub-acute thyroiditis

Manifestations depend on severity of deficiency and other factors.

disease have responded to zinc supplementation. Eye lesions that may occur in severe chronic zinc deficiency include severe photophobia and keratopathy.

## BIOMARKERS OF ZINC DEFICIENCY

A specific marker of zinc status is yet not determined owing to homeostatic control of body zinc. Levels of zinc in red blood cells, leukocytes, neutrophils and plasma or serum are some of the markers of zinc status. Clinical signs of zinc deficiency may occur when serum zinc concentrations drop below 65 µg/dL (**Table 4**). Values less than 33 µg/dL are particularly associated with loss of the senses of taste and smell, abdominal pain, diarrhea, skin rash, and loss of appetite. Other biomarkers include measurement of the activity of zinc-dependent enzymes such as carbonic anhydrase or alkaline phosphatase, urinary zinc excretion (normal range 3.3–21.4 µmol/24 hours) and hair zinc (normal range 150–240 µg/g). Functional indices such as taste acuity, cognitive ability or dark adaptation are also used to detect zinc deficiency.

## PREVENTION AND TREATMENT

Prevention and correction of zinc deficiency is vital for normalizing the function of cells in multiple tissues. It enhances the child's ability to combat disease states and not just single infectious organisms. Best preventive measure for zinc deficiency is increasing intake of foods rich in absorbable zinc. Preventive zinc supplementation is highly effective, with demonstrated benefits for pneumonia, diarrhea and growth impairment. The body requires zinc to develop and activate T-lymphocytes. Individuals with low zinc levels have shown reduced lymphocyte proliferation response to mitogens and other adverse alterations in immunity that can be corrected by zinc supplementation. Therapeutic uses of zinc are illustrated in **Table 5**.

**Table 4** Suggested lower cut-offs (2.5th percentile) for the assessment of serum zinc concentration in population studies, derived from NHANES II data

Age group	Serum zinc concentration, µg/dL (µmol/L) <sup>a</sup>		
	< 10 yrs	≥ 10 yrs	
	Children	Females (Nonpregnant)	Males
AM Fasting <sup>b</sup>	na <sup>c</sup>	70 (10.7)	74 (11.3)
AM	65 (9.9)	66 (10.1)	70 (10.7)
PM	57 (8.7)	59 (9.0)	61 (9.3)

Source: International Zinc Nutrition Consultative Group; Food Nutr Bull; 2004.

a. Conversion factor: µmol/L = µg/dL ÷ 6.54

b. Based on data from subjects 20 years and older only

c. na = not available

A meta-analysis of trials in prepubertal children indicated benefit of zinc supplement for weight and height increments, especially in underweight children and in children more than 6 months of age with evidence of stunting. Zinc supplementation also showed increased food intake in anorexia. However, loss of appetite may not be observed in zinc-deficient children having protein deficiency. Cognitive function and hedonic tone improve significantly after zinc therapy.

Recent review on preventive zinc supplementation in healthy children under five years of age showed a reduction of 13% in diarrheal morbidity and 19% reduction in pneumonia morbidity and similar reduction in mortality but no effect on malaria. A meta-analysis of zinc supplementation trials indicated reduced rate of respiratory tract infections in children.

Zinc is recommended as an additional therapy in severe malnutrition and chronic and acute diarrhea. Pooled analysis of randomized controlled trials mainly in India, Africa, South America and Southeast Asia suggest that 4–40 mg elemental zinc per day in the form of zinc acetate, zinc gluconate or zinc sulfate reduced the severity and duration of diarrheal episodes. For intravenous administration, zinc chloride is frequently used.

Acrodermatitis enteropathica appears in early infancy but with adequate zinc supplements a total recovery occurs.

Excessive intake of zinc (**Table 6**) can lead to toxic effects like nausea, vomiting, abdominal pain, diarrhea, convulsions. Chronic high dose zinc ingestion leads to lethargy, anemia, and neurological side effects predominantly due to lowering of copper levels.

## IN A NUTSHELL

1. A large percentage of the population from developing countries is affected by mild to moderate zinc deficiency.
2. Zinc supplementation is highly beneficial as a preventive measure and also as a promoter for normal growth and development.
3. Zinc is useful as adjunctive therapy in the treatment of common infectious diseases, especially diarrhea and pneumonia.
4. Adverse effects of zinc deficiency on cognitive function, taste acuity and stunting are reversible if detected and treated at an early stage.

## MORE ON THIS TOPIC

Aggarwal R, Sentz J, Miller MA. Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: A meta-analysis. *Pediatrics*. 2007;119:1120.

**Table 5** Treatment with zinc supplements\*

Condition	Zinc salt	Dose <sup>a,b</sup>
Zinc deficiency	Zinc sulfate	Full term infants and children up to 5 years 100 µg of elemental zinc/kg/day For preterm infants (up to 3 kg body weight) 300 µg of zinc/kg/day to TPN Children: 8–10 mg/day Adolescents: 15–20 mg/day
Dermatological disease	Zinc carbonate, zinc oxide and zinc chloride	Astringents
Overperspiration	Zinc hydroxybenzene sulfonate	Deodorant and antiperspirant
Eye problems	Zinc sulfate	Eye drops, oral zinc supplement
Diarrhea	Zinc sulfate	WHO and UNICEF recommend short-term zinc supplement (20 mg/day, or 10 mg for infants under 6 months, for 14 days in diarrheal diseases)
Diabetes mellitus	Zinc sulfate, zinc oxide	15–20 mg/day
Delayed growth	Zinc sulfate	Children: 8–10 mg/day Adolescents: 15–20 mg/day
Acrodermatitis enteropathica	Zinc sulfate, gluconate or other salt	Infants and toddlers: 90–130 mg/day Older children: 180–220 mg thrice daily
Wilson disease	Zinc sulfate, zinc gluconate, zinc acetate	220 mg thrice daily

\*. These are to be taken as general suggestions. Choice of zinc salt and dose may vary as per the case.

a. Zinc supplements should not be taken within 2 hours of iron, copper, calcium, folic acid or phosphate supplements.

b. Zinc supplement is usually administered 1 hour before or 2 hours after food. In the presence of gastric irritation, zinc has to be given with food.

**Table 6** Tolerable upper intake levels (ULs) for zinc<sup>a</sup>

Age	Male	Female	Pregnant	Lactating
0–6 months	4 mg	4 mg		
7–12 months	5 mg	5 mg		
1–3 years	7 mg	7 mg		
4–8 years	12 mg	12 mg		
9–13 years	23 mg	23 mg		
14–18 years	34 mg	34 mg	34 mg	34 mg
19+ years	40 mg	40 mg	40 mg	40 mg

a: The ULs do not apply to individuals receiving zinc for medical treatment and are under physician's care.

Source: Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc. Washington, DC: National Academy Press; 2001.

Fischer Walker CL, Ezzati M, Black RE. Global and regional child mortality and burden of disease attributable to zinc deficiency. *Eur J of Clin Nutr*. 2009;63:591-7.

Hess SY, Lonnerdal B, Hotz C, et al. Recent advances in knowledge of zinc nutrition and human health. *Food Nutr Bull*. 2009;30:S5-S11.

Krebs NF. Update on zinc deficiency and excess in clinical pediatric practice. *Ann Nutr Metab*. 2013;62(suppl 1):19-29.

Penny ME. Zinc supplementation in public health. *Ann Nutr Metab*. 2013; 62(suppl 1):31-42.

Prasad AS. Zinc: role in immunity, oxidative stress and chronic inflammation. *Current Opin Clin Nutr Metabol Care*. 2009;12:646-52.

Wessells KR, Brown KH. Estimating the global prevalence of zinc deficiency: Results based on zinc availability in National food supplies and the prevalence of stunting. *PLoS ONE* 2012;7:e50568.

Yakoob MY, Theodoratou E, Jabeen A, et al. Preventive zinc supplementation in developing countries: impact on mortality and morbidity due to diarrhea, pneumonia and malaria. *BMC Public Health*. 2011;11(Suppl 3):S23.

## Chapter 22.15

# Trace Elements in Nutrition and Health

P Leelakumari, KE Elizabeth

Trace elements are minerals required only in minute amounts for living organisms for normal body function and growth. They are present in concentrations less than 0.01% body dry weight. Trace element deficiencies occur commonly in children with protein-energy malnutrition (PEM), picky eaters, low birthweight (LBW) babies and those on total parenteral nutrition. Excess intake of dietary fiber, oxalates and phytates will reduce the trace element absorption. Levels of trace elements in the blood can be estimated by colorimetry, atomic absorption spectrophotometry, and neutron activation analysis. A WHO Expert Consultation has categorized nutritionally significant trace elements into three groups: (i) *Essential trace elements*: iron, iodine, zinc, selenium, copper, molybdenum, and chromium; (ii) *Elements which are probably essential*: manganese, silicon, nickel, boron, and vanadium; and (iii) *Potentially toxic elements*: fluorine, lead, cadmium, mercury, arsenic, aluminum, lithium and tin. We have already discussed iodine and zinc in detail. This chapter will deal with the rest of important trace elements. Fluorosis, a major public health problem, will be dealt in the next chapter.

## IRON

Iron deficiency is the main cause of anemia in all age groups including higher income groups. In India, two-thirds of children and women and half of men suffer from anemia. Iron is mainly used for production of hemoglobin and myoglobin. It is also a component of iron containing enzymes. Iron is available as heme iron, which is present in meat and nonheme iron found in vegetables. Heme iron is better absorbed. Fish, meat, cereals, legumes, green-leafy vegetables, dates and jiggery are good sources of iron. Cooking in iron vessels increases the iron content of food. Recommended daily amount (RDA) of iron is 10–20 mg/day. Iron deficiency anemia is detailed in Section 38 on hematological disorders.

## COPPER

Copper is widely distributed in biological tissues as organic complexes, many of which are metalloproteins. Adult human body contains 80 mg of copper with a range of 50–120 mg. Tissue copper level ranges from less than 1 mcg/g (dry weight) in many tissues to more than 10 mcg/g (dry weight) in liver and brain. Concentration of copper may be 6–10 folds greater in liver of infants during the first 2 months of postnatal life. Copper in human blood is mainly distributed between erythrocytes and plasma. In the erythrocytes, 60% of copper occurs as metalloenzymes (superoxide dismutase, cytochrome C oxidase, tyrosine oxidase), the remaining 40% being loosely bound to other proteins and amino acids. Total erythrocyte copper is 0.9–1 mcg/mL of packed red cells. In the plasma, 93% of copper is firmly bound to the enzyme ceruloplasmin and the remaining 7% is less firmly bound to albumin and amino acids.

Normal serum copper level is 0.8–1.2 mcg/mL and hypocupremia is defined as serum copper level of 0.8 mcg/mL or less (WHO) and is usually accompanied by hypoceruloplasminemia.

## Biological Functions

Copper is an essential element in human body. It is the cofactor for many enzymes, needed for hemoglobin synthesis, essential for zinc, iron and vitamin C functions, melanin synthesis, neurotransmitter synthesis, cross linkage and synthesis of elastin and collagen and central nervous system (CNS) functions.

## Dietary Sources

Good dietary sources (> 2 mcg/g) include liver, fish, oysters, organ meat, legumes, nuts and sea food. Daily requirement is 11 mcg/kg/day. The upper limit of safe range of population mean intake is 12 mg/day for males 10 mg/day for females, and 150 mcg/kg for infants (WHO). Toxicity leads to hepatic cirrhosis, hemolytic anemia, zinc deficiency and gastritis.

## Deficiency

Copper deficiency occurs in LBW and preterm babies, protein energy malnutrition and during total parenteral nutrition. Clinical features of deficiency include hypochromic anemia, neutropenia, hypopigmented hair, abnormal bone formation with skeletal fragility, osteoporosis and neurological manifestations. Metabolism of copper is deranged in Wilson's disease. Menkes kinky hair syndrome is an X-linked metabolic disturbance of copper metabolism characterized by mental retardation, abnormal hair texture, hypocupremia (< 65 mcg/dL) and low circulating ceruloplasmin (< 20 mg/dL).

## CHROMIUM

Chromium is an essential micronutrient that potentiates action of insulin and thus influences carbohydrate, lipid and protein metabolism. It facilitates weight loss and prevents diabetes. Dietary sources include yeast, liver, cereals, nuts, egg, butter and cheese. Average basal requirement of chromium is less than 20 mcg/day and the mean population intake to meet basal needs may be 25 mcg/day. Upper limit of safe range of population mean intake is 250 mcg/day (WHO).

## Deficiency and Excess

Deficiency may occur in PEM, and during total parenteral nutrition (TPN). Deficiency leads to impaired growth, elevated serum cholesterol and triglycerides, hyperglycemia, increased incidence of aortic plaques, corneal lesions and decreased fertility. Tissue chromium status may not be actually reflected by fasting plasma or serum chromium status. Serum chromium level less than 0.14–0.15 ng/mL may indicate severe chromium deficiency.

Chromium toxicity due to oral intake is rare. Toxicity usually occurs in industrial environment where concentration in the air is high or contact with skin is frequent. Toxicity leads to renal failure and dermatitis. Elevated serum chromium (> 0.15 ng/mL) is a useful indicator of excessive exposure to chromium. Another indicator is high urinary chromium level.

## SELENIUM

Selenium is a component of enzymes superoxide dismutase, glutathione peroxidase, deiodinase enzymes, thiolase and glycine reductase; and plays important role in antioxidant defense system. Selenium maintains liver integrity and helps thyroid hormone synthesis. There are many epidemiological studies on protective role of selenium against cancer. Selenium can protect against heart disease by influencing platelet aggregation. Grains, garlic, green-leafy vegetables, and meat are good dietary sources of selenium. Selenium compounds are well absorbed in humans. The rate limiting step in the overall bioavailability of dietary selenium is its



conversion within the tissues to its metabolically active form (e.g., its incorporation into glutathione peroxidase). A level of 40 µg/day is considered as the acceptable intake of selenium for Indians. The selenium content of cereals and pulses range between 30 and 400 µg/g. Safe upper limit of population mean intake of selenium for adult is 400 µg/day.

### Deficiency and Toxicity

Deficiency is common in PEM and TPN. Clinical features include myalgia, cardiomyopathy, arthritis and liver necrosis. The endemic cardiomyopathy associated with selenium deficiency is known as *Keshan disease*. It can be clinically categorized into four types as acute, subacute, chronic and insidious. Once the disease is established, selenium supplementation does not help. The major histopathological picture of the disease is multifocal myocardial necrosis. The coronary arteries are essentially unaffected. *Kashin-Beck disease* is an endemic osteoarthropathy associated with low selenium status. It occurs in children of age 5–13 years, endemic in certain regions of China. Degeneration and necrosis of hyaline cartilage lead to joint swelling and deformity.

Toxicity leads to alopecia, dental caries and a typical garlic odor in mouth. A significant handicap of research in selenium toxicity is the lack of selective and sensitive indicator of selenium overexposure in humans.

### MOLYBDENUM

The principal molybdenum containing enzymes in humans are xanthine oxidase/dehydrogenase, aldehyde oxidase and sulfite oxidase. Xanthine oxidase is involved in the conversion of purines to uric acid. Legumes and green-leafy vegetables are good sources. Animal foods except liver are poor sources of molybdenum. Plants grown in neutral or alkaline environment will be good sources and those grown in acidic medium will be poor sources.

Hexavalent molybdenum compounds are well absorbed from gastrointestinal tract (GIT). Intestinal absorption of molybdenum is inhibited by high intraluminal concentrations of sulfate anions generated by protein breakdown and oxidation of methionine and cysteine. Sulfates also reduce the tissue utilization of molybdenum and also increase the urinary excretion of molybdenum.

### Dietary Intake

Recommended dietary intake for breastfed infants is 2 µg/kg. Between weaning and 3 years of age it is 5–7 µg/kg and declines thereafter to 1.5–3 µg/kg. For adolescents and adults, the recommended dietary intake is 1.5–2.5 µg/kg. Molybdenum content of human liver is 1.3–2.9 mg/kg of dry matter and that of kidney is 1.6 mg/kg, lung 0.15 mg/kg, brain 0.14 mg/kg. Reported mean molybdenum content of human hair is 0.07–0.16 mg/kg.

### Deficiency and Toxicity

Studies in Henan Province, China suggest a high incidence of esophageal cancer with molybdenum deficiency. Other manifestations include central scotoma, irritability and coma. Molybdenum deficiency is also associated with dental caries. Molybdenum deficiency coexisting with selenium deficiency may be obligatory for the development of Keshan disease. Liver diseases, uremia, rheumatic diseases and cardiovascular diseases are associated with high serum molybdenum level.

### MANGANESE

Manganese is both an activator and a constituent of several enzymes. Manganese metalloenzymes include arginase, pyruvate

carboxylase and manganese superoxide dismutase. Manganese is essential for oxidative phosphorylation and for normal bone structure, and found mainly in bone, liver, pancreas and kidney. Rich dietary sources of manganese include unrefined cereals (wheat, barley, rice bran), nuts, leafy vegetables and tea. Average requirement is 2–5 mg/day. Indian diet rich in foods of plant origin supply an average of 8.3 mg of manganese per day, whereas highly refined hospital diets of United States supply an average of 0.63–1.78 mg/day only. Intestinal absorption is influenced by the dietary manganese content. Manganese absorption is negatively influenced by the dietary fiber content and iron.

### Deficiency and Toxicity

Manganese deficiency can lead to impaired growth, skeletal abnormalities, disturbed reproductive function, and defects in carbohydrate and lipid metabolism. Studies report low whole blood concentration of manganese in certain types of epilepsies. Whole blood manganese concentration (normal: 8.4 µg/L) is useful in assessing the status. Urinary manganese level is another indicator of its status. Activity of manganese superoxide dismutase and the ratio of manganese superoxide dismutase to copper zinc superoxide dismutase are other indicators of manganese status of humans.

Manganese is reported to be the least toxic of the trace element when administered orally. The most common form of manganese toxicity is the result of chronic inhalation of large amounts of airborne manganese in mines, steel mills and some chemical industries. The major signs of manganese toxicity in animals are depressed growth, decreased appetite, impaired iron metabolism and altered brain function. Signs of toxicity in Chilean manganese miners were first manifested in the form of severe psychiatric abnormalities, including hyperirritability, violent acts and hallucinations; these changes were called manganic madness. As the disease progressed, there was a permanent crippling neurological disorder of the extrapyramidal system with morphological lesions similar to those of Parkinson's disease.

Toxicity can also lead to cardiomyopathy, goiter and cholestasis.

### VANADIUM

Vanadium helps in regulation of enzymes Na<sup>+</sup>/K<sup>+</sup> ATPase, adenylate cyclase and protein kinase. All protein-rich foods are good sources of vanadium. Normal range of serum vanadium level is 0.016–0.939 ng/mL. Most values are less than 0.15 ng/mL. Dietary intake of 10 µg/day meets basal vanadium requirement. Daily intake of 10 mg/day can produce toxicity. Serum vanadium level more than 1 ng/mL indicates excessive exposure to vanadium.

### Deficiency and Toxicity

Deficiency can lead to skeletal and joint deformities. Vanadium is a toxic element. Toxicity leads to defective growth, loss of appetite, gastrointestinal disturbances, etc. Cardiovascular diseases are reported in few studies. Toxicity usually occurs as a result of industrial exposure to high-level airborne vanadium.

### SILICON

Silicon is the second most abundant element in the earth's crust. It is not found free in nature but occurs chiefly as the oxide and silicate. Animal experiments showed that silicon is needed for the normal development of connective tissue and bone. It helps in bone formation by facilitating the formation of glycosaminoglycans and collagen component of bone matrix. For the normal bone development in experimental animals, a requirement of 100–250 µg/g has been identified but no data are available for human

requirement. Foods of plant origin contain more silicon than that of animal origin. Whole grasses and cereals may contain 3–6% as silica. The general manifestations of silicon toxicity are collectively called silicosis. It can lead to urolithiasis.

## NICKEL

The four nickel containing enzymes found in plants and microorganisms are urease, hydrogenase, methyl coenzyme M reductase and carbon monoxide dehydrogenase. Typically, less than 10% of nickel ingested in food is absorbed. Nickel absorption is enhanced by iron deficiency. Severe deficiency leads to impairment of growth and hematopoiesis. Excess can lead to dermatitis, liver necrosis and lung cancer. Chocolate contains significant amount of nickel. Serum nickel concentrations of more than 1 µg/L indicates chronic excessive intake of nickel.

## BORON

Boron affects steroid hormone metabolism in humans and also affects major mineral metabolism in a human body. Foods of plant origin, especially fruits, leafy vegetables, nuts and legumes are rich sources of boron. Wine, cider and beer are also rich in boron. Recent studies show that 1 µg/g of dry diet meets the needs. Boron in food is rapidly absorbed in GIT and is highly excreted in urine. It is distributed throughout the tissues with the tissue concentration being 0.05–0.6 µg/g of fresh weight. The normal concentration of boron in blood is apparently between 0.1 and 0.2 mg/mL. Brain function may be affected in deficiency.

## MORE ON THIS TOPIC

- Arthur JR, Beckett GJ. New metabolic roles for selenium. *Proc Nut Soc.* 1994;53: 616–24.
- Bhaskaram P. Micronutrient malnutrition, infection, and immunity: an overview. *Nutr Rev.* 2002;60:S40–5.

- Bienz D, Cori H, Hornig D. Adequate dosing of micronutrients for different age groups in the life cycle. *Food Nutr Bull.* 2003;24:S7–15.
- Black MM. Micronutrient deficiencies and cognitive functioning. *J Nutr.* 2003;133:3927S–3931S.
- Diaz JR, de las Cagigas A, Rodriguez R. Micronutrient deficiencies in developing and affluent countries. *Eur J Clin Nutr.* 2003;57:S70–2.
- Elizabeth KE. Trace elements. In: Parthasarathy A, PSN Menon, Gupta P, Nair MKC. *IAP Textbook of Pediatrics.* 5<sup>th</sup> ed. New Delhi: Jaypee Brothers Medical Publishers (P Ltd); 2013. pp. 152–5.
- Ramakrishnan U. Prevalence of micronutrient malnutrition worldwide. *Nutr Rev.* 2002;60:S46–52.
- Trace elements in human nutrition and health. Report of a WHO Expert Committee. Geneva: WHO, 1996.
- Vitamin and Mineral Requirements in Human Nutrition. 2<sup>nd</sup> ed. Geneva: WHO; 2005.
- Williams AF. Pediatric nutrition. In: Gibney MJ, Elia M, Ljungqvist O, Dowsett J (Eds). *Clinical Nutrition.* Oxford: Blackwell Science; 2006. pp. 379–427.

## IN A NUTSHELL

1. Most of the trace elements are essential or probably essential, but a few are potentially toxic.
2. Trace elements are required only in minute quantities and are present in selected food items.
3. Deficiency of these micronutrients causes various pathologic effects in a human body. Excess can also cause serious adverse reactions in the body. So, optimum trace element balance in body is essential.
4. Optimum trace element balance should be considered in TPN and food fortification.
5. Trace element deficiencies should be diagnosed in the early phase and corrected. Along with optimum dietary intake recommendations, factors influencing the absorption and bioavailability should be considered.

## Chapter 22.16

### Fluorosis

Sunil Kumar Gupta

Fluorine is the 13th most abundant element available in the earth crust. Fluorine, a pale yellow gas with a pungent and irritating odor, exists as a diatomic molecule with remarkably low dissociation energy. As a result it is highly reactive and has strong affinity to combine with other elements to produce compounds known as fluoride, a cause of fluorosis.

Systemic fluorosis is an endemic problem in several regions across the world including developing as well as the developed countries. WHO standards permit 1.5 mg/L and Bureau of Indian Standards (BIS) permit 1.0 mg/L as the safe limits of fluoride for human consumption. BIS 2009 further states that fluoride may be kept as low as possible. There is no RDA of fluoride for human health. Values of adequate intake (AI) are given in **Table 1**. The minimal daily fluoride intake in infants that may cause very mild or mild fluorosis is estimated to be about 0.1 mg/kg body weight.

#### EXTENT OF PROBLEM

Fluorosis is prevalent worldwide with countries like Pakistan, Bangladesh, Argentina, United States of America, Morocco, Middle East countries, Japan, South African countries, New Zealand, Thailand, etc., reporting sporadic to widespread cases. The problem has reached alarming proportions in India affecting at least 19 states out of which Andhra Pradesh, Tamil Nadu, Uttar Pradesh, Gujarat and Rajasthan are the most severely affected. People in several districts of India are consuming water with fluoride concentrations of up to 44 mg/L.

#### SOURCES OF FLUORIDE

Usually the surface water is not contaminated with fluoride, whereas ground water may contain high fluoride due to leaching of fluoride from fluoride rich rocks during the percolation of water through different strata. Minerals like fluor spar ( $\text{CaF}_2$ ), cryolite ( $\text{Na}_3\text{AlF}_6$ ) and fluorapatite  $\text{Ca}_5[\text{F}(\text{PO}_4)_3]$  also  $3\text{Ca}_3(\text{PO}_4)_2\text{CaF}_2$  or  $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$  are found commonly in different igneous and sedimentary rocks.

Main sources of fluoride for human are water, food, air, medicament, cosmetics. Although there are several sources of fluoride intake, it is roughly estimated that 60% of the total intake is through drinking water. This is the most assimilable form of fluoride and hence the most toxic. The fluoride of food items

depends upon the fluoride content of the soil and water used for irrigation, therefore the fluoride content of the food items may vary from place to place. The available data indicate that in general the fluoride content of the various food items is as follows (given in decreasing amount of fluoride): cereals > leafy vegetables > pulses > fish > meat > fruits. Prolonged use of certain drugs has been associated with the chronic adverse effects of fluoride, e.g., sodium fluoride (now discontinued) for treatment of osteoporosis, niflumic acid for the treatment of rheumatoid arthritis, use of fluoride mouth rinses (Proflo) to render the tooth stronger. The use of fluorides in industry can also lead to occupational exposure, e.g., inorganic fluoride compounds are released in air during the production of aluminum as well as phosphate fertilizers.

Highly significant associations have been found between estimated fluoride ingestion from fluoridated toothpaste and fluorosis. In the fluoridated brands, there is a deliberate addition of fluoride, which may range from 1,000 mg/L to 4,000 mg/L (ppm). Apart from the available drinking water supply, the bottled mineral water may also be a source of excessive fluoride ingestion.

#### CHEMOBIOKINETICS AND METABOLISM (FLOW CHART 1)

Ingested fluoride is rapidly absorbed through gastrointestinal tract and lungs. The peaks are reached after 30 min in blood. The rapid excretion takes place through renal system over a period of 4–6 hour. In children less than 3 years of age only about 50% of total absorbed amount is excreted, but in adults and children over 3 years—about 90% is excreted. Approximately 90% of the fluoride retained in the body is deposited in the skeleton and teeth. The biological half-life of bound fluoride is several years. Transplacental passage of fluoride has also been reported. Fluoride also excreted in low concentrations in saliva, sweat, and milk.

#### PATHOPHYSIOLOGY

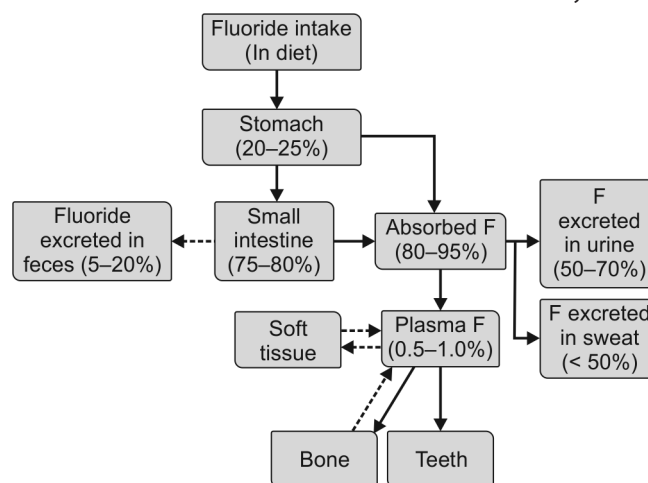
Ingestion of fluoride causes decrease in the ionized calcium. Resultant hypocalcemia causes secondary hyperparathyroidism, leading to increased activity of osteoclasts in bone by activating membrane bound 3'5' cyclic adenosine monophosphate (AMP). This increased osteoclastic activity causes increase in citric acid and lactic acid release from ruffled border of osteoclasts, increasing hydrogen ion concentration, and hence lysis of lysosomes. Release of lysosomal enzymes *viz.* acid protease, collagenase, hyaluronidase in bone and other tissues of the body, catalyze the reactions favoring the depolymerization of the glycoprotein of bone and of cartilage. This causes breakdown of hydroxyproline, which is

**Table 1** Adequate intake (AI) for fluoride (mg/day)

Life stage	Age	Males (mg/day)	Females (mg/day)
Infants	0–6 months	0.01	0.01
Infants	7–12 months	0.5	0.5
Children	1–3 years	0.7	0.7
Children	4–8 years	1.0	1.0
Children	9–13 years	2.0	2.0
Adolescents	14–18 years	3.0	3.0
Adults	19 years and older	4.0	3.0
Pregnancy	All ages	-	3.0
Breastfeeding	All ages	-	3.0

Source: Harrison's Principles of Internal Medicine; 2012. pp. 590–91.

**Flow chart 1** Metabolism of fluoride in human body



responsible for stabilization of collagen triple helix. As the protein polymer desegregates and dissolves, the mineral-binding capacity is also reduced and calcium is liberated, which helps in maintaining the serum calcium level. As a result the solubility of hydroxyapatite crystals also increases, causing its breakdown, along with reduced laying down of collagen by reducing hydroxylation of proline and lysine. This event simultaneously leads to elevation of GAG (glycosaminoglycans) (seromucoid). The net result of degradation of ground substance [collagen fibers, GAG (proteoglycans and glycoprotein)] in bones, tendons, muscles, and other calcified tissues like teeth leads to symptoms of fluorosis (**Flow chart 2**).

Elevated content of GAG in bone and its reflection in serum is considered as an index to assess fluoride toxicity and fluorosis at very early stages. The ratio of N-acetyl neuraminic acid in serum [serum sialic acid (SSA)] to GAG is a sensitive index to detect fluoride toxicity at very early stages both in human and animal models. The ratio of SSA/GAG revealed a 30–50% reduction in human sera in fluoride poisoning. Serum alkaline phosphatase (SAP) activity is high in fluorosis, indicating increased osteoblastic activity. Both mature and immature osteoblasts are increased and secrete more osteocalcin.

## DETERMINANTS OF THE DISEASE

Chronic fluoride exposure and the biological response leading to ill-effects depend on the following factors: concentration of fluoride in drinking water, food, and cosmetics; low calcium and high alkalinity of drinking water; age of the individual; duration of intake; pregnancy, lactating mother; derangement in hormonal profile either as a result of fluoride ingestion or cause, aggravates the disease. The affected hormones are calcitonin, parathyroid, vitamin D and cortisol, necessary for healthy bone formation and bone function.

## CLINICAL PRESENTATION

### Acute Fluoride Intoxication

Initial symptoms are nonspecific and include diffuse abdominal pain, diarrhea, vomiting, excessive salivation with thirst, perspiration and painful spasms in the limbs. Later on the clinical presentation are related to derangement of enzyme systems such as those engaged in metabolism, energetic, and cellular respiration and in endocrine functions. Symptoms particularly relate to alimentary, cardiovascular, respiratory and central nervous systems. The acute lethal dose of fluoride for man is probably about 5 g as NaF. Death occurs in 2–3 days.

### Management of Acute Toxicity

Monitor and support vital signs, cardiac monitoring for arrhythmia, treat them especially in the presence of refractory hyperkalemia. Gastric lavage, if emesis has not occurred. Charcoal is probably not of benefit. Monitor serum electrolyte, calcium, and magnesium levels and treat accordingly. Administer milk, oral calcium salts, or aluminum or magnesium based antacids to bind fluoride. Consider hemodialysis if required.

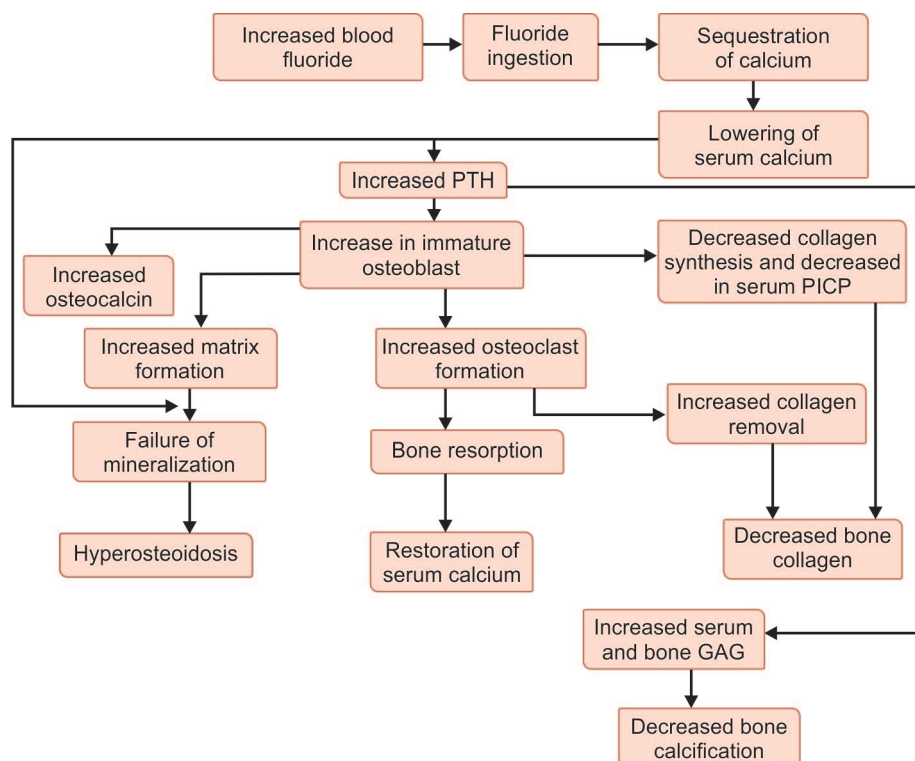
### Chronic Fluoride Ingestion

Toxic effects manifests as skeletal or dental fluorosis, or non-skeletal manifestations, including premature aging.

### Dental Fluorosis

Features vary and include the following: white opacities, faint to dark yellow stain, pitting, chipped off edges, black discoloration, enamel hypoplasia, delayed eruption, and edentate (loss of teeth at an early age) (**Figs 1A and B**). Incidence of mottled teeth was observed even with range of 0.7–1.5 mg F/L in drinking water.

**Flow chart 2** Pathophysiology of fluorosis







**Figures 1A and B** (A) Dental fluorosis: grade 4 (Photograph indicating discrete or confluent pitting. Brown stains are widespread, and teeth presenting corroded like appearance); (B) Enamel hypoplasia (Fluoride induced)

The minimal daily fluoride intake in infants that may cause very mild or mild fluorosis in human beings was estimated to be about 0.1 mg/kg body weight.

#### *Skeletal Fluorosis*

Pain and stiffness in joints results in an arthritis type picture; pain and stiffness in back causes restriction of movement of the skin. Stiffness spreads and may present as discomfort and paresthesia in limbs and trunk. Poker Back sign is a late presentation. Joint deformity is a late presentation. The commonly involved joints are knee, hip, spine, etc. Exostosis in long bones may be apparently visible.

#### *Clinical Fluorosis*

Fluorosis presents as heel pain, knock knee, painful and restricted joint movements, deformities in limbs, hunch back (**Figs 2A to C**) and in extreme cases with paralysis, muscular wasting and premature aging.

#### **Systemic Manifestations**

**Neurological** Nervousness and depression, tingling sensation in fingers and toes, polydipsia and polyurea, headache.

**Gastrointestinal** Dyspepsia, acute abdominal pain, diarrhea, constipation, melena.

**Muscular** Muscle weakness and stiffness, pain in the muscle and loss of muscle power.

**Allergic** Very painful skin rashes (pinkish red or bluish red spot, round or oval shape), due to perivascular inflammation. The rashes fade and clear up within 7–10 days.

**Red blood cells** Excessive fluoride accumulates on the erythrocyte membrane, causing loss of calcium content. This results and is formation of echinocytes. The life span of these echinocytes is less causing early destruction, leading to anemia.

**Ligaments and blood** Ligaments tend to harden and calcify and the blood vessels get blocked.



**Figures 2A to C** Clinical fluorosis: (A) Deformity of leg; (B) Knock knee; (C) Hunch back

**Fertility** Fluoride reduces fertility by decreasing Leydig cell function, testosterone levels and spermatogenesis. It also disturbs the sertoli cell function.

**In utero exposure** High fluoride exposure during pregnancy causes intrauterine growth retardation and effects primary dentition in infant.

**Mental efficiency** Excessive fluoride intake reduces mental work capacity and hair zinc content. In animal studies it is reported to cause decreased 5-hydroxyindoleacetic acid and increased norepinephrine in brain.

**Thyroid** Fluoride has inhibitory effect on iodine uptake. Goiter prevalence is more in fluoride prone areas.

**Others** Excess fluoride may have an association with certain neoplasms, may impair glucose tolerance, and inhibit lactation.

## DIAGNOSIS

Clinical examination, examination of teeth and three simple clinical diagnostic tests described in **Figure 3** are generally followed for the initial diagnosis of the problem. Biochemical evaluation includes estimation of serum calcium; serum alkaline phosphatase; fluoride levels in whole blood, serum and urine; ascorbic acid levels in serum and leukocyte; serum parathyroid hormone; serum sialic acid and serum GAG. Bone fluoride content is increased in fluorosis.

## Radiological Evaluation

Involvement of the axial skeleton is characteristic, and changes are most marked in the spine (**Figs 4A to D**), pelvis and ribs. Radiographs reveal osteosclerosis, periosteal bone formation; calcification of interosseous membrane, ligaments, capsules, muscular attachments, tendons, exostoses; and osteophytosis. In early fluorosis osteosclerosis and thickening at the junctions of trabeculae is observed. Interosseous membrane calcification in forearm (**Figs 4A to D**) and calcification of the sacrotuberous ligament is considered a characteristic feature. In children skiagram of long bones are also helpful, which are characterized by osteopenia and bony deformities (**Figs 5A and B**).

## Bone Scintigraphy

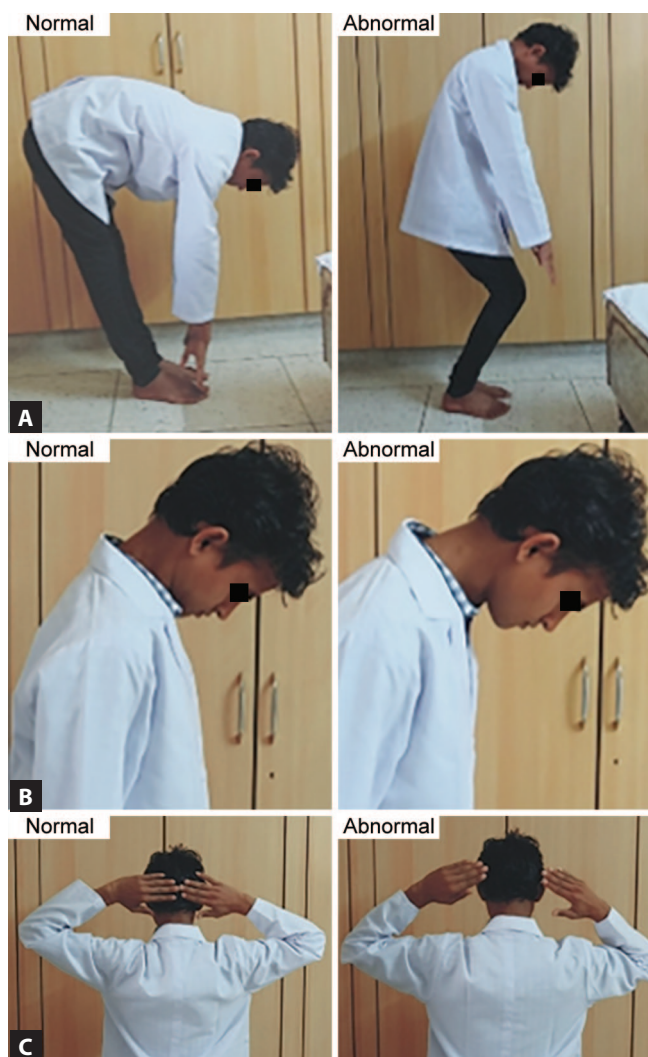
Metabolic superscan on skeletal scintigraphy reveals increased tracer uptake in axial and appendicular skeleton, reduced soft tissue uptake, poor or absent renal images, prominent costochondral junction and *tie sign* in sternum. These findings are indicative of high bone turnover state in endemic skeletal fluorosis.

## CT Examination

Plain CT scan reveals increased bone density (osteosclerosis), osteopenia, osteoporosis, trabecular blurring or haziness, compact bone thickening, periosteal bone formation and ossification of the attachments of tendons, ligaments, and muscles. Interosseous membrane calcification and ossification of the posterior longitudinal ligament can also be visualized. Syndesmophytes (calcification or heterotopic ossification inside a spinal ligament or of the annulus fibrosus) may be present.

## MRI

The findings reported include vertebral sclerosis, encroachment and narrowing of neural foramina and, in some cases a combination of premature degeneration with anterior disc herniation, lateral disc herniation leading to indentation of thecal sac and narrowing of neural foramina, and generalized iliac wings sclerosis.



**Figures 3A to C** Clinical tests for diagnosis of fluorosis. (A) Normal person can touch the toes with fingers. Fluorosed person cannot bend without folding his knees; (B) Normal person can touch the chest with chin. Fluorosed person cannot touch the chest with chin; (C) Normal person can fold the arms and touch the back of the head. Fluorosed person cannot fold the arms and touch the back of the head

## DIFFERENTIAL DIAGNOSIS

### Dental Fluorosis

Dental fluorosis should be differentiated from dental caries. The pitting, chipping and discoloration occurs on incisal edge and occlusal surface (biting surface) of teeth, whereas in fluorosis, these changes occur on labial surface of teeth initially and later on extending to incisal edge and occlusal surface also. Fluoride dental stains, which are internal stain and very difficult to remove (decolorize), should be differentiated from external stains caused due to eating of fruits and stain of brinjal, banana, and tetracycline. Pyorrhea and halitosis should not be confused with dental fluorosis.

### Skeletal Fluorosis

Fluorosis need to be differentiated from rickets, renal osteodystrophy and other congenital malformations. Urinary and serum fluoride levels, radiographs of skeletal, calcification of the interosseous



membranes in the forearm and sclerosis of the vertebral column will clinch the diagnosis. Joint pains in skeletal fluorosis (arthritic presentation) have to be differentiated from those caused by osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis,

etc. If required, bone biopsy for estimation of fluoride content of bone provides conclusive evidence. In later stages skeletal fluorosis is marked by restriction of spine movements. Increased sclerosis of spine on radiography will confirm the diagnosis.

### Nonskeletal Fluorosis

The preskeletal stage of fluoride intoxication poses problems for diagnosis. In these cases radiograph of the skeleton will neither show sclerosis or calcification of the ligaments nor significant elevation of urinary levels of fluoride. Moreover, the manifested symptoms are so varied that they may be identifiable with those of various other diseases. The complaints of the victims in this regard are so common place that they may be easily mistaken for those resulting from other ailments, e.g., dyspepsia, musculoskeletal pain, headache, etc.

## TREATMENT AND PREVENTION

### Treatment

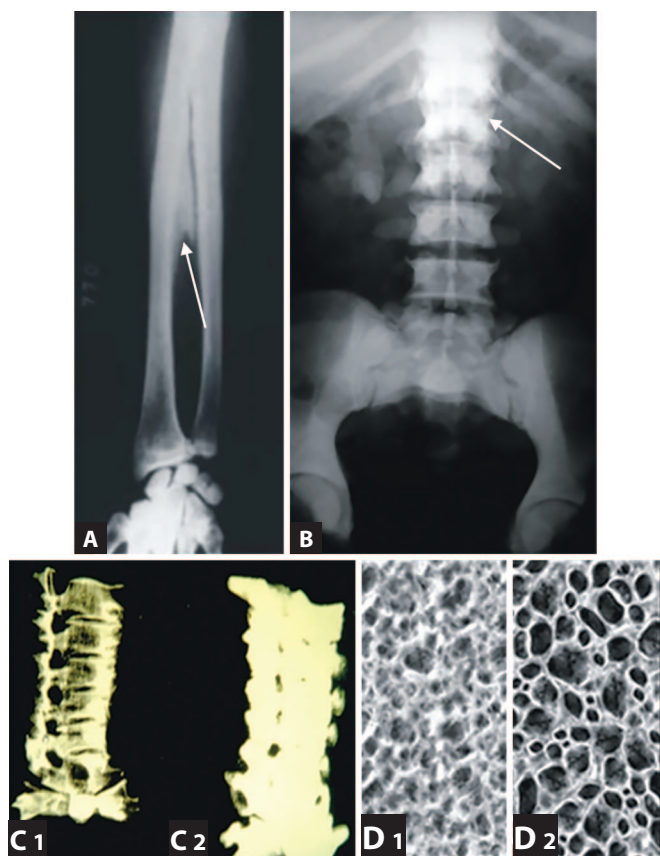
Vitamins C and D, and, salts of calcium, were prescribed in an attempt to reverse the effects of fluorosis. Latest studies indicated that fluorosis could be reversed partially, at least in children by a therapeutic regimen of calcium, vitamin C and vitamin D supplementation. Calcium in gut directly inhibits the absorption of fluoride ions, improves the serum calcium levels, inhibits the excessive release of parathyroid hormone thereby preventing excessive activation of osteoblasts and osteoclasts and hence preventing hyperosteoidosis and osteopenia. Calcium also helps in bones and teeth mineralization.

Calcium should be given as recommended dietary allowance (RDA) plus 25 mg elemental calcium per mg of fluoride for neutralizing excessive fluoride intake. Vitamin D<sub>3</sub> (60,000 IU once or twice a week) enhances calcium absorption and retention without causing hypercalcemia. Ascorbic acid (500–1000 mg/day) controls collagen formation and hence maintains the teeth and bone structure. It provides the conditions favorable for laying down of collagen, improving the hydroxylation of proline. Calcium and vitamin C should be supplemented at different time to avoid development of conditions favorable for formation of renal stones. For stained and disfigured teeth, cosmetic dental treatment is advised.

### Prevention

Providing defluoridated water for drinking purpose is the best way to prevent fluorosis. Many methods based on precipitation, adsorption, ion exchange, electrochemical and membrane processes have been developed in the past few decades to remove fluoride from drinking water. Two commonly used field defluoridation techniques in India are Nalgonda process and activated alumina process. In these processes aluminum compounds are used for removal of fluoride from water. Apart from removal of fluoride these processes result in moderate to high residual aluminum in treated water, creating a predisposing condition for formation of aluminofluoride complexes. Aluminofluoride complexes are of grave health concern due to their neurotoxicity mediated through stimulation of various guanine nucleotide binding proteins (G Proteins).

Fluorosis can also be mitigating by effecting minor changes in the diet and dietary habits of the population compatible with their social system and available resources. The main aim should be to restrict use of fluoride rich food; avoid use of fluoride rich cosmetics; and use of food rich in calcium, vitamin C and proteins. Rainwater storage can be a major source of fluoride free drinking water for both humans as well as animals. A hygienic storage of rain water for ingestion can help relieve the fluorosis problem to a good extent.



**Figures 4A to D** (A) Calcification of interosseous membrane; (B) Fluorosis affected spine (osteosclerosis lumbosacral region); normal (C1) versus fluorosis affected (C2) Spine; and (D1, D2) Histopathological pictures of osteoporotic spine



**Figures 5A and B** (A) Anterior bowing of tibia and fibula and deformity of elbow, curving of thigh. X-rays showing osteopenia; (B) Bowing of thigh, X-ray showing severe osteopenia

**MORE ON THIS TOPIC**

Bureau of Indian Standards. Drinking Water—Specification, Doc: FAD 25(2047) C, IS 10500 (Second Revision). India, 2009.

Fawell J, Bailey K, Chilton J, et al. Fluoride in drinking-water. Geneva: World Health Organization; 2006.

Gupta SK, Gupta RC, Seth AK. Reversal of fluorosis in children. *Acta Paediatrica Japonica*. 1996;38:513-9.

Gupta SK, Khan TI, Gupta AB. Environmental Health Perspective of Fluorosis in Children—Treatment and Prevention. Saarbrücken, Germany: LAP Lambert Academic Publishing; 2012.

WHO. Fluorides. Geneva: World Health Organization; 2002.

WHO. Guidelines for Drinking Water Quality. 4<sup>th</sup> ed. Geneva: World Health Organization; 2011.

**IN A NUTSHELL**

1. Fluorosis affects mainly bone and teeth but practically affects all systems of body.
2. Fluoride ingestion should be avoided in pregnant and lactating mother.
3. It is possible to revert the fluorosis presentations partially at least in children by medical management (calcium, vitamin D and vitamin C supplementation).
4. Avoiding f-rich food (especially tea and fluoridated tooth-paste) and use of food rich in calcium and vitamin C are highly effective, both as treatment measure in children and preventive measure to all ages.
5. Defluoridation of water is an effective way of disease prevention.



## Chapter 22.17

# Enteral and Parenteral Nutrition

Ashish Bavdekar

Nutritional support refers to enteral or parenteral provision of calories, protein, electrolytes, trace elements, vitamins, minerals along with sufficient fluids. The word *enteral* means *through the gastrointestinal tract* and any route other than the gut which is used for nutrient delivery into the body is referred to as *parenteral*. The basic goal of nutrition support is to meet the metabolic needs of the child in order to mitigate the breakdown of muscle protein and to provide substrate for the anabolic state during recovery.

All efforts should be made in hospitalized children to detect malnutrition at an early stage. Patients should be considered malnourished or at risk of developing malnutrition if they have inadequate nutrient intake for 7 days or if they have a weight loss of 10% or more of their preillness body weight. Patients who cannot maintain adequate oral intake are candidates for nutritional support and should be considered for enteral feeding first. Enteral nutrition (EN) and parenteral nutrition (PN) should be combined when enteral support alone is not possible. When administering nutrients enterally, access to the gastrointestinal tract should be gained in the most natural and least invasive manner. The parenteral route needs to be used only when the patient is at risk for malnutrition due to poor oral intake, where a trial of enteral feeding has failed, or where severely diminished intestinal function due to underlying diseases or treatment is anticipated. Choosing the enteral or parenteral route requires knowledge of their advantages and disadvantages. The advantages of enteral nutrition are: (i) preserves gastrointestinal (GI) structure and function, gut hormonal response, normal gut flora, normal blood supply to the gut, and the integrity of gut-associated lymphoid tissue (GALT); (ii) it may help prevent bacterial translocation and sepsis; (iii) complications are far lesser than PN; and (iv) EN is far less expensive than PN. The advantages of parenteral nutrition are (i) no risk of aspiration of tube feeding; (ii) better patient acceptance; (iii) more reliable delivery; and (iv) it is the only method of nutrition in severe intestinal failure.

## ENTERAL NUTRITION

Enteral nutrition is defined as delivery of food directly into stomach or duodenum or jejunum over tube or stoma or/and oral provision of dietary foods for special medical purposes.

### Indications

- To provide nutritional requirements which cannot be met by regular food intake in a patient with at least a partially functional gut (**Table 1**).
- As treatment of specific diseases—Crohn's disease and food intolerance, etc.
- In a neurologically impaired child, if feeding times are excessive.

### Contraindications

**Absolute contraindications** include intestinal perforation, necrotizing enterocolitis, bowel obstruction or ileus, inability to access the GI tract—trauma, burns, or significant hemodynamic instability. Relative contraindications (in these situations, EN should be given as much as tolerated and the remaining requirement completed by PN) include intractable vomiting or diarrhea; acute abdominal distention; high output gastric, enteric fistula; severe upper gastrointestinal bleeding; and intestinal dysmotility.

### Enteral Formulations

Enteral formulations should supply an adequate intake of nutrients in a form and volume that the child can tolerate. Enteral feeds supply

**Table 1** Indications for enteral nutrition

Inadequate intake	Sucking/swallowing disorders – preterm babies, neurologic impaired children Congenital abnormalities of upper GI tract—to fistula Local problems—trauma, extensive facial burns Critical illness with impaired oral intake—on ventilation Severe GE reflux
GI disorders	Exocrine pancreatic insufficiency—cystic fibrosis Inflammatory bowel disease Malabsorption syndrome—food allergy, severe celiac disease Intractable diarrhea of infancy Severe immunodeficiency Chronic liver disease with malnutrition Chronic pseudo-obstruction Extensive intestinal disease
Other indications	Chronic organ diseases, heart, kidneys Disease management, Crohn's disease, glycogen storage disease

a balanced mix of all of the essential nutrients needed for meeting physiological requirements and growth. Most enteral formulations can be used as a sole source of nutrition for prolonged periods of time. They usually have an energy density of 1 kcal/mL and can be delivered via tube but may also be taken orally. Feeds with a higher energy density (1.5 kcal/mL) are useful in children with increased energy requirements. Enteral formulations are usually gluten free, lactose free or low lactose and iso-osmolar (300–350 mOsm/kg). While selecting an appropriate formula, one should consider the site, route and mode of delivery. It is individualized according to patients' nutritional needs and the underlying clinical condition. Standard enteral formulations are either polymeric, semi-elemental or elemental (**Table 2**). Polymeric formulas meet the requirements of most pediatric conditions and are generally effective in the presence of an intact bowel. Polymeric preparations are easily available in India, semi-elemental with some difficulty and pure elemental preparations have to be procured from abroad.

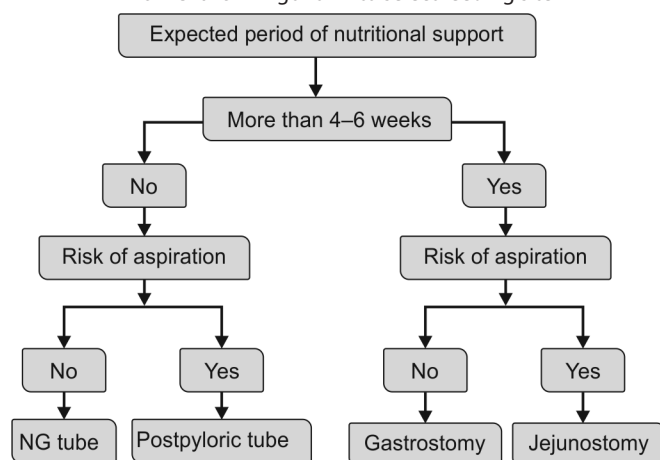
Besides the standard formulae, the following specialized formulae are also available for specific indications: (a) MCT enriched formulas for fat malabsorption disorders; (b) high caloric formula (1.5 kcal/mL) for conditions where fluid restriction is required, e.g., renal failure; (c) immunomodulating formula with glutamine, omega-3 fatty acids, nucleotides; and branch chain amino acid formula for liver disorders.

### Site and Mode of Delivery

Enteral nutrition can be administered either into the stomach or beyond the pylorus, depending on the morphology and function of the GI tract and the risk of aspiration of gastric contents. Whenever possible, gastric feeding is selected as it is more physiological, easier to achieve secure positioning, associated with flexible feeding schedules, tolerance of volume and hyperosmolar solutions because of the reservoir capacity of the stomach, lower frequency of diarrhea and dumping syndrome. Gastric acidity also has an antibacterial function. Postpyloric feeding is indicated only in clinical conditions in which aspiration, gastroparesis, pyloric obstruction, or previous gastric surgery precludes gastric feeding or when early postoperative feeding after major abdominal surgery is planned. If the expected duration of feeding is short (< 6–8 weeks), feeding can be delivered by nasogastric or nasoenteric feeding tube. But if the expected duration is more than 6–8 weeks, a feeding gastrostomy or jejunostomy is recommended (**Flow chart 1**). Polyvinyl chloride (PVC) tubes are less desirable because they can release potentially toxic phthalate esters into fat-containing feedings and need to be changed every 3–5 days as they become rigid. Silicone

**Table 2** Enteral formulations

	<i>Polymeric</i>	<i>Semi-elemental</i>	<i>Elemental</i>
Nitrogen source	Whole proteins	Small peptides	Amino acids
Carbohydrate source	Glucose polymers	Glucose polymers	Glucose polymers
Fat source	LCT or LCT + MCT	LCT + MCT	LCT + MCT
Caloric density	1–2 kcal/mL	1–1.7 kcal/mL	0.67–1 kcal/mL
Osmolality	300 mOsm/kg	300–450 mOsm/kg	300–600 mOsm/kg
Advantages	Palatable, relatively inexpensive	Hypoallergenic, easily absorbed	Nonallergenic, immunomodulatory
Disadvantages	Requires intact GI tract	Bad taste, expensive	Some are expensive, hyperosmolar, bad taste
Indications	Multiple	Allergy, malabsorption	Multiple allergies, severe malabsorption

**Flow chart 1** Algorithm to select feeding site

and polyurethane tubes can usually be safely kept in place for up to 8 weeks. Feeding tube diameter is selected according to the weight and age of the child. The smallest external diameter possible should be used because it causes less patient discomfort than larger tubes. *The required length of the tube is the distance between the nose and the umbilicus.*

Intermittent bolus feedings consist of fixed volumes of feeding delivered several times daily usually every 1–3 hour. If well tolerated, intermittent gastric feeding is preferred because it is more physiological, they elicit cyclical surges of trophic GI hormones, are less expensive and less restrictive. Continuous feeding is the continual delivery of feeding over 12–24 hour. Usually a feeding pump is used to regulate feeding delivery. There is very limited data to suggest that continuous feed is better tolerated compared to bolus feeds, except maybe in patients with severely impaired GI function where continuous feeding might be beneficial. On the other hand, continuous enteral feeding is associated with impaired gallbladder emptying in infants. A constant infusion of nutrients at less than 3 kcal/min is required to prevent delayed gastric emptying and vomiting. Postpyloric feeding needs to be continuous and should be increased cautiously, particularly when hyperosmolar feeds are used as it may lead to dumping syndrome. When the child can eat, both methods of feed delivery can be combined by tube feeding overnight for 10–12 hours and oral intake during the day. This combination is particularly beneficial for the preservation of sensory and motor oral functions.

### Complications of Enteral Feeding

Though much safer than PN, enteral tube feeding may be poorly tolerated and does carry some risks (**Table 3**). Refeeding syndrome

is discussed below. Long-term tube feeding is associated with failure to develop (or regression of) oromotor feeding skills.

### Refeeding Syndrome

Various metabolic complications can arise as a result of providing enteral/parenteral nutritional feeding to malnourished patients. During prolonged fasting, energy is derived from fats by generating ketones and there is suppressed insulin secretion and increased glucagon secretion. Sudden reversal of catabolism through nutritional support (particularly excessive carbohydrate) leads to a surge of insulin secretion, which causes massive intracellular shift of phosphate, magnesium, and potassium with a subsequent fall in serum concentrations. Glucose and levels of the B vitamins thiamine may also fall. This causes hemolytic anemia, muscle weakness, and impaired cardiac function which could lead to cardiac failure, fluid overload, arrhythmia, and death. The risk is greatest in the first week of feeding. To prevent this syndrome, it is important to gradually increase the volume, protein and energy content of feeds, and supplement vitamins and electrolytes (especially phosphorus) during nutritional repletion.

### Monitoring Enteral Nutrition

Children receiving enteral nutrition should be monitored regularly to assess growth, fluid, energy and nutrient intake, therapeutic efficacy, and to prevent complications. Biochemical monitoring and assessment of acute weight changes are keys to preventing metabolic complications. The most common metabolic complications are electrolyte abnormalities, alteration in fluid status and hyper- and hypoglycemia. Clinical observations and assessment of intake and output help prevent development of GI complications. The most common complication is diarrhea. Vomiting, abdominal distension and pain, and constipation may also occur. Growth and development are key indicators of tube-feeding efficacy. Psychological aspects should be monitored to prevent problems such as feeding aversion and loss of feeding skills. Despite the broad range of possible complications, enteral nutrition is a relatively safe and effective way of improving nutritional status, clinical condition and growth of pediatric patients, particularly if procedural protocols are followed and regular quality control is applied.

### PARENTERAL NUTRITION

In a number of illnesses (both surgical and medical), the nutritional demands of the child cannot be met adequately through the enteral route for prolonged periods. The concept of providing all the required nutrients like proteins, carbohydrates, fats and vitamins via the intravenous route, is called parenteral nutrition. The advent of successful PN has indeed reversed the prognosis of

**Table 3** Enteral feeding complications and preventive and therapeutic measures

Complications	Cause	Prevention/Treatment
Diarrhea	Unsuitable feed in a child with impaired gut function	Change to semi-elemental/elemental feed
	Excessive feeding	Give more frequent smaller feeds, or change to continuous feeds
	Intolerance of bolus feeds	Change to iso-osmolar feeds or slowly increase feed concentration, try continuous infusion
	High feed osmolarity	Prepare feeds in hygienic environment
Nausea/vomiting	Microbial contamination of feed	
	Excessive feeding	Reduce volume and rate and increase slowly as tolerated
Regurgitation/aspiration	Slow gastric emptying	Encourage lying on right side. Give prokinetics
	Gastroesophageal reflux	Correct positioning, feed thickener, drugs, continuous feeds, postpyloric feeding, fundoplication
	Dislodged tube	Secure tube adequately and regularly review position
	Intolerance of bolus feeds	Smaller, more frequent feeds or continuous infusion

many such illnesses, which were hitherto fatal. The popularity of PN is now fast growing in our country too, despite the constraints of cost and infrastructure. Although widespread availability is very much desired, it is important that the technique is developed with considerable expertise and used judiciously with full knowledge of its indications, limits, dangers and benefits.

### Indications

Parenteral nutrition should be used only if EN cannot be used for any reason. PN is required in any situation in which the baby should not be fed, will not feed, or cannot be fed adequately for prolonged periods. It is usually indicated when there is bowel dysfunction resulting in inability to tolerate EN for more than 1–3 days in infants and 4–5 days in older children. Other deciding factors are underlying malnutrition, nature of concurrent therapeutic measures (e.g., ventilation) and the expected outcome of the disease. In the Indian setup, social and monetary background is also an important consideration. The range of indications of PN has grown considerably in recent years. Some common indications are discussed below:

#### Surgical Conditions

Parenteral nutrition has dramatically changed the outcome in extensive resections of the small intestine, enterocutaneous fistulae and short gut syndromes. The most gratifying results with PN are in surgical neonates with successful surgical correction, e.g., tracheoesophageal fistula, duodenal atresia, omphalocele, and Hirschsprung disease. The need for PN in such conditions can be predicted early and therapy can be started immediately after corrective surgery.

#### Low Birthweight Infants (LBWs)

The numerous feeding difficulties, the poor intestinal function, and the greatly increased requirements make PN a logical choice in preterms less than 28–32 weeks gestation and/or less than 1,000 g. It is also indicated in newborns who are unlikely to achieve at least 50% enteral feeds by day 5.

#### Malabsorption Syndromes

One of the commonest indications for PN has been severe persistent diarrhea in children irrespective of the etiology: infectious diarrhea, congenital enteropathies, or immune deficiency. The recent use of special enteral diets has definitely reduced the need of PN in these cases. However, due to unavailability of these diets in India, there is still an important role of PN in these conditions. Disorders with severe small intestinal mucosal pathology (e.g., microvillus inclusion disease) often require long-term PN as gastrointestinal losses of fluids, electrolytes and proteins continue even after stopping all enteral feedings. A judicious combination of enteral and parenteral nutrition will obviously allow restoration of normal nutritional status while maintaining gastrointestinal function.

### Nongastrointestinal Indications

An increasingly common indication of PN today is in management of children with malignant diseases, as chemotherapy and radiation may impair intestinal mucosa, damage circulatory vessels and lymphocytes and interfere in gastrointestinal motility. PN is also increasingly used in a host of other conditions such as end stage liver disease (pre/post-liver transplants), renal failure (with appropriate amino acids) and multiple trauma or extensive burns (to combat excessive nitrogen losses).

### Nutrient Sources

The basic solutions comprise a protein source, a lipid source, and a carbohydrate source to be mixed with electrolytes, vitamins and trace metals, all appropriate to the age, body weight and energy requirements of the child.

#### Proteins

These solutions are mixtures of crystalline amino acids (AA), at least 40% of which are essential amino acids. Neonates and young infants are particularly sensitive to imbalance in amino acid solutions. They need conditional amino acids like histidine, cysteine and taurine. Amino acid requirements are given in **Table 4**. Caution should be exercised while using AA solutions primarily designed for adults.

#### Lipids

Parenteral lipid emulsions are concentrated sources of calories and are available in 10% or 20% strengths. In children only 20% is used providing 2 kcal/mL. Being isotonic and low in osmotic activity, lipids can be given through peripheral veins for prolonged periods. Lipid emulsions are available as soy, fish oil or SMOF (soybean oil, MCTs, Olive oil, Fish oil). Lipids are started in dose of 1 g/kg/day up to a maximum of 2–3 g/kg/day.

#### Carbohydrates

Glucose is the carbohydrate of choice, as it is an energy substitute with ubiquitous utilization by all tissues of the body. It typically provides 40–55% of caloric intake. The monohydrate form provides 3.4 kcal/g. Glucose substitutes such as sorbitol, fructose, and xylitol, have also been tried although they are metabolized only in the liver and tend to cause osmotic diuresis.

#### Electrolytes, Vitamins, Minerals and Trace Elements

Daily estimated requirements of electrolytes, vitamins and minerals (Na, K, Ca, P, Mg) must be added to PN. There are limitations to the amount of calcium and phosphorus that can be supplied as they can precipitate in PN solutions. Intravenous preparation for phosphorus is not easily available in India and has to be supplied orally.

## Other Components

Heparin in doses of 0.5–1.0 U/mL may be added to the PN solution to prevent thrombophlebitis and stimulate lipoprotein lipase. Insulin may be added for maintaining sugar levels in patients with hyperglycemia.

## PN Assembly and Regimens

The route of providing PN is either by central venous access (tip of catheter is in superior or inferior vena cava or right atrium) or peripheral venous access. The central access is preferred if PN is to be given more than 2 weeks, if peripheral access is poor, if patient is fluid restricted and hypertonic solutions have to be used (osmolality > 900–1,000 mOsmol/L). Traditionally PN solutions are two-in-one solutions with the IV lipid administered separately. This is used in many hospitals since it allows for the easy identification of precipitates and for increased electrolyte administration. The three-in-one solutions have the amino acids, glucose and lipids mixed together and are usually administered at home for ease of care, but are also being used in some pediatric hospitals. In India small volume three-in-one solutions are not available and hence cannot be used in small children. Filters are placed in line between the PN solution and the patient and are very important. A 0.22 micron filter is used for the two-in-one solution to remove most pathogenic bacteria (For three-in-one solutions, a 1.2 micron filter is used which removes only *Candida* and large lipid droplets).

Parenteral nutrition is introduced gradually over a period of 2–4 days depending on size and age of child. The calculated quantities of amino acids, dextrose and electrolytes are mixed in the same bottle under laminar air flow. This mixture and the lipid emulsion are administered by separate IV sets and the two lines coupled by a Y connector just before entry into the vein. Both the solutions should be regulated by infusion pumps to provide accurate steady flow rates. Progressive build up regimens for neonates, infants and older children have been described (Table 4). Enteral feeds should be started as soon as possible in trophic amounts. Once enteral feeds are tolerated, PN is weaned off. PN should not be decreased until enteral feeds exceed 50 mL/kg/day. However, do not exceed total (enteral + parenteral) proteins 3.5 g/kg/day and fat 5 g/kg/day. Stop PN when third fourth of daily enteral intake has been achieved.

## Complications

### Technical

Central venous access has potential arterial hemorrhage, air embolism and cardiac arrhythmias. Complications of peripheral access include thrombosis, perforation of vein, with necrosis of tissue, and thrombophlebitis. Nonthrombotic occlusions are caused by calcium phosphate precipitates, medication precipitates, lipid residue, or mineral precipitates. The use of 0.1N hydrochloric acid is most effective for clearing catheter occlusions due to precipitation of calcium-phosphate. For catheter occlusions due to precipitates associated with medications in the high pH range such as tobramycin and phenytoin, sodium bicarbonate 1 mEq/mL has been anecdotally reported to be effective. 70% ethanol is the most effective solvent to dissolve lipid residue.

**Table 4** Amino acid requirement in parenteral nutrition (g/kg/day)

Preterm infants	1.5–4.0
Term neonates	2.0–3.5
Child 5–20 kg	1.0–2.5
20–40 kg	1.0–2.0
Adolescent	0.8–2.0

## Infections

Sepsis associated with PN is life-threatening. Sources are multiple and include entry site of catheter, connections, PN fluid, etc. There is a need to differentiate between a central line infection and colonization. About 22% of all hubs are colonized with bacteria. Infections may be difficult to recognize as some patients may be febrile only during PN infusions or when the central line is flushed. A white blood cell count may be normal in circumstances where the infection is at the exit site. The common organisms are *Staphylococcus epidermis*, *S. aureus* and occasionally gram-negative and fungal sepsis. Therapy is determined by the organism involved and antibiotic sensitivity. Strict asepsis during catheter insertion, preparation and administration of PN, use of laminar flow system and training of staff dealing with PN can go a long way in reduction of sepsis. Tubing for lipids should be changed every 12–24 hours and the dextrose tubing be changed every 72 hours unless it is a three-in-one solution.

## Metabolic

- Complications of protein metabolism** The use of crystalline amino acids has significantly reduced the risk of hyperammonemia. Amino acid infusion may have to be reduced till ammonia levels normalize. Metabolic acidosis is more frequent when a large infusion of amino acids is given to preterm infants.
- Complications of carbohydrate metabolism** Hyperglycemia is usually a problem in central venous administration when dextrose is delivered directly into the central venous flow. Other causes to be considered are hypokalemia, sepsis and steroid use. Hyperglycemia could lead to glycosuria, osmotic diuresis and dehydration.
- Complications of fat metabolism** Hypertriglyceridemia and high free fatty acid levels are associated with PN. These can be prevented by either using mixed solution of MCT and LCT or regular monitoring of serum triglyceride levels.
- Complications related to electrolytes and minerals** Hyponatremia, hypo/hyperkalemia hypocalcemia, hypomagnesemia and hypophosphatemia are commonly associated with PN. These are often iatrogenic and preventable by monitoring. Trace element and vitamin deficiencies are common on long-term PN. They need to be supplemented especially in LBW infants.

## Hepatobiliary Complications

These appear in 40–60% of neonates and 10–15% of older children on PN, and include steatosis, cholestasis, cholelithiasis, fibrosis or cirrhosis. The cause is multifactorial and involves duration of PN, LBW, associated trophic enteral feeds, sepsis, remaining bowel length in surgical resections, type of amino acid and lipid solutions used. Treatment includes starting at least minimal EN if possible, starting cyclical PN, reducing dose of lipids and using fish oil based emulsions and adding ursodeoxycholic acid.

The fear of PN related complications has always been a deterrent in the institution of this potentially life-saving technique. However, the complication rates in our unit have shown a marked decline with intensive and continuous training of staff, especially the resident doctors and nurses. Especially designed, locally manufactured intravenous sets, use of a laminar flow workstation for compounding and other such adaptations have contributed further. The most significant reductions occurred in local complications, such as thrombophlebitis from 89% in 1986 to 29.4% in 1991 and septicemia from 52% to 11.7%.

## Monitoring

Meticulous monitoring is necessary not only to detect complications, but to document clinical benefit. Most septic and



metabolic complications can be prevented or detected before they cause serious consequences, if the biochemical monitoring protocol is followed rigidly. Monitoring should be more frequent in the initial stages of PN and perhaps, less frequent once PN is well established. The monitoring protocol at our hospital is given in **Table 5**. It is mandatory to develop micromethod systems for biochemical monitoring in newborns and young infants. In absence of these, blood sampling volumes should be carefully recorded and replenished when indicated. Adjustments in daily electrolytes, nutrients and fluid orders are based on biochemical monitoring.

### Cost Analyses

Parenteral nutrition is expensive and quite often methods are devised locally to save costs. This is perfectly acceptable as long as care is taken to ensure that these measures do not affect the safety of the patient. Cost saving may be achieved by (i) reducing wastage by sharing solutions between patients and preventing over-prescription; (ii) decreasing complications by using peripheral lines, preventing metabolic complications, and strict asepsis; and (iii) Indigenization of equipment for delivery of PN. A reduction in cost should not be attempted by repeated use of same PN solutions over days; compromise on biochemical monitoring, disposables, or compromise on infusion pumps; and substituting hypertonic glucose for lipids as source of energy.

**Table 5** Suggested monitoring protocol for parenteral nutrition

Serum electrolytes	3 times/week initially, then weekly
Serum urea nitrogen	3 times/week initially, then weekly
Calcium, magnesium, phosphorous	3 times/week initially, then weekly
Glucose	2 times/day
Serum proteins	Weekly
Liver function tests	Weekly
Hematocrit	Weekly
Urine glucose	Daily
Serum triglycerides	4 hour after a dose increase of lipids initially, then weekly

### IN A NUTSHELL

1. Nutrition support plays an important role in the management of hospitalized children.
2. Use the gut for enteral nutrition (EN) whenever possible.
3. Standard polymeric formulations are effective in most patients.
4. Gastric feeding should be preferred over transpyloric feeding whenever possible.
5. Parenteral nutrition (PN) is lifesaving in some conditions where EN is not possible.
6. Strict monitoring is required to prevent and treat complications in PN.
7. Regimens for PN differ in children and small preterms.

### MORE ON THIS TOPIC

- ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr. 2002;26:1SA-138SA.
- Axelrod D, Kazmerski K, Iyer K. Pediatric enteral nutrition. J Parenter Enteral Nutr. 2006;30:S21-6.
- Bhave SA, Bavdekar AR. Pediatric parenteral nutrition in India. Indian J Pediatr. 1999;66:S141-9.
- Braegger C, Decsi T, Dias JA, et al. Practical approach to paediatric enteral nutrition: a comment by the ESPGHAN committee on nutrition. J Pediatr Gastroenterol Nutr. 2010;51:110-22.
- Koletzko B, Goulet O, Hunt J, et al. 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005;41:S1-87.
- Lochs H, Dejong C, Hammarqvist F, et al. ESPEN Guidelines on Enteral Nutrition: Gastroenterology Clin Nutr. 2006;25:260-74.
- Mehta N, Compher C, ASPEN Board of Directors. ASPEN Clinical Guidelines: Nutrition Support of the Critically Ill Child. JPEN J Parenter Enteral Nutr. 2009;33:260-76.

## Chapter 22.18

# Nutrition in the 21st Century

Gouri Rao Passi, Piyush Gupta

What are our children eating today? Has the pattern changed? Will these changes have lasting implications on their health? Do we need to do anything about it? And what can we possibly do? These are questions which we all need to ask, whether we are parents, pediatricians, health activists or government policy makers. Because, it seems obvious, that the market economy, the media, our changing patterns of work and social structure have made deep and lasting alterations in the eating patterns of children.

### GROWING PRESENCE OF PROCESSED FOOD

July 1991 marked the beginning of globalization in India. Many transnational corporations entered India, resulting in an explosive growth in the food processing industry and affected the nutritional habits of Indians children and adolescents. Increasing incomes shifted food patterns away from cereals. The ubiquity of television and powerful hold of the media on public imagination also caused the inevitable shift towards increasing intake of processed foods and a penchant for fast foods. According to the National Restaurant Association of India (NRAI) 2010 report, the fast food industry in India is currently estimated to be, growing at a compound annual growth rate of 35–40%. The majority comprises of global players (McDonald, KFC, Pizza Hut, etc.) but domestic players (Nirula, Haldiram, and others) are not lagging behind.

Urban India has witnessed a marginal decrease in consumption of rice and wheat and increase in milk and egg intake. What is more worrisome is a widespread increased intake of tea, biscuits, salted snacks, prepared sweets, edible oils, sugar and jaggery with a parallel decline in the intake of fruit and vegetables. Diets have shifted towards more sugars and fats, less fruit and fewer vegetables. The desired focus on intake of nutritive (cereals) and protective foods (fruits) is lacking. Approximately 95% of Indians have diets deficient in fruit (below the ICMR norm). Vegetable intake appears adequate in all expenditure classes (100–300 g/day), however a significant proportion is contributed by tubers (potato, in particular). These are rich in carbohydrates, leaving the diets inadequate in green and yellow vegetables. Intake of soft drinks, biscuits, processed foods, salted snacks, prepared sweets and other purchased foods constitutes 100–427 (average 167) g/capita/day. They may add up to 50% of the required calories per day in the high-income classes.

### FAST FOOD AND JUNK FOOD

#### Junk Food

Junk food is defined as *any food, which is low in essential nutrients and high in calories and sodium. They contain little or no proteins, vitamins, or minerals; but are rich in salt, sugar, fats, and calories.*

#### Fast Food

*Fast food* refers to food which can be prepared and served quickly and includes chips, sandwiches, burgers, french fries, chicken nuggets, pizza, or ice cream. Fast-foods are usually processed and prepared in an industrial fashion. Over the past half century, both nationally and internationally, expansion of fast food companies has been in close parallel with the obesity epidemic. The United States now has approximately 250,000 fast food restaurants, and total fast food consumption has risen from 2% to 10% of total energy intake per person over a 20-year period. Surveys have

revealed that the top 3 reasons US consumers choose fast food over healthier alternatives are: fast food is quick (92% of respondents), restaurants are easy to visit (80%), and the food tastes good (69%).

#### Nutritive Value of Fast Foods

An occasional meal in a fast food restaurant will probably not have major implications. But teenagers consuming these foods daily need to carefully consider their nutritional impact. A typical meal in a fast food restaurant (consisting of burger, french-fries, and milk shake) may furnish about 50% of the daily caloric requirement of a teenage boy, 40% or more of the protein allowance, and up to one-third of his thiamin, riboflavin, and niacin allowances. It also provides significant amounts of calcium and iron. But if the milk is replaced with coffee or a soft drink the calcium content of the meal goes down. Most fast food meals are low in fiber, vitamins A and C and some trace minerals.

Fast food as children's meals first made their entry in the late 1970s. They are extremely popular with toddlers and adolescents. In nutritional terms, fast food children's meals are rich in total fat and trans fats, have high caloric density, and low nutritional value. A recent study observed that barely 3% of the fast food children's meals meet the standard criteria for healthy meals. Eating away from home, specifically consumption of fast food, is a risk factor for childhood obesity. A study in school going children of 10–17 years old in Lucknow (2011) showed that more than 50% consumed fast foods more than 3 times a week. A significant correlation was observed between consumption of fast food and obesity/overweight. A strong positive correlation has also been observed between visits to fast food restaurants and weight gain with insulin's resistance. The specific aspect of fast food consumption that contributes most to obesity and insulin resistance is possibly higher amounts of industrially produced *trans fatty acids* (TFAs). Transisomers of fatty acids are formed by the partial hydrogenation of vegetable oils to produce margarine and vegetable shortening. They contain increased ratios of plasma low-density-lipoprotein to high-density-lipoprotein cholesterol. Intake of foods that are major sources of transisomers of fatty acids (margarine, cookies, cake, and white bread) are significantly associated with higher risks of coronary heart disease. In the United States, an average daily intake of 5 g of TFAs has been estimated to increase an individual's risk of heart disease by 25%. A child meal at a fast food outlet can have up to twice this amount of trans-fat. Another aspect of fast foods which contribute to obesity is the increasing size of portions being marketed by fast food companies.

Fast foods also have a high salt content. A study of salt content in the 22 junk food samples in India was in the range 0.2–4.2 g per 100 g of sample. The highest salt content was found in instant noodles. WHO recommends salt intake of less than 5 g per person per day for the prevention of cardiovascular disease.

### SUGAR SWEETENED BEVERAGES

Sugar-sweetened beverages (SSBs) are drinks sweetened with sugar, high-fructose corn syrup, or other caloric sweeteners. The term soft drink includes sodas along with other sugar-sweetened beverages such as fruit drinks, fruitades (drinks made by adding water to powder or crystals), lemonade, and iced tea. The term soda means sugar-sweetened carbonated beverages such as colas. These are one of the largest sources of nondietary (empty) sugars for urban children and adolescents. A child can gain around 200 kcal from one can of soda due to 40 g of sugar in it. The sugar is usually high fructose corn syrup (HFCS) which is 45% sucrose and 55% fructose. Added to a normal diet, this can cause a weight gain of 6–7 kg in a year. A systematic review published in 2006 (30 studies) has clearly documented a positive correlation between the intake of sugar sweetened beverages and obesity. Fructose contributes to greater

weight gain by enhancing lipogenesis by increased production of triacylglycerols and reducing production of insulin and leptin in peripheral tissues. It needs to be seen whether high fructose corn syrup is more detrimental than other sugars or not. Intake of sweetened sodas has also been linked to with an increased risk for the development of type 2 diabetes. Increased intake of caffeine in sodas (10–16 mg/100 g) is also associated with increase in blood pressure of adolescents. Other problems associated with colas are increased risk of dental caries, decrease in nutritious liquids like milk and an increased risk of fractures due to abnormal calcium phosphorus ratios due to high phosphate content.

### Fruit Juice and Fruit Drinks

American Academy of Pediatrics (AAP) defines *fruit juice* as either natural or 100% concentrate without added sweeteners. Anything less than 100% concentrate is labeled as drink, beverage, or cocktail. *Fruit drinks* are defined as calorically sweetened beverages with a small percentage of fruit juice or juice flavoring containing carbonated water. *Fruit drinks* have less than 20% concentrate and *nectars* have around 20–99% concentrate. Sometimes, fortifiers such as vitamin C or calcium are also added to the fruit drinks. Fruits and 100% juices contain water, simple carbohydrates (sucrose, fructose, glucose, sorbitol), high amount of vitamins (C, A) and minerals (potassium, calcium etc.). However fruit drinks, even 100% juice is not equivalent to whole fruits. Fruits supply fibers and phytochemicals to diet, which are not present in juices. Fruit juice robs the child of opportunities to learn skills like peeling, chewing, and differentiating between colors, textures and shapes. Fruit drinks, thought to be complete source of energy, vitamins and minerals are actually a mere sweet drinks and poor source of nutrition. Whole fruits are less calorogenic as compared to fruit juices and fruit drinks.

### Energy Drinks

These are nonalcoholic beverages containing stimulants like caffeine, herbal extracts (guarana, ginseng, yerba mate, ginkgo biloba), glucuronolactone, taurine, inositol, L-carnitine and B-vitamins as the main ingredients, besides having carbohydrates, to enhance physical and mental endurance. Energy drinks are consumed to improve the stamina and energy levels before and during exercise, to rehydrate the body, to keep awake in demanding situations, to compensate for loss of sleep especially during exams, or to get a kick as a mood elevator by mixing it with alcohol. The main constituent of energy drink is caffeine; up to 80 mg per serve. Natural caffeinated beverages including coffee, cocoa, tea, and cola drinks are not regarded as energy drinks.

Energy drinks are widely consumed by adolescents as they claim to improve performance, endurance and alertness. Recent reports have shown that apart from brief caffeine high, there are no real health benefits of these drinks. Their excess can be harmful. Intake of energy drinks prior to physical activities may be undertaken while keeping their possible deleterious effects in mind. Their use during physical activity is not recommended.

### ORGANIC FOOD

Organic foods are grown without application of synthetic fertilizers, pesticides, fumigants (containing nitrogen or other heavy metals), human excreta, growth hormones, or genetically engineered techniques. The land on which they are grown has to be free of any of these prohibited substances for at least 3 years, before organic crop is grown. Organic animal products (milk, egg, chicken, meat, etc.) are produced from animals fed on 100% organic food for at least 12 months.

Organic foods are said to be rich in antioxidants, phenolics, vitamins A, C and E, potassium, phosphorus, nitrates, Omega-3

fatty acids, and alpha linoleic acid (ALA). Worthington reported higher levels of vitamin C, iron, magnesium and phosphorus, lower quantities of proteins though of better quality, lesser nitrates and lesser amount of heavy metals in crops produced by organic farming system. A recent meta-analysis has shown higher concentrations of protein, ALA, total omega-3 fatty acid, cis-9, trans-11 conjugated linoleic acid, trans-11 vaccenic acid, eicosapentaenoic acid, and docosapentanoic acid in organic dairy products. Purported advantages of organic foods include lower risks of eczema and pesticide exposure but it is counterbalanced by fears of increased risks of bacterial contamination, aflatoxins and heavy metals.

Organic foods are claimed to be pesticide free and promoted as superior and safer options for today's health-conscious consumer. However, scientific data, proving the actual health benefits of organic foods, especially in children is lacking. The Indian Government has developed strict guidelines and certification procedures to keep a check on manufacturers for this financially attractive market with a certification scheme having a logo "India Organic". The American Academy of Pediatrics in its recently issued guidelines did not recommend organic foods over conventional food for children.

### FOOD CONTAMINATION

A variety of inorganic and organic chemical substances (xenobiotics) may contaminate the food chain during production, storage, processing, preparation or distribution before the food is consumed. Some of these contaminants are naturally occurring and others are man-made chemical substances such as fertilizers and pesticides. These substances are now recognized as major ecological and health risks.

### Natural Toxins

A peculiar type of progressive spastic paraplegia (lathyrism) occurring in some parts of Central India is attributed to consumption of a legume. *Lathyrus sativum*, commonly known as *khesari dal*, is used by poor people in this area. The toxic substance responsible for the neurological lesions is identified as an unusual amino acid, *Beta-diamino-propionic acid*. *Lathyrus sativum* is a hardy, drought resistant crop, which gives a high yield with minimum of agricultural inputs. It is a rich source of vegetable proteins. Its use for periods longer than 3–6 months may cause crippling manifestations of neurolathyrism with insidious onset and protracted course.

Cotton seeds are known to contain a toxic-polyphenolic pigment called *gossypol*, which binds lysine and prevents release of this essential amino acid, thus impairing the nutritional quality of cotton-seed protein. Gossypol also causes anorexia, diarrhea, hemolysis, hypoprothrombinemia, gastrointestinal hemorrhages and pulmonary edema. Seeds of some toxic weeds, which grow along with the cereal crops, get mixed up with the latter at the time of harvesting. These contain toxic alkaloids which may cause minor gastrointestinal illness or at times more serious manifestations such as veno-occlusive disease. Other toxic substances include trypsin inhibitors in green peas and aconite beans, and phytohemagglutinin in red kidney beans.

### Bacterial Toxins

These toxins are produced by bacteria such as *Clostridium perfringens* and *C. botulinum* or fungi (molds) such as aflatoxin from *Aspergillus flavus* and unidentified mycotoxins in pearl and finger millets. Mycotoxins are the most potent natural toxins responsible for human health risks. These toxic metabolites are produced by fungi infesting foodstuffs, especially cereals and nuts, which have been stored under conditions of elevated temperature and high humidity. Mycotoxins of importance in India include aflatoxin, fumonisins, trichothecenes, ergot alkaloids

and ochratoxins. The ICMR multicenter study on the occurrence of aflatoxin contamination in risk commodities namely, maize and groundnut showed that 21% of groundnut samples and 26% of maize samples analyzed exceeded Indian tolerance limits of 30 µg/kg. Presence of microbial agents such as *Salmonella*, *Shigella*, *Staphylococci*, *E. coli* and *B. cereus* in the food may cause severe life-threatening illness.

### Pesticides

Pesticides may be obtained from natural sources, such as nicotine, *Pyrethrum* and rotenone or these may be of synthetic chemical origin. The latter are broadly classified under three groups, viz., organochlorine compounds, organophosphorus compounds and carbamates with recent introduction of some new agents such as dioxin and chlorodimeform. In some countries, salts of copper are still being used for crop protection. *Organochlorine compounds* like DDT, chlordane, heptachlor, aldrin, dieldrin, benzene hexachloride (BHC) and endosulfan, persist in the environment for a considerable time. They are fat-soluble and easily enter the food chain. They mostly affect the nervous system, with manifestations such as hypersensitivity, excitability, convulsions and paralysis. They have also been linked with hematological malignancies. *Organophosphorus compounds* are easily biodegraded and do not accumulate in animal tissues. These act by inhibiting the enzyme cholinesterase. Toxic symptoms include increase in the pulse rate, excessive salivation, sweating, muscle tremors, convulsions and coma. Death may occur due to asphyxia. Other chemical contaminants include nitrosamines which are formed from nitrates and nitrites (such as those used in curing meats) and are carcinogenic in animals and heavy metals like lead, iodine, mercury, zinc, arsenic, copper, and selenium which are found in varying quantities in foods.

### Accidental Contamination

Water seeping through the soil which is rich in chemicals such as fluorides causes epidemic fluorosis in certain regions of the country. Discharge of industrial chemical effluents in rivers leads to chemical intoxication of food. Accidental suction of sewage in water supply system may cause widespread epidemics of hepatitis and other enteric infections. And a very large amount of arsenic has been observed in ground water, in Bangladesh and Bengal. Prolonged boiling of milk in untinned copper vessels was suspected to be a cause of Indian Childhood Cirrhosis, which has become rare due to change in habits and switching over to stainless steel utensils for cooking. Mixing of seeds or fava beans with food may cause severe hemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency.

Food is adulterated by mixing (a) spices with colored salts of lead and other heavy metals, (b) food and spices with nonedible substances, (c) mustard oil with oil of *Argemone mexicana*, which causes epidemic dropsy, (d) cooking oil with aviation lubricant which caused the Moroccan tragedy—paralysis occurring in consumers of this spurious cooking oil containing ortho tricresyl phosphate.

### POSSIBLE INTERVENTIONS

Interventions to promote healthy food habits include media and education campaigns, labeling and consumer information, taxation, subsidies, and other economic incentives; school and workplace approaches; local environmental changes; and direct restrictions and mandates.

### Media

Several focused media campaigns have been conducted to increase knowledge about and consumption of specific healthy

foods. A variety of media have been used, including television, radio, print, or billboard advertising; in-store media education; and leaflets mailed or delivered door-to-door. In America “5-A-Day For Better Health!” campaign to increase consumption of fruits and vegetables to at least 5 servings a day, was initiated by the National Cancer Institute with collaboration from industry and the federal government.

### Nutritional Labeling

Labeling the nutritional value of foods both on packaged foods and on menu cards has been proposed as a method to allow consumers to make informed choices. Labeling should include calories, added sugar, total fat, trans fat, saturated fat, sodium and protein content.

### Legislation

On January 21, 2011, WHO formally issued a recommendation asking for a ban on junk food in schools and playgrounds in order to promote healthy diet and tackle child obesity. UK banned junk food in schools in 2005. A ban on junk food ads during television programs aimed at children below 16 years came into force in August 2008. Denmark imposed a fat tax on junk food in October 2011. In India according to FSSAI, junk food is not defined, but instead calls within the category of proprietary food—which is food not standardized under regulations. This category of food is only expected to declare their composition or nature of food and comply with general regulations under the food act. In March 2003, Denmark became the first country to restrict the use of TFAs in food products. And in 2006, the New York City Department of Health and Mental Hygiene put forth a bold proposal to eliminate all artificial TFAs from restaurant food. Food contamination can be reduced by banning production and sale of dangerous pesticides as has been done in various nations.

### Economic Incentives

There have been many attempts to increase use of healthy foods and restrict junk food by using economic incentives. These include lowering costs of healthy foods, increasing taxation on high calorie beverages, changing taxation and subsidies to encourage agricultural growth of vegetables and fruits over animal and dairy products.

#### IN A NUTSHELL

1. Child should be offered a plate filled with plenty of brightly colored vegetables, fruits and sprouts.
2. Ice cream, chocolates and other heavy desserts can be replaced by low fat fresh yogurt.
3. Fresh lime juice, coconut water and fresh fruit juices should be preferred to sodas and soft drinks as beverages.
4. Prefer grilled fresh sandwiches to fried ones. Similarly, when choosing the meat or poultry select baked, broiled, grilled items rather than fried ones.
5. Avoid giving chocolate bars as gifts or reward to the children for their good habits or academic achievements.
6. Limit the portion size of the food ordered. Regular size meal may be opted against ‘mega meal offer’ or ‘combo meal offer’.
7. While eating away from home, avoid opting for dishes with rich creamy layers and lots of spices.
8. Replace *naan* with *tandoori roti* as low fat option breads in Indian menu.
9. Dishes can be stir fried rather than deep fry to decrease the fat content.
10. Dough used for preparing *poori/pakor*as should be thick and avoid using *ghee* or oil for making the dough as this might increase oil absorption.



## MORE ON THIS TOPIC

- Batra P, Sharma N, Gupta P. Organic foods for children: Health or hype. *Indian Pediatr.* 2014;51:349-53.
- Bedi N, Dewan P, Gupta P. Energy drinks: Potions of illusion. *Indian Pediatr.* 2014; 51: (in press).
- Forman J, Silverstein J. Committee on Nutrition; Council on Environmental Health; American Academy of Pediatrics. Organic foods: health and environmental advantages and disadvantages. *Pediatrics.* 2012;130:e1406-15.
- Gupta H, Gupta P. Fruit drinks how healthy and safe? *Indian Pediatr.* 2008;45: 215-7.
- Integrated Disease Surveillance Project, Non-Communicable Disease Risk Factor Survey, New Delhi: National Institute of Medical Statistics; 2009.
- Kaushik JS, Narang M, Parakh A. Fast food consumption in children. *Indian Pediatr.* 2011;48:97-101.
- Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. *Am J Clin Nutr.* 2006; 84:274-88.
- O'Donnell SI, Hoerr SL, Mendoza JA, TsueiGoh E. Nutrient quality of fast food kids meals. *Am J Clin Nutr.* 2008;88:1388-95.
- Pereira MA, Kartashov AI, Ebbeling CB, et al. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. *Lancet.* 2005;365:36-42.
- Stender S, Dyerberg J, Astrup A. High levels of industrially produced trans fat in popular fast foods. *N Engl J Med.* 2006;354:1650-2.

## Chapter 22.19

# National Nutrition Programs

Dipty Jain, Veena Kamat, Vinit Warthe

The problem of malnutrition in India has been recognized since inception of Five Year Plans and a number of nutrition programs have been introduced for combating it. These programs were initially started as a short-term emergency measure and were by no means expected to eradicate the problem of nutritional disorders from country. However, they have been effective to some extent in reducing the quantum of severe form of nutritional disorders and associated morbidity and mortality.

## THE NATIONAL NUTRITION POLICY

Government of India adopted the National Nutrition Policy in 1993 in view of widespread malnutrition and its effect on health. The National Plan of Action on Nutrition was developed in 1995. The goals of National Nutrition Policy are highlighted in **Box 1**.

### BOX 1 Goals of the National Nutritional Policy

- Reduction in the incidence of moderate and severe malnutrition and stunted growth among children by half.
- Reduction of incidence of low birthweight babies to less than 10%.
- Elimination of blindness due to vitamin A deficiency.
- Reduction in iron deficiency anemia among pregnant women to 25%.
- Universal iodization of salt for reduction of iodine deficiency disorders to below endemic level of 10%.
- Production of 250 million tonnes of food grains annually.
- Promoting appropriate diets and healthy lifestyle.

The policy highlights the importance of direct nutrition interventions for vulnerable groups as short-term measures; and long-term institutional and structural changes, to create conditions for improved nutrition. These are listed below:

### Short-term Measures

- Nutrition intervention for especially vulnerable groups.
- Program for 0–6 year children, mothers, and adolescent girls, e.g., Integrated Child Development Service (ICDS).
- *Fortification of essential foods* Salt with iodine and or iron, vitamin A, and fat with vitamin A.
- Control of micronutrient deficiency amongst vulnerable group, e.g., vitamin A prophylaxis, National Nutritional Anemia Prophylaxis Program.
- Popularization of low-cost nutrition foods.

### Long-term Institutional and Structural Changes

Long-term institutional and structural changes are aimed at improving food production, improvement of dietary pattern through production of nutritionally rich foods, improving purchasing power for food, strengthening the public distribution system, implementing land reforms, imparting basic health and nutrition knowledge, prevention of food adulteration, developing a system of nutrition surveillance, monitoring of nutrition programs, and promoting research for various aspects of nutrition.

## NUTRITION PROGRAMS

The Government of India has initiated several large scale feeding programs aimed at supplementing the nutrition and overcoming specific deficiency diseases. Recently Government has notified the National Food Security Act, 2013 on 10th September, 2013 with

the objective to provide for food and nutritional security in human life cycle approach, by ensuring access to adequate quantity of quality food at affordable prices to people to live a life with dignity. A number of programs were implemented in the past with some degree of success and some failures. Some of these programs are briefly described below:

### Special Nutrition Program

It was launched in the country in 1970, by the Ministry of Social Welfare. It was initiated for the benefit of children less than 6 years of age, pregnant and nursing mothers. The program was taken up in rural areas, tribal areas and slums. The supplementary food under this program supplied about 300 kcal and 10–12 g of protein per child per day and 500 kcal and 25 g of protein for a pregnant woman per day. The supplementary food was supplied six days per week. The aim was to cover the calorie gap between the recommended and actual intakes in low-income families.

Wheat Based Supplementary Nutrition Program was introduced in 1986. This program follows the norms of Special Nutrition Program or of the nutrition component of ICDS. It consists of supply of free wheat and supportive costs for other ingredients, cooking, transport, etc.

### Balwadi Nutrition Program

It was launched in 1970 by the Ministry of Social Welfare. The target age group was children aged 3–6 years. The program was implemented through *Balwadis*. Four national level organizations including the Indian Council of Child Welfare were given grants to implement the program. It provided 300 calories and 10 g of protein per child (3–5 years) per day for 270 days a year.

### Applied Nutrition Program

It was introduced as a pilot project in Odisha in 1963. It was later extended to Tamil Nadu and Uttar Pradesh. The objectives of the program were to promote production of fruits and vegetables and to ensure their consumption by pregnant woman, nursing mothers and children. Nutritional education was one of the main components of the program. The goal was to teach rural communities through demonstration how to produce food for their own consumption. The beneficiaries were children aged 2–6 years, pregnant woman and lactating mothers. Nutrition worth 25 paise per child per day and 50 paise per woman per day was provided 52 days in a year. The objective of the program was to provide better seeds and encourage kitchen gardens, poultry farming, beehive keeping, etc.

### Integrated Child Development Service Scheme

Integrated Child Development Service scheme was launched on 2nd October, 1975 (5th Five year Plan) in pursuance of the National Policy for Children in 33 experimental blocks. Later, the goal was for universalization of ICDS throughout the country. The primary responsibility for the implementation of the program is with the Department of Women and Child Development, Ministry of Human Resources Development at the Center and the nodal departments at the state which may be Social Welfare, Rural Development, Tribal Welfare, Health and Family Welfare or Women and Child Development. Beneficiaries included children below 6 years; pregnant and lactating women; women in the age group of 15–44 years; and adolescent girls in selected blocks. Objectives are listed in **Box 2**. The package of services provided by ICDS included supplementary nutrition to children below 6 years and pregnant women; immunization; health check-ups; referral services; treatment of minor illnesses; nutrition and health education to women; preschool education of children in the age group of 3–6 years; and convergence of other supportive services like water supply and sanitation.

**BOX 2 Objectives of ICDS**

- Improve the nutrition and health status of children in the age group of 0–6 years.
- Lay the foundation for proper psychological, physical and social development of the child.
- Effective coordination and implementation of policy among the various departments.
- Enhance the capability of the mother to look after the normal health and nutrition needs through proper nutrition and health education.

Supplementary nutrition aims to provide 500 kcal and 12–15 g protein per day to children between 6 months and 6 years; 800 kcal and 20–25 g proteins per day to severely malnourished children; and 600 kcal and 18–20 g of protein to pregnant women per day. For children below 3 years the food is given as a *take home ration*. Growth monitoring and nutrition surveillance are also done in the *anganwadis*. Children below the age of three years of age are weighed once a month and children between 3 and 6 years of age are weighed quarterly. Weight-for-age growth cards are maintained for all children below six years. This helps to detect growth faltering and helps in assessing nutritional status. Besides, severely malnourished children are given special supplementary feeding and referred to medical services. Recently, teenage clinics and adolescent care and counseling are also being integrated into this program.

**Scheme for Adolescent Girls (Kishori Shakti Yojna)**

There was a gap in between women and child age group which was not covered by any health and social welfare program whereas girls in this crucial group need special attention. On one side they need appropriate nutrition, education, health education, training for adulthood, training for acquiring skills as the base for earning an independent livelihood, training for motherhood, etc. Similarly on the other side their potential to be a good community leader has to be realized. A scheme for adolescent girls was launched by the Department of Women and Child Development, Ministry of Human Resource Development in 1991. All adolescent girls in the age group of 11–18 years (70%) received the following common services: watch over menarche, immunization, general health check-ups once in every 6-month, training for minor ailments, deworming, prophylactic measures against anemia, goiter, vitamin A deficiency, and referral to PHC, district hospital in case of acute need.

**Mid-day Meal Scheme**

To enhance school enrollment, retention, attendance and simultaneously improve nutritional levels among children, the National Program of Nutritional Support to Primary Education (NP-NSPE) was launched as a Centrally Sponsored Scheme on 15th August 1995. In September 2004 the scheme was revised to provide cooked mid-day meal with 300 calories and 8–12 g of protein to all children studying in classes I–V in Government and aided schools. In October 2007, the scheme has been further revised to cover children in upper primary classes VI to VIII.

Objectives is to improve the nutritional status of children in classes I–VIII; and encouraging poor children, belonging to disadvantaged sections, to attend school more regularly. To achieve these objectives, a cooked mid-day meal with the following nutritional content is provided to all eligible children (**Table 1**). The programs aim to provide 1/3 of the energy and ½ of the overall protein requirements.

The Central Government supplies the full requirement of food grains for the program free of cost. For its implementation in rural areas, *Panchayats* and *Nagarpalikas* are also involved or setting up of necessary infrastructure for preparing cooked food. For this

purpose NGOs, women's group and parent-teacher councils can be utilized. The total charges for cooking, supervision and kitchen are eligible for assistance under Poverty Alleviation Program. In several states, supplementary feeding was assisted by food supplies from Cooperation for American Relief Everywhere (CARE) and World Food Program (WFP). There are problems of administration and quality of food that have affected the program outcomes.

**Table 1** Nutritional content provided by a cooked mid-day meal to all eligible children

Components	Primary	Upper primary
Calories	450 kcal/day/child	700 kcal/day/child
Protein	12 g/day/child	20 g/day/child
Micronutrients	Adequate quantities of iron, folic acid and vitamin A	

**Vitamin A Prophylaxis Program**

The program was launched in 1970 with the objective of reducing the disease and preventing blindness due to vitamin A deficiency. The strategy consisted of administration of prophylactic vitamin A as per the following dosage schedule: 100,000 IU at 9 months with measles immunization, 200,000 IU at 16–18 months, with DPT booster, and then 200,000 IU every 6 months, up to the age of 5 years. Other components include health and nutrition education to encourage colostrum feeding, exclusive breastfeeding for the first six months, introduction of complementary feeding thereafter and adequate intake of vitamin A rich foods, and early detection and proper treatment of infections

**National Nutritional Anemia Prophylaxis Program**

The program was launched in 1970 run by Maternal and Child Health (MCH) Division of Ministry of Health and Family Welfare. The objective was to prevent nutritional anemia in mothers and children. The program is now extended to adults and adolescents.

**Strategies**

- The pregnant (expectant), nursing mothers and acceptors of family planning are given 100 mg of elemental iron and 0.5 mg of folic acid tablets for 100 days.
- Children (6 months–5 years) given 20 mg of elementary iron (60 mg of ferrous sulphate) and 0.1 mg (100 mg) of folic acid per mL in liquid formulation for 100 days.
- School children (6–10 years) given 30 mg of elemental iron and 250 mg of folic acid for 100 days.
- Adolescents (11–19 years) are given 100 mg of elemental iron and 0.5 mg of folic acid tablets for 100 days on priority basis.
- Multiple channels and strategies like double fortified salts/sprinklers/ultra-rice are required to address the problem of iron deficiency anemia.
- New strategies to be tried are use of traditional food processing techniques to increase bioavailability of iron; improve dietary behavior through nutrition education; and consume iron-fortified processed complementary foods.

**National Iodine Deficiency Disorders (IDD)****Control Program**

National Goiter Control Program, launched in 1962, was renamed as National Iodine Deficiency Disorders Control Program (NIDDCP) in 1992. The goal was to reduce prevalence of iodine deficiency disorders below 10% in entire country by 2012 AD. The objective included conduct of surveys to assess the magnitude of Iodine deficiency disorders in the country, ensuring supply of iodated salt in place of common salt, assess every 5 years the extent

of iodine deficiency disorders and impact of iodated salt, monitor the quality of iodated salt, and health education and publicity. Based on assumption that the mean intake of salt is 5 g per, say the recommended level of iodination in NGCP was one part of iodine in 25,000 to 50,000 parts of salt. WHO recommends that iodine concentration in salt should be within 20–40 ppm, to provide 150 µg of iodine per person per day (presuming that 20% iodine is lost during transport, 20% lost during cooking, and average salt consumption 10 g per person day).

## CONCLUSION

The government has been implementing a wide range of nutrition intervention programs for achieving food security at the household and individual levels. Various challenges have been identified in the review of nutritional interventions, e.g., growing demand of food production with growing population, depletion of natural resources, adverse consequences of globalization, growing concern about micronutrient deficiency, and intersectoral co-ordination mechanisms. Taking into consideration these challenges, the following strategies were recommended for 12th Five Year Plan:

- Strengthening of ICDS with special focus on pregnant and lactating mothers and children below 3 years age.
- A multisectoral program to address maternal and child nutrition in selected high burden districts.
- A nationwide information, education and communication campaign against malnutrition, coordinated by the Ministry of Women and Child Development, in consultation with the Planning Commission and Ministry of Health and Family Welfare.

In children, nutrition and growth are intricately interlinked—aberrations of one aspect tend to significantly affect the others. Therefore, appropriate nutritional policies play a pivotal role.

The changing profile in malnutrition and the expanding horizons in nutrition and child development have warranted a thorough revision and re-organization of the national nutrition policies.

## IN A NUTSHELL

1. Nutritional interventions should be targeted at the most vulnerable group i.e., children of 0–6 years, mothers and adolescent girls.
2. To reduce malnutrition social welfare programs must be implemented effectively and agencies involved in delivery of services should have strong sense of responsibility, transparency, time bound programs and accountability.
3. Changing profile of malnutrition demands that nutritional policies should be directed to felt need of population.
4. Provision of micronutrient is one of the most cost effective nutritional interventions so programs related to micronutrients should be strengthened.
5. Today's healthy children are tomorrow's healthy citizens. Future of nation lies in effective elimination of childhood malnutrition.

## MORE ON THIS TOPIC

- Elizabeth KE. Nutrition and Child Development. 4<sup>th</sup> ed. Hyderabad: Paras; 2010.
- Gupta P. Textbook of Preventive and Social Medicine. 3<sup>rd</sup> ed. New Delhi: CBS; 2010.
- Haddad L. Why India needs national nutritional strategy. BMJ. 2011;343.
- Kishore J. National Health Programs of India. 11<sup>th</sup> ed. New Delhi; 2014.
- National Food Security Bill 2013, Department of Food and Public Distribution. New Delhi: Govt of India; 2013.
- Parthasarathy A, Menon PSN, Gupta P. IAP Textbook of Pediatrics. 5<sup>th</sup> ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2012.



# Section 23 IMMUNIZATION

**Section Editors** Vipin M Vashishtha, Ajay Kalra

## Chapter 23.1

### Basic Concepts of Vaccination

Chandrakant Lahariya

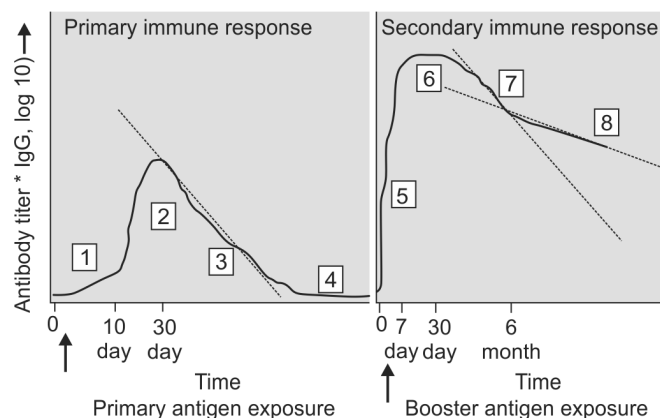
Vaccine is *an inactivated or attenuated pathogen or a component of a pathogen (nucleic acid, protein) that, when administered to the host, stimulates a protective response of the cells in the immune system.* Or *an immune-biological substance designed to produce specific protection against a given disease.* The process of administering the vaccine is called vaccination. Immunization is the artificial induction of active immunity by introducing into a vulnerable host the specific antigen of a pathogenic organism. The aim of vaccination is to protect the individuals who are at risk of getting disease. The children, elderly and people with chronic diseases are the ones who are most commonly at risk. Additionally, other high risk groups such as travelers to endemic areas are at risk and should receive vaccines. Additionally, vaccination is a common strategy to eradicate, eliminate or contain disease (e.g. by mass immunization strategy) (**Table 1**). A description of relevant terms used in vaccinology is provided in **Table 2**.

### IMMUNE RESPONSE

The vaccines are different from immunoglobulin in a way that vaccine helps in developing the protective antibody in the body of individual to whom these are administered and protection is available after a lag period. However, immunoglobulins provide immediate protection. The vaccine administration is followed by two types of immune responses—primary and secondary. The primary series is the series of doses required for a primary response. There is slow development of antibody in the body after first dose of

vaccine is administered and there is period of 3–4 weeks to reach the peak antibody response (**Fig. 1**). When a subsequent dose is administered, higher and quicker immune response is received. The non-live vaccines usually require multiple doses for a satisfactory primary response. There should be a minimum of 4 weeks interval between successive doses, though larger intervals may result in higher antibody levels. The booster doses are generally given 6 or more months after the completion of primary series. The booster doses have rapid and higher antibody response, high affinity for antibody and provide longer duration of protection.

The antibody responses to vaccines are usually identified by correlates of protection. The correlates are an immune response that is responsible for and statistically interrelated with protection and are usually linked to B cell-dependent response. However, for a number of new vaccines, it is assumed that T cells also play a role in correlates of protection.



**Figure 1** Primary and booster response  
Source: Siegrist in Vaccines eds Plotkin, Orenstein & Offit.

**Table 1** Objectives of immunization strategies

Strategy	Characteristics
Control	The disease control describes the activities aimed at reducing the incidence of diseases, the duration of disease, the effect of infection and consequently the risk of transmission and the financial burden on the community. This could be done up to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction. <i>Example:</i> Diarrheal diseases.
Elimination of disease	Reduction to zero of the incidence of a specified disease in a defined geographical area as a result of deliberate efforts. Continued intervention measures are required. <i>Example:</i> Neonatal tetanus.
Elimination of infections	Reduction to zero of the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts, however, measures are continued to prevent re-establishment of transmission are required. The term elimination is sometimes used for describing eradication from a geographical area. <i>Example:</i> Measles, poliomyelitis.
Eradication	Termination of all transmissions of infection by extermination of infectious agent through surveillance and containment. <i>Example:</i> Smallpox.
Containment	Regional eradication of a communicable disease.
Extinction	The specific infectious agent no longer exists in nature or in the laboratory. <i>Example:</i> None.

**Table 2** Key concepts in vaccinology

Term	Definition
Antigen	A substance (protein, polysaccharide, glycolipid, tissue transplant, etc.) that is capable of inducing specific immune response. Introduction of antigen may be by the invasion of infectious organisms, immunization, inhalation, ingestion, etc.
Antibody	Protein molecule produced in response to exposure to a foreign or extraneous substance (e.g. Invading microorganism responsible for infection) or active immunization. May also be present as a result of passive transfer from mother to infant, via immunoglobulin, etc.
Immunoglobulin	Immunoglobulins are glycoprotein molecules that are produced by plasma cells in response to an immunogen and which function as antibodies. The immunoglobulins derive their name from the finding that they migrate with globular proteins, when antibody-containing serum is placed in an electrical field.
Anti-sera	It is blood serum containing polyclonal antibodies. It is used to pass on passive immunity against many diseases such as tetanus, diphtheria, botulism.
Active immunity	It is the immunity which an individual develops as a result of infection or by specific immunization and is usually associated with presence of antibodies or cells having a specific action on the microorganisms concerned with a particular infectious disease or on its toxin.
Passive immunity	Immunity conferred by an antibody produced in another host and acquired naturally by an infant from its mother or artificially by administration of an antibody containing preparation (antiserum or immunoglobulin).
Innate or natural immunity	Immunity to disease that occurs as part of an individual's natural biologic make up. It is present at birth and cannot be acquired.
Adaptive or acquired immunity	It is acquired by the body through contact with pathogens. It is specific in nature and has B-cells, T-cells, antibodies and secondary lymphoid organs as its components.
Humoral immunity or B-cell mediated immunity	It is immunity provided by the B-cells (bone marrow-derived lymphocytes), which proliferate and manufacture specific antibodies after antigen presentation by macrophages. The antibodies thus produced are of five types, viz. IgG, IgM, IgA, IgD and IgE.
Cellular immunity or T-cell mediated immunity	It is mediated via T-cells which are responsible for recognition of antigen. On contact with antigen, the T-cells initiate a chain of responses, e.g., activation of macrophages, release of cytotoxic factors, mononuclear inflammatory reactions, delayed hypersensitivity reactions, secretion of immunological mediators, etc.
Primary immune response	Following the first exposure to a foreign antigen, a lag phase occurs in which no antibody is produced, but activated B cells are differentiating into plasma cells. The lag phase can be as short as 2–3 days, but often is longer, sometimes as long as weeks or months. The amount of antibody produced is usually relatively low. Over time, antibody level declines to the point where it may be undetectable. The first antibody produced is mainly IgM (although small amounts of IgG are usually also produced).
Secondary or booster immune response	If a second dose of the same antigen is given days or even years later, an accelerated secondary or anamnestic immune response occurs. This lag phase is usually very short (e.g., 3 or 4 days) due to the presence of memory cells. The amount of antibody produced rises to a high level. Antibody level tends to remain high for longer duration. The main type of antibody produced is IgG (although small amounts of IgM are sometimes produced).
Seroconversion	It means greater than or equal to fourfold rise in antibody titer from prevaccination to postvaccination level or detectable postvaccination titer in a vaccine, who had no detectable antibody before vaccination.
Seroprotection	It is the state of protection from disease, due to the presence of humoral immunity or antibody detectable in plasma or serum. It is usually used in the context of the levels of antibody required for protection.
Protective level of immunity or correlates of protection	A specific response to a vaccine that is associated with protection against infection, disease, or other defined endpoint
Potency	Potency is the specific ability or capacity of the vaccine as measured by a laboratory test. Quantitative measure of specific ability of a product to achieve a defined biologic effect.
Immunogenicity	The ability of an antigen to induce antibodies. Alternatively, it is also defined that the capacity of vaccines to produce cell-mediated and/or antibodies-mediated immunity and/or immunological memory.

## TYPE OF VACCINES

There are a number of different types of vaccines (**Table 3**). There are differences in the route, timings, and doses of these vaccines. Another approach of grouping, the vaccines is by polysaccharide and conjugate vaccines, which have a few different characteristics, as detailed in **Table 4**.

## SURVEILLANCE FOR VACCINE PREVENTABLE DISEASES

Surveillance was first defined by Alexander Langmuir in 1963 as “the systematic collection, consolidation, analysis and

dissemination of data on specific disease”. In the recent years, surveillance constitutes a critical part of public health practice. The surveillance system is used for detecting outbreaks, assess disease burden and define disease epidemiology. It is also used for monitoring progress towards disease eradication, elimination and control, to identify circulating strains by serotypes and genotypes and to monitor vaccine performance in terms of efficacy, effectiveness against various strains and disease severity. The surveillance data is necessary to guide public health planning, developing, implementing, and decision making. It is crucial not only to improve the quality and effectiveness of collection, analysis, interpretation and display of data, but also to listen to persons who

**Table 3** Types of vaccines, their characteristics, advantages and disadvantages

Type	Characteristics	Advantage and disadvantages	Examples
Live-attenuated vaccines	These live vaccines are produced from live and attenuated organisms. The organisms are serially cultured till they lose infectivity but retain immunogenicity. These cause infection which very closely resembles natural stimulus to immune system. These can stimulate generation of memory cellular as well as humoral immune responses. Since these can multiply in the host, fewer quantities must be injected to induce protection. A single administration of vaccine often has a high efficacy in producing long-lived immunity. Multiple booster doses are not required. Also provides herd immunity.	May very rarely revert to its virulent form and cause disease (cVDPV). Live vaccines cannot be given safely to immunosuppressed individuals.  Administration of live-attenuated vaccines to people with impaired immune function can cause serious illness.  Fragile and gets easily destroyed by heat and light, proper storage is critical.	<i>Viral:</i> Polio (Sabin), measles, rubella, vaccinia, varicella zoster, yellow fever, rotavirus, influenza (intranasal) <i>Bacterial:</i> <i>Mycobacterium</i> (BCG), oral typhoid
Killed	These are preparations of the normal (wild type) infectious, pathogenic microorganisms that have been rendered nonpathogenic, usually by treatment with using heat, formaldehyde or gamma irradiation so that they cannot replicate at all. Less interference from circulating antibodies than live vaccines. Immune response is mostly humoral. Antibody titer diminishes with time.	<i>Advantages:</i> Safe to use for immunocompromised and pregnant individuals. Cheaper than live vaccines. <i>Disadvantages:</i> Since the microorganisms cannot multiply, a larger quantity and multiple doses may be required to stimulate immunity. Periodic boosters must be given to maintain immunity. Only humoral immunity can be induced. Most killed vaccines have to be injected.	Polio (Salk); Pertussis; Plague vaccine; Influenza vaccine; Typhoid vaccines
Toxoid	A <i>toxoid</i> is a bacterial toxin (usually an exotoxin) whose toxicity has been inactivated or suppressed either by chemical (formalin) or heat treatment, while immunogenicity retained.		Tetanus, diphtheria
Recombinant	The vaccines are produced using recombinant DNA technology or genetic engineering. Recombinant vaccines are those in which genes for desired antigens of a microbe are inserted into a vector.		Hepatitis B vaccine and HPV vaccines

Abbreviations: BCG, bacillus Calmette-Guérin; cVDPV, circulating vaccine-derived poliovirus; DNA, deoxyribonucleic acid; HPV, human papillomavirus.

**Table 4** Difference between polysaccharide and conjugate vaccines

Characteristics	Polysaccharide vaccine	Conjugate vaccine
Structure	Unique type of inactivated subunit vaccine composed of long chains of sugar molecules that make up the surface capsule of certain bacteria	Developed by attaching a polysaccharide antigen to a carrier protein, which helps the body recognize the antigen as a foreign substance that must be destroyed
Type of antigen	Thymic independent (Ti)	Thymic dependent (Td)
Mechanism of generating immunity	Stimulation of humoral immunity to mount immune response against the disease	Stimulation of both humoral and cell-mediated immunity for augmented immune response
Cell lines stimulated	B-cells	B-cells and T-cells, both
Immunogenicity	Low as compared to conjugate vaccines. The antibody induced is of less functionality as predominantly IgM is produced and very little IgG	High as compared to pure polysaccharide vaccines. IgG capsular antibodies and memory B-cells are also produced
Duration of protection	Shorter as compared to conjugate vaccines	Longer and consistent
Impact on carriage of bacteria	Little or only short-lived impact	Can cause reduction in carriage of bacteria
Age limitation	Not consistently immunogenic in children less than 2 years of age. Good response in adults	Can mount protective immune response in infants
Booster response	No booster response	More likely to maintain consistent immune response after repeated doses
Examples	Pneumococcal, meningococcal (groups A, C, W135, Y), <i>Salmonella typhi</i> (Vi)	Hib, pneumococcal, meningococcal

Abbreviations: Hib, *Haemophilus influenzae* type b; Ig, immunoglobulin.

are empowered to set policy in order to understand and stimulate policymakers' interests and actions. The design of a surveillance system depends upon disease characteristics and control goals:

- *Polio eradication*: Highly sensitive *case-based AFP and lab surveillance*
- *Measles control*: *Outbreak surveillance* with lab confirmation
- *Measles elimination* highly sensitive *case-based surveillance*
- Pertussis, diphtheria, invasive *Haemophilus influenzae* type b (Hib), pneumococcal and meningococcal disease, rotavirus diarrhea: *Sentinel site surveillance* for clinical syndrome plus lab confirmation
- *Hepatitis B, neonatal tetanus*: Sero-prevalence and special *population-based surveys*.

All countries use combination of surveillance systems depending upon the need and feasibility. The commonly used surveillance strategies are summarized in **Table 5**. Additionally, in India, sentinel hospital surveillance system is used for bacterial meningitis for (Hib, pneumococcal and meningococcal meningitis) and is currently being done at 11 sites in six states. Indian Rotavirus Strain Surveillance Network (IRSSN) has been functioning through four laboratories in seven regions and 10 hospitals of India. The South Asian Pneumococcal Alliance (SAPNA) and Invasive Bacterial Surveillance were conducted between 1993 and 2006 at six sites in India. The acute encephalitis syndrome surveillance was also done in India in 2006–09 at four geographical sites in the country. The Central Bureau of Health Intelligence (CBHI) at union level and State Bureaus of Health Information in the states regularly collect surveillance data on various vaccine preventable diseases (VPDs) in India. The Integrated Disease Surveillance Project (IDSP) also provides information on a few VPDs. The Indian

Council of Medical Research and National Vector Borne Disease Control Programme are also involved in the surveillance of a few VPDs in India. The Government of India and WHO collaboration of National Polio Surveillance Project (NPSP) through a wide network collect information on Acute Flaccid Paralysis for Polio eradication efforts. Lately the NPSP has also assisted in setting up outbreak-based measles surveillance system in India. These are only a few examples. The steps suggested for VPDs in any public health program are summarized in **Box 1**.

#### BOX 1 Steps in vaccine preventable disease surveillance

1. *Collect data*: The data could be collected by various types of surveillance systems (see **Table 5**).
2. *Compile data*: The units collecting data send it or compilation to an identified facility in the chain.
3. *Analyze and interpret the data*: At one place, to avoid duplication of efforts, data received is analyzed and interpreted at regular intervals. This analysis, amongst other areas, is for surveillance quality by completeness of reporting, timeliness of reporting and description by time, place and person (when, where and who gets the disease?).
4. *Take action*: The analysis and interpretation of data should be used for actions to correct any problems identified and to prevent avoidable morbidity and mortality. The appropriate authorities need to be informed. For example, if you find that there are: more cases than you expect—conduct an outbreak investigation and response; if the cases occurring in vaccinated children—this could be due to over-reporting, vaccination given at the wrong age; incorrect technique of administration or dosage and breaks in the cold chain, etc.
5. *Provide feedback*: Feedback to the reporting sites intends to comment about reporting quality, offering information to help them in solving problems and is essential to keep the staff motivated.

**Table 5** Types of disease surveillance

Type	Characteristics
Active surveillance	A system employing staff members to regularly contact health-care providers or the population to seek information about health conditions. Active surveillance provides the most accurate and timely information, but also expensive.
Passive surveillance	A system by which a health jurisdiction receives reports submitted from hospitals, clinics, public health units, or other sources. Passive surveillance is a relatively inexpensive strategy to cover large areas. Data quality and timeliness are difficult to control in such surveillance design. The reports are awaited and no attempts are made to seek reports actively from the participant in the system.
Sentinel surveillance	In a sentinel surveillance system, a prearranged sample of reporting sources agrees to report all cases of defined conditions, which might indicate trends in the entire target population. When properly implemented, these systems offer an effective method of using limited resources and enable prompt and flexible monitoring and investigation of suspected public health problems. Examples of sentinel surveillance are networks of private practitioners reporting cases of influenza or a laboratory-based sentinel system reporting cases of certain bacterial infections among children. Sentinel surveillance is excellent for detecting large public health problems, but it may be insensitive to rare events.
Periodic population-based surveys	Population-based surveys can be used for surveillance, if they are repeated on a regular basis. Examples of population-based surveys in surveillance include the HIV-prevalence surveys, household surveys, and the demographic and health surveys that many developing countries conduct every five years. Population-based surveys require careful attention to the methodology, particularly, the use of standard protocols, supervision of interviewers, comparable sampling strategy, and standard questionnaires.
Integrated surveillance	A combination of active and passive systems using a single infrastructure that gathers information about multiple diseases or behaviors of interest to several intervention programs.
Syndromic surveillance	An active or passive system that uses case definitions that are based entirely on clinical features, without any clinical or laboratory diagnosis (for example, collecting the number of cases of diarrhea rather than cases of cholera, or <i>rash illness</i> rather than measles). Because syndromic surveillance is inexpensive and is faster than systems that require laboratory confirmation, it is often the first kind of surveillance begun in a developing country.
Behavioral risk factor surveillance system (BRFSS)	An active system of repeated surveys that measure behaviors that are known to cause disease or injury (for example, tobacco or alcohol use, unprotected sex, or lack of physical exercise). Because the aim of many intervention program strategies is to prevent disease by preventing unhealthy behavior, these surveys provide a direct measure of their effect in the population, often long before the anticipated health effects are expected.



## VACCINE EPIDEMIOLOGY

Vaccine epidemiology is the study of the impact of vaccines and treatment on infectious diseases to understand better the response to these interventions at the individual and population levels in order to improve their effectiveness.

### Basic Reproductive Number ( $R_0$ )

One of the key determinant of incidence and prevalence of infection is the basic reproductive number or  $R_0$ , which measures the average number of secondary cases generated by one primary case in a susceptible population. A number of factors determine its magnitude, including the course of infection in the patient and the factors that determine transmission between people. The magnitude of  $R_0$  varies according to location and population—it is strongly influenced by birth rate, population density and behavioral factors. The magnitude of  $R_0$  can be ascertained by cross-sectional and longitudinal serological surveys. Another related term is effective reproduction number or  $R_t$ , which is infections caused by each new case occurring at time,  $t$ . For organism to survive:

- $R_0 = 1$  (Case must attempt to infect at least one person)
- $R_0 > 1$  (Expansion of infected individuals)
- $R_0 < 1$  (Shrinking pool of infected individuals)

To calculate the magnitude of  $R_0$ , a few key epidemiological, demographic and vaccination program-related parameters should be known. The parameters such as average age at the infection prior to mass vaccination,  $A$ ; life expectancy of the study population,  $L$ ; and the average duration of protection by maternal antibody,  $M$  are considered. While the life expectancy and average age of protection by maternal antibody are known, the average age of infection prior to mass vaccination has been studied in select populations and provided in **Table 6**. This information in the following formula could be used for deriving the magnitude of  $R_0$ :

$$R_0 \equiv (L - A)/(A - M)$$

There are a number of studies conducted in different parts of the World to assess the average age of infections  $A$ , and to derive basic reproductive number. The findings are summarized in **Table 6**. The study of epidemiological principles provides an opportunity for deriving some useful and applicable information for disease control. For example, it is possible to estimate the fraction of each birth cohort that must be immunized to block transmission of a given disease,  $p_c$  can be calculated by the following formula:

$$p_c \equiv [L - A]/(L - b)/\varepsilon$$

Where, the parameter  $b$  is the average age at first vaccination,  $L$  is life expectancy (related to the net birth rate), and  $A$  is the average age at infection prior to mass immunization. Vaccine efficacy  $= \varepsilon$ , ranging from 0 to 1. The magnitude of  $p_c$  — the fraction of the susceptible population that must be immunized to block transmission of a disease could be derived with the use of  $R_0$ , as follows:

$$p_c = [1 - 1/R_0]/\varepsilon$$

This concept of  $R_0$  is useful at multiple levels. For example, it provides assessment of the critical fraction of each population immunized, if eradication is targeted ( $p_c$ ). For a vaccine which is considered reasonably protective, the eradication criteria or threshold would be:

$$p_c > \frac{[1 - 1/R_0][1 + L/V]}{\varepsilon}$$

Where,  $p_c$  is the critical fraction of each cohort immunized,  $R_0$  is the basic reproductive number,  $L$  is life expectancy,  $V$  is the duration of vaccine protection and  $\varepsilon$  is vaccine efficacy. (More on vaccine efficacy in subsequent paragraphs.) The eradication threshold for imperfect vaccines (the vaccinated individuals acquire infection but progression to disease is slower) would be:

$$p_c > \frac{[1 - 1/R_0][1 + L/V]}{\varepsilon [1 - R_{ov}/R_0]}$$

Where  $p_c$  is the critical fraction of each cohort immunized,  $R_0$  is the basic reproductive number for unvaccinated,  $R_{ov}$  is the reproductive numbers for vaccinated,  $L$  is life expectancy,  $V$  is the duration of vaccine protection and  $\varepsilon$  is vaccine efficacy. This epidemiological concept explains that eradication is difficult when  $R_0$  large and population density plus net birth rate high.

### Force of Infection

The force or rate of infection is the risk of being infected. The force of infection depends upon prevalence of infectious individuals, rate of contact between individuals, and infectiousness of individuals, etc. As transmission is a dynamic process, force of transmission can change over period of time. The force of infection could be estimated by the following formula:  $\lambda(a) = p(a)/[L(1 - e(-a/L))]$ ; where, force or rate of infection  $\lambda$  and the average age of infection  $A$ , the proportion seropositive at age  $a$  is  $p(a)$ , average force or rate of infection  $\lambda$  over the interval 0 to  $a$  years of age and  $L$  is life expectancy. The relation of this with other concepts is as follows:

$$A \approx 1/\lambda; R_0 \approx L/A; \text{ and } p_c = (1 - 1/R_0) = (1 - A/L)$$

**Table 6** Average age of infection and basic reproductive number of select diseases

Infection	Average age at infection, A	Location/time period	
Measles virus	5–6 years 2–3 years	USA 1955–58 Bangkok, Thailand 1967	
Rubella virus	9–10 years	Sweden 1965	
Varicella virus	6–8 years	USA 1921–28	
Polio virus	12–17 years	USA 1920–60	
Mumps virus	7–8 years	England & Wales 1975	
Smallpox virus	10–15 years	Bangladesh 1940	
Infection	Location	Time period	$R_0$
Measles	England Canada	1947–50 1912–13	13–15 11–13
Varicella	USA	1943	7–8
Mumps	Netherlands	1970–80	11–14
Rubella	West Germany	1970–79	6–7
Polio	USA	1955	5–6
Influenza A (H1N1)	England	2010	1–1.5

## Vaccine Efficacy and Effectiveness

The vaccines have effect at both individual and population levels. The *biological or individual level effect* of vaccines includes effects on susceptibility (VEs), on infectiousness (VEi) and on the disease progression (VEp). The *population level effects* of vaccination depend on the coverage and distribution of the vaccines, as well as on how well different groups mix with each other. These effects could result from biologic effect as well as behavioral effects of the vaccination. Overall, public health effect of vaccination program depends on the effect in both vaccination and the unvaccinated population. This gives at least three types of population level effects of vaccination:

1. *Indirect effect*: The population level effect of widespread vaccination on people not receiving vaccine.
2. *Total effect*: Combination of population level effect and effect of vaccination on individuals receiving vaccine.
3. *Overall public health effect*: The effect of vaccination program based upon weighted average of indirect effect on the individual not receiving vaccine and total effect on individual receiving vaccination.

In this context, the terms vaccine efficacy, vaccine effectiveness and program effectiveness are commonly used.

### Vaccine Efficacy

*Vaccine efficacy* is the percentage reduction in disease incidence attributable to vaccination [usually] calculated by means of the following equation:

$$VE (\%) = (RU - RV) / RU \times 100$$

Where RU = The incidence risk or attack rate in unvaccinated people and RV = The incidence or attack rate in vaccinated people. The equation for vaccine efficacy can be reformulated as:

$$VE = 1 - RV / RU \times 100$$

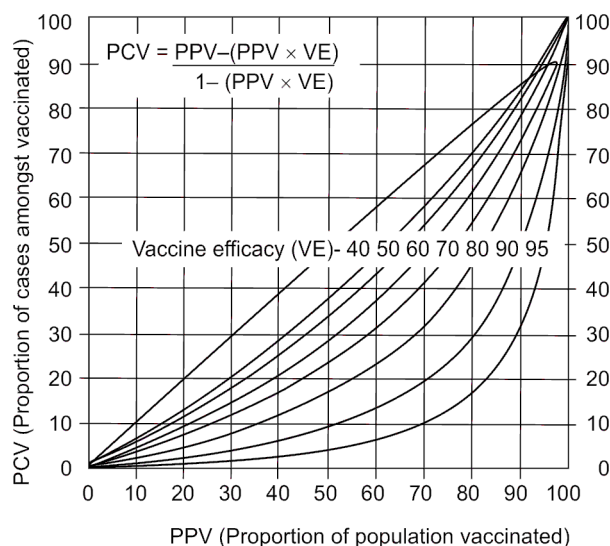
Where RV/RU is the relative risk or rate ratio in vaccinated and unvaccinated. The vaccine efficacy is measured by observational studies under field conditions within a vaccination program or measured by trials conducted under normal program conditions. The vaccine efficacy for a number of vaccines is known, i.e., measles vaccine 90–95%; mumps: 72–88% and rubella 95–98%. In the vaccine trials, the vaccine efficacy is amongst other things (including safety) are assessed and this is an important criterion for licensing of the vaccines and for decision on programmatic use. Vaccine efficacy is dependent upon internal or individual factors for example, efficacy of measles vaccination depends on the presence of inhibitory maternal antibodies, the immunologic maturity of the vaccine recipient and the dose and strain of vaccine virus.

### Vaccine Effectiveness

*Vaccine effectiveness* is the reduction in the clinical events that might be expected to be associated with the disease but could also to be caused by other agents. Under programmatic conditions, effectiveness of measles vaccine depends upon: the coverage, cold chain maintenance, correct injection techniques and safety, inaccurate record-keeping/recall resulting in misclassification errors, and population-specific factors (HIV infection, malnutrition, etc.). The most commonly deployed study design to assess a vaccine's effectiveness is retrospective case control analysis and the odds ratio thus obtained can be used to calculate vaccine effectiveness as:

$$\text{Effectiveness} = (1 - OR) \times 100$$

The vaccine effectiveness could be assessed by observational studies—cohort studies, household contact study, case-control study and screening. How the information from screening could be used for arriving of vaccine effectiveness is shown in **Figure 2**. The



**Figure 2** Relationship between percentage of cases vaccinated and vaccine efficacy

vaccine efficacy and effectiveness have been used interchangeably in scientific literature. The vaccine effectiveness is often referred as vaccine efficacy in the field conditions. In simple terms, vaccine effectiveness is a combination of vaccine efficacy and field conditions such as coverage, immune status of population, conditions under which vaccine administered (cold chain), etc. In general, efficacy is always higher than effectiveness. However, vaccines which show herd effect could have higher effectiveness than vaccine efficacy. For example, under programmatic conditions vaccine effectiveness is lower than vaccine efficacy while herd effect improves effectiveness and can take it above efficacy. If analyzed from an outbreak, the formula for estimation of *vaccine effectiveness* is *attack rate among vaccinated versus attack rate among nonvaccinated*.

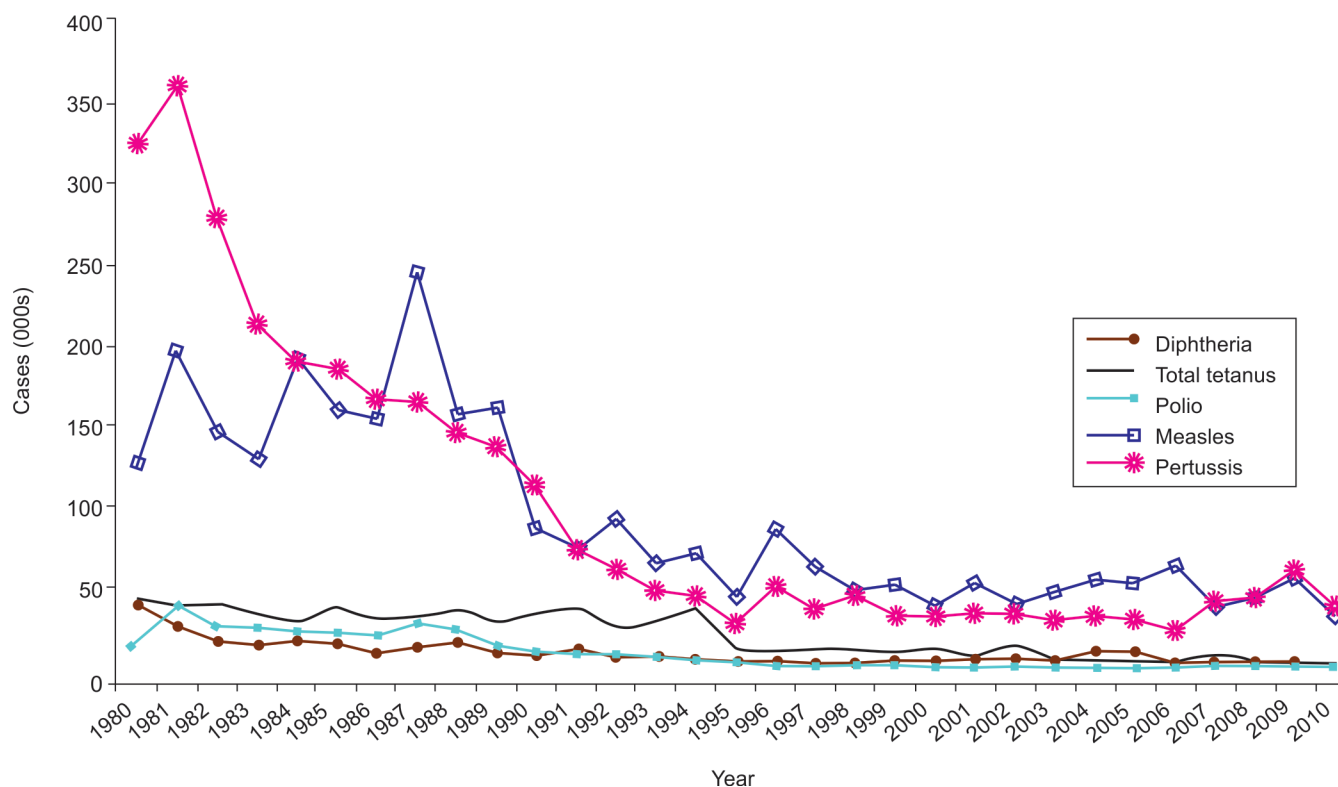
### Program Effectiveness

The *program effectiveness* refers to the assessment of effectiveness of individual antigens in districts, states and national level by various epidemiological techniques. The program effectiveness is also assessed by looking at the trends in the occurrence of VPDs (**Fig. 3**) in identified settings and situation, before and after vaccine introductions. Overall mortality reduction is often considered as an indicator of vaccine program effectiveness/impact. Program effectiveness is combination of more than one vaccine's effectiveness. The impact is the population level effect of vaccination program, which depends upon many factors including vaccine efficacy, herd immunity and effectiveness. The serological and epidemiological studies can be used to determine the vaccine efficacy and program effectiveness. Amongst serological studies, two broad types such studies utilized for vaccine efficacy. The *seroconversion studies*, which are useful to measure the induction of an immune response in the host and, in absence of disease, indicate persistence of antibody and immunity. These studies are particularly useful in choosing the appropriate age for vaccination. *Seroprevalence studies* monitor the prevalence of antibodies due to disease in the population and indicate the pattern of occurrence of disease.

The screening of the population is another approach which has been used frequently for assessing the vaccine efficacy. This method provides an estimate of vaccine efficacy, if some other information is available. The formula used for assessing vaccine efficacy is given here and **Figure 2** is used for assessing vaccine efficacy:

$$PCV = [PPV - (PPV * VE)] / [1 - (PPV * VE)]$$

Whereas PCV = Proportion of cases occurring amongst vaccinated individuals; PPV = Proportion of population vaccinated;



**Figure 3** Reported vaccine preventable disease cases in India; 1980–2010

Source: Central Bureau of Health Intelligence (CBHI), India.

and VE = Vaccine efficacy. If any of the two values in this formula is known, then third value can be derived.

### Vaccine Failure

When a person who has been fully vaccinated develops the disease against which they have been vaccinated, it is referred to as vaccine failure. This could be of two types:

1. *Primary vaccine failure* occurs when the recipient does not produce enough antibodies when first vaccinated. Infection can therefore occur at any time post vaccination. This can occur in about 10% of those who receive the measles-mumps-rubella (MMR) vaccine.
2. *Secondary vaccine failure* occurs when an adequate number of antibodies are produced immediately after the vaccination, but the levels fall over time. The incidence of secondary vaccine failure therefore increases with time after initial vaccination and booster doses are required. This is a feature of many of the inactivated vaccines.

### HERD IMMUNITY

*Herd immunity* may be defined as the resistance of a group or a community in total, against the invasion and spread of an infectious agent as a result of a large proportion of individuals in the group being immunized. The herd immunity or contact immunity develops in case of certain live vaccines (e.g. OPV) wherein the nonvaccinated individuals also develop immunity to the pathogen just by coming in contact with the vaccinated individual. The level of herd immunity can be assessed through cross-sectional and longitudinal serological surveys. Additionally, the level of herd immunity can be measured by reference to the magnitude of reduction in the value of  $R_0$ . Herd immunity threshold ( $H$ ) is defined as the minimum proportion to be immunized in a population for elimination of infection.

$$H = 1 - 1/R_0 = (R_0 - 1)/R_0$$

As the immunization coverage increases, the incidence and prevalence rate may decrease not only due to the direct effect of immunization *per se* but also because of herd effect.

### HERD EFFECT

Herd effect or herd protection is *the reduction of infection or disease in the unimmunized segment as a result of immunizing a proportion of the population* or is *the change induced in epidemiology (incidence reduction) among unvaccinated members when a good proportion is vaccinated*. Herd effect is seen only for infections where humans are the source, and it extends beyond the age, a vaccine is given. Hib vaccine given to infants indirectly also offers protection to other under five children, and also adult of other family members.

### EPIDEMIOLOGIC SHIFT

Epidemiological shift or transition denotes the change in the pattern of disease in a specified population. The impact on person characteristics of disease is, shift in the age, observed consistently in communities with partial immunization coverage. The phenomenon is termed as epidemiological shift and diseases of importance are hepatitis A, rubella and varicella, wherein the severity of disease worsens with advancing age. Vaccination artificially alters natural selection leading to extinction of some genotypic families and sustained propagation of others at the expense of the genotype against which the vaccine efficacy is higher; e.g., Type 2 polio virus got eradicated way back in 1999 mainly due to better vaccine efficacy of tOPV against it while Type 1 and 3 continue to circulate even till today.

One of the well-documented examples of epidemiological shift is the introduction of MMR vaccine in Public Health Vaccination program in Greece with inconsistent coverage. The MMR vaccine was introduced in Greece in 1975. The immunization coverage ~50–60% among boys and girls aged 1 year. This way, a large proportion of women susceptible kept on increasing. In 1993, it was noted that



Greece had highest incidence of congenital rubella syndrome (CRS). The reason was with low MMR coverage, the shifting epidemiology and susceptible population. The epidemiological shift can cause more harm than good. This highlights the need and importance for high coverage at the time introduction. This is sometimes referred as *perverse outcome*, where disease severity increases with age at infection, vaccination can increase the burden of disease, by raising average age of infections (the total number of infections fall but the total number of severe disease increases, i.e., CRS, measles encephalitis, orchitis due to mumps, etc).

## INTRODUCTION OF NEW VACCINES

Usually, the countries have their own criteria for decision making on introducing a new vaccine in national immunization programs. The usual criteria are disease burden, availability of safe and effective vaccine, cost effectiveness and program sustainability. The usual questions, which are deliberated before making decisions on the introduction of new vaccines for any target group or National Immunization Program includes:

1. Is the disease under consideration a public health problem?
2. Is the immunization the best control strategy for this disease?
3. Is the existing immunization program working well enough to add a new vaccine?
4. What will be the net impact of the vaccine?
5. Is vaccine a good investment and what are the alternatives?
6. How will the vaccine be funded and how the program would be sustained once external funding is over?
7. How will the addition of the new vaccine be implemented?

The vaccine epidemiology provides or helps to provide answers to these questions. These answers are supported by information on disease surveillance, modeling, vaccine efficacy and program effectiveness.

## DESIGNING IMMUNIZATION SCHEDULE

The immunization schedule aims to strike a balance between immunological and epidemiological determinants. It aims for achieving protective immune response prior to the age when children are most vulnerable. It also aims for balance between inducing reasonable protection prior to vulnerable age versus inducing optimal immune response. Starting late might induce a higher response, but miss the vulnerable age, wider intervals between doses gives a better response, but delays induction of immunity, leaving children vulnerable in a crucial period in their life. The disease epidemiology varies in different populations, therefore, a schedule that is used in one population is not the best for another; need to individualize and tailor to suit local needs. The determinants of optimal immunization schedule can be organized in four broad categories:

1. *Immunological*: Minimum age at which vaccine elicit an immune response; number of doses required; interval between doses, if multiple doses are required
2. *Epidemiological*: Susceptibility for infection and disease; disease severity and mortality.
3. *Programmatic*: Opportunity to deliver with other scheduled interventions; increase coverage by limiting the required contacts.
4. *Safety of the vaccines*.

The decisions on opting for a particular immunization schedule are affected by a number of epidemiological determinants as summarized here and also described below:

**Vaccine and antigen type** The immunization schedule is affected by the types of vaccines, i.e., live versus non-live vaccines. There is higher intensity innate response with live vaccines. With higher antigen content following replication and prolonged antigen persistence with live vaccines. Similarly, use of adjuvants enhances response to non-live vaccines. It is also dependent upon antigen type as polysaccharide antigens are T-cell independent and have

lower antibody response of shorter duration and no booster response. The protein antigens or antigens conjugated with some proteins have a higher immune response and booster effect (**Table 3**).

**Number of doses** The number of doses required varies by vaccines. In general, live vaccines induce immunity with a single dose and inactivated vaccines require multiple doses. Some live vaccines only induce immunity in a relatively small proportion of vaccines, requiring multiple doses to induce immunity in an optimal proportion of population, e.g., OPV. Number of doses required may also vary by age. More doses of conjugate vaccines are required in young infants. Duration of immunity also influences the requirement for additional doses, either to boost or to re-induce immunity (for T-cell independent antigens). The non-live vaccines generally require booster doses for long-term immunity. Since vaccines seldom produce sustained mucosal immunity, natural boosting from mucosal infection occurs frequently.

**Age and route of administration** The age reflects the maturity of the immune system. For example, children younger than 2 years are usually do not respond to polysaccharide antigens. Greater numbers of doses are required for primary response (PS-conjugate vaccines). At younger age, there is inhibitory effect of maternal antibodies and that is why measles vaccine is administered at 9 months of age.

**Route of administration** The route of administration is less of an issue with live vaccines. However, most non-live vaccines have to be given intramuscular (IM) or intradermal (ID) because of presence of adequate number of antigen presenting cells (APCs) in these areas. Mucosal immunization with non-live vaccines is difficult with the only exception of oral cholera vaccine (killed  $\pm$  B subunit). The core principle is that organisms should be able to replicate at site of administration. Following replication, organisms disseminate and induce generalized immune response.

**Programmatic considerations in scheduling vaccination** The efforts are made to match the optimal schedules (based on immunological and epidemiological considerations) with programmatic realities in the local population to achieve maximum effect on disease control. The predominant modality of vaccine delivery, e.g., fixed sites or outreach, need to be considered, including the number of contacts required with health systems, exploring options of linking with delivery of other interventions and explore delivery mechanisms that increase coverage and reach the *hard to reach*, e.g., campaigns, immunization days, etc.

## ASSESSMENT AND EVALUATION OF THE IMMUNIZATION PROGRAM

It is imperative to ensure the quality of immunization services, is evaluated and assessed on the regular basis. The epidemiological methods provide useful tools for such evaluations.

**Thirty-cluster survey** This is a standard WHO methodology to determine immunization coverage based on a survey of small number of individuals (e.g., 210 in 30 clusters of 7 children each). The home visits are made and immunization record or history is taken for children aged 12–23 months. The survey provides fairly correct information about immunization coverage in the area. However, it is important that these clusters are selected based upon standardized methodology and statistical tools.

**Seventy-five household survey** In this approach, 75 households near the health facility are surveyed. This methodology follows the notion that if the households closest to the facilities could provide the best estimates of immunization coverage.

Missed opportunity survey, Lot Quality Assurance Survey (LQAS), Multi-indicator Cluster Survey (MICS) and Coverage Evaluation Surveys (CES) are the other methods.



### IN A NUTSHELL

1. Vaccines are the proven cost-effective interventions to reduce mortality and morbidity (in all age groups). There are licensed vaccines against nearly 27 pathogens and nearly 130 are under research and stage of clinical trials.
2. Vaccines have successfully controlled scourge caused by pathogens such as smallpox (eradicated) and poliomyelitis (nearly eradicated).
3. Vaccinology combines the principles of microbiology, immunology, public health, epidemiology and pharmacy, amongst other.
4. The knowledge of principles of vaccine epidemiology, i.e., basic reproductive number, vaccine efficacy and effectiveness, herd immunity, epidemiological shift and disease surveillance need to be widely understood by all practitioners who administer vaccines.

### MORE ON THIS TOPIC

- Anderson RM, May RM. Directly transmitted infectious diseases; control by vaccination. *Science*. 1982;215:1053-60.
- Beaglehole R, Bonita R, Kjellstrom. *Basic Epidemiology*. Geneva: World Health Organization; 2002.
- Gordis L. *Epidemiology*. 5<sup>th</sup> ed. Philadelphia, PA: Elsevier Saunders; 2014.
- Government of India. *Immunization Handbook for medical officers*. New Delhi: Ministry of Health and Family Welfare; 2010.
- Government of India. *Multi Year strategic Plan for Universal Immunization Program in India (2005-2010)*. New Delhi: Ministry of Health and Family Welfare; 2005.
- Plotkin SA, Orenstein WA, Offit PA. *Vaccines*. 6<sup>th</sup> ed. Philadelphia, PA: Elsevier Saunders; 2013.
- Porta M, Greenland S, Last JM. *A Dictionary of Epidemiology*, 5<sup>th</sup> ed. New York, USA: Oxford University Press; 2008.
- World Health Organization. *State of the World's Vaccines and Immunization*. Geneva: WHO, UNICEF, The World Bank; 2009.

## Chapter 23.2

# Vaccine Administration Practices

Satish V Pandya

Selecting proper route and site of vaccine administration and ensuring optimum delivery with right technique are of paramount importance. Health-care providers need to take measures to prevent transmission of infection during the process of administration. Steps taken to ensure comfort and pain alleviation for the vaccines go a long way in sustaining faith in the vaccination programs. This also requires adequate training of paramedical staff and good communication skills for the health-care providers. With large number of vaccines to be administered proper documentation is very important to prevent errors in schedule, duplication of doses and missing of doses of vaccination.

### ROUTES AND TECHNIQUES OF VACCINE ADMINISTRATION

Various routes are recommended for administration of vaccines. These include intramuscular, subcutaneous, intradermal, oral, and nasal. Route of vaccine administration varies with individual vaccine. The route depends upon the immunogenicity and composition of vaccine. It is determined during pre-licensure studies. One vaccine may have option of more than one route. The route of administration used should be as mentioned by the manufacturers and guidelines published by professional organizations such as Advisory Committee for Vaccination and Immunization Practices by Indian Academy of Pediatrics (ACVIP-IAP). The site of administration is also determined so as to give optimum immune response and minimize injury to surrounding tissues. Deviation from labeled route and site can result in adverse effects and less than desired immune response. For example, if hepatitis B vaccine is given in gluteal region the immunogenicity is lowered.

Most parenteral vaccines are given by either intramuscular or subcutaneous route (as an exception *Bacillus Calmette-Guérin* (BCG) and sometimes rabies vaccine are given intradermally). Subcutaneous route is used for measles, measles-mumps-rubella (MMR), varicella, meningococcal polysaccharide, Japanese encephalitis and yellow fever vaccines. Either subcutaneous or intramuscular routes can be used for pneumococcal polysaccharide vaccine and inactivated polio vaccine (IPV). Rest of the vaccines are to be given intramuscularly. If vaccines recommended to be given by subcutaneous route are given intramuscularly, then no harm is done. However, those designated to be given intramuscularly should not be given subcutaneously as this will cause more local side effects and may have reduced immunogenicity.

### Intramuscular Injections

This route is generally recommended for adjuvant-containing vaccines. Vaccines containing adjuvant (e.g., aluminum adsorbed DTaP, DTwP, DT, hepatitis B, hepatitis A) must be injected deep intramuscularly. Such vaccines when given by other routes such as subcutaneous or intradermal can cause significant local inflammatory reactions and result in pain, induration, skin discoloration and granuloma formation.

Site of intramuscular injection depends upon the volume of vaccine to be administered, size of the muscle mass and thickness of overlying subcutaneous tissue. The quadriceps

muscle mass in anterolateral aspect of thigh is recommended for infants less than 12 months of age and deltoid muscle in upper arm is recommended for older children above 12 months of age, adolescents and adults. Anterolateral aspect of thigh can also be used for older children but it may cause transient limping. When more than two vaccines are to be administered on the same limb anterolateral aspect of thigh is preferred to get a larger muscle mass. However, the injections should be separated by distance of more than one inch to differentiate local reactions. If a vaccine and an immune globulin are to be administered simultaneously (e.g., Hepatitis B vaccine and HBIG), separate anatomic site should be used for each one.

Gluteal region is not generally recommended for routine vaccination due to potential risk of injury to sciatic nerve. This site is uncommonly used when a large volume of immune globulins preparations are to be administered intramuscularly. The needle is inserted in upper outer quadrant and directed anteriorly. A 22–25 gauge needle is usually used for most intramuscular vaccines. The ideal needle length depends upon the thickness of subcutaneous tissue, desired depth below the muscle tissue in which the vaccine is to be injected and the technique used. There are two techniques used for intramuscular injections:

1. The *bunching* technique consists of gently bunching the muscle with freehand and the needle is inserted perpendicular to the skin. A 7/8–1 inch (22–25 mm) needle is recommended with this technique.
2. The second technique consists of stretching the skin flat over the injection site with thumb and index finger and inserting the needle perpendicular to the skin. A 5/8 inch (16 mm) needle is recommended with this technique.

These recommendations for infants and older children are based on studies with ultrasonography to determine the thickness of subcutaneous tissue and muscle layer over deltoid and anterolateral thigh of children. For adolescents and adults, the needle length may be determined based on the weight and sex of the vaccines. The range may be from 5/8-inch to 1.5 inch (16 mm to 38 mm). Aspiration by pulling back on the syringe plunger is not recommended as there are no large blood vessels at the routinely recommended sites. It is also more painful to infants.

After intramuscular injection, the needle should be withdrawn a few seconds after finishing the administration to prevent backflow of vaccine into the needle track. After withdrawal of needle, the site should be pressed for few seconds with a cotton swab. It should not be rubbed. In patients with bleeding disorders who require intramuscular vaccination, the administration of vaccine should be scheduled shortly after specific therapy. Firm pressure should be applied at the site for 2 minutes or more. If feasible, subcutaneous route may be preferred.

### Subcutaneous Injections

With subcutaneous injection, the risk of local neurovascular injury is reduced and is recommended for those vaccines which are less reactogenic but immunogenic when administered by this route. Live-virus vaccines such as measles, mumps and rubella are the examples. The usual sites for subcutaneous injections are thigh for infants less than 12 months of age and upper, outer triceps area for children above 12 months age. A 5/8-inch needle of 23–25 gauge is recommended. The vaccine is administered below the dermal layer of tissues. To avoid entry into the muscles, skin and subcutaneous tissue should be held and raised as a fold between thumb and finger and needle is inserted at an angle of 45°.

### Intradermal Injections

Intradermal administration is mainly recommended for BCG vaccination. It is also used for rabies vaccine when administered

on a large scale with large number of vaccines. The deltoid region of left upper arm is recommended for BCG vaccine. A 3/8–3/4 inch, 25–27 gauge needle is used. The needle is inserted into the epidermis at angle parallel to the long axis of the upper arm. The entire bevel should penetrate the skin and a bleb should be raised by injected solution. This confirms intradermal injection rather than subcutaneous injection. Inadvertent injection into subcutaneous layer may result in suboptimal immunogenic response.

Summary of recommended site, route, technique, and needle length for various ages is given in **Table 1**.

### Oral Administration

Oral polio vaccine (OPV) and rotavirus vaccines are given orally. The vaccinee should be administered slowly over in side of the cheek to prevent gag reflex. One should ensure that the vaccine is swallowed and retained. If OPV is spat out or regurgitated within 10 minutes of administration, it should be repeated immediately. However, readministration of rotavirus vaccine is not recommended if it is spat out or regurgitated. (Manufacturer's instructions should be followed). Breastfeeding before or after oral administration of vaccine is not contraindicated.

### Intranasal Route

Live-attenuated influenza vaccine (LAIV) is administered intranasally. This vaccine is not available in India at present. The administration device is a nasal sprayer with a dose divider clip that allows introduction of one 0.1 mL spray into each naris. The tip should be inserted slightly into the naris before administration. The vaccine dose need not be repeated, if the person coughs or sneezes after administration. Introduction of low levels of vaccine virus into the environment is likely and unavoidable. Severely, immunocompromised persons should not administer LAIV.

### ENSURING COMFORT AND ALLEVIATING PAIN

Several methods are used to reduce discomfort and alleviate pain associated with vaccine administration in young infants and children. Supportive and compassionate attitude of the health-care providers reduce the anxiety of parents and children. A child friendly environment with various distractions such as

colorful pictures, toys and music may help to comfort the child. Pretreatment with topical lidocaine—prilocaine emulsion cream (EMLA) or patch causes superficial anesthesia and decreases the pain associated with vaccination. It does not seem to interfere with immune response. Topical refrigerant spray can work for short periods following vaccination. Use of antipyretics before or at the time of vaccination is not evidence based. However, antipyretics can be used to treat fever and local discomfort following vaccination. Breastfeeding and oral administration of sweet fluids (sucrose) just before injection have calming effect and may serve as potential analgesics.

### STERILE INJECTION PRACTICES

The World Health Organization (WHO) defines a safe injection as one that

- Does not harm the patient
- Does not expose the health worker to avoidable risk
- Does not result in waste that puts other people at risk.

There is risk of transmission of blood-borne pathogens when injections are administered. Thorough hand washing with soap and water for 2 minutes using WHO, 6 steps is recommended before each vaccine contact to reduce the risk of microbial contamination and transmission of microbes between recipients and health-care providers. Hand cleansing with an alcohol-based antiseptic hand rub is an alternative. The use of protective gloves is not routinely recommended unless the health-care provider is likely to have contact with potentially infectious body fluids or has open lesions on the hands.

Bacterial infection at injection site and abscess formation can occur, if proper care is not taken. The skin at injection site needs to be prepared to prevent contamination with bacteria on the skin. This can be achieved with 70% isopropyl alcohol or other disinfectant. This should be allowed to dry before giving injection.

Transmission of pathogens can occur, if the needles, syringes, vaccines and other equipment used for injection are contaminated. This can be prevented by certain measures. The needles and syringes should be sterile. A separate needle and syringe should be used for each injection. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary.

**Table 1** Injection site, type of needle and technique

Age	Site	Type of needle	Comments
Intramuscular injections (needle should enter at 90° angle)			
Preterm and neonates	Anterolateral thigh (junction of middle and lower third)	22–25G, 5/8 inch	Skin should be stretched between thumb and forefinger
Infants (1 to < 12 months)	Anterolateral thigh	22–25G, 1 inch	Bunch the skin, subcutaneous tissue and muscle to prevent striking the bone
Toddlers and older children (12 months–10 years)	Deltoid	22–25G, 5/8 inch	Skin should be stretched between thumb and forefinger
	Or Anterolateral thigh	22–25G, 1 inch	Bunch the skin, subcutaneous tissue and muscle
Adolescents and adults (11 years onwards)	Deltoid or anterolateral thigh	< 60 kg 1 inch	
		> 60 kg 1.5 inch	
Subcutaneous injections (needle should enter at 45° to the skin)			
Infants	Thigh	22–25G, 5/8 inch	
Children >12 months	Outer triceps	22–25G, 5/8 inch	
Intradermal injections			
All ages	Left deltoid	26/27G, 0.5 inch	A 5 mm wheal should be raised

The septum of a multidose vial should be swabbed with alcohol prior to each withdrawal and needle should not be left in the vial. Single-use disposable syringes and needles should be used. To prevent needle-stick injury syringe and needle should be discarded as single unit in a puncture-proof container. Recapping of needle should not be done. Autodisable syringes help to prevent reuse of disposable syringes. Needle-shielding devices ensure protection against needle-stick injuries.

*Jet injectors* are needle-free devices that drive liquid medication through a nozzle orifice, creating a narrow stream under high pressure that can deliver the vaccine into intradermal, subcutaneous or intramuscular tissues. They prevent needle-stick injuries and overcome other problems associated with disposable syringes and needles. They are safe and effective and immune responses generated are equivalent or higher than those with needle injection. Local reactions such as redness, induration, pain and ecchymosis at the site of injection are more frequent.

Paramedical staff needs to be trained to ensure safe immunization practices. Periodic supervision is equally important.

## ERRORS OF ADMINISTRATION

Errors in medication are not uncommon. Vaccination is no exception. Programmatic errors such as giving inappropriate medication instead of vaccine can cause avoidable morbidity and mortality. Such events also put vaccination programs in disrepute and cause setback. It is absolutely necessary to take all measures to prevent such errors.

- Syringes should be filled only before administration because several vaccines look similar in appearance when filled in syringe. There should be a system of multiple checks to minimize human error and to ensure that only right vaccinee is given to the right vaccine.
- Vaccine should be inspected for expiry date. If the label has come off, the vaccine should be discarded. The vial should be shaken thoroughly to obtain a uniform suspension. Any abnormal looking vaccine or diluents should be discarded irrespective of expiry date.
- For reconstitution of lyophilized vaccines, only vaccine-specific supplied diluents should be used. The reconstitution should be done just prior to administration. Reconstituted vaccine should be discarded, if not used within the stipulated time (2–4 hours).
- Different vaccines should not be mixed in same syringe unless specifically licensed for such a use. Change of brand for a vaccine with same composition is generally not recommended but may be done in case of non-availability of the same brand or if the records are not clear about the brand used in past.
- Principles of cold-chain maintenance are discussed separately in another chapter of this section.

## DOCUMENTATION AND RECORD KEEPING

In the present era of availability of multiple vaccines, immaculate record keeping is an important aspect of good immunization practices. Availability of vaccines with several different brand names, combinations with different brand names, vaccines with different number of serotypes and patients getting vaccination at different setups often result in confusion regarding the true immunization status of the child. Deviation from recommended schedule and missed doses make the matters worse. Some of the commonly encountered problems with record keeping are illegible dates, no mention about brands, no mention about valency of vaccine, confusing signs used by individual practitioners (for example, a tick mark is done against “OPV/IPV” though only OPV has been administered) and confusion between due date and date

of administration. Such improper vaccination records result in missing of doses, duplication of doses and improper schedules.

The ideal vaccination record should have following:

- Date of vaccination
- Product administered
- Manufacturer’s name or brand name
- Lot or batch number
- Expiry date
- Site and route of administration
- Name, address and title of the health-care provider administering the vaccine.

Additionally, the record should be legible, next due date should be written away from the record of date of administration to avoid confusion, vaccination record card should be of good quality paper to prevent wear and tear and the card should show a recommended schedule of vaccination from birth to adolescence. Computerized vaccination record is recommended in office practice. This will ensure easy retrieval in case of lost or damaged record card and can instantly generate a schedule according to age and vaccines administered in past.

## PREPAREDNESS FOR LIFE-THREATENING ADVERSE EVENTS FOLLOWING VACCINATION

Ideally, the vaccinee should be observed for at least 15–20 minutes following vaccination for any allergic reactions. Each health-care facility offering vaccination program should have a functional resuscitation place. It should be equipped with working suction facility, airway, oxygen, bag and mask, intubation equipment, intravenous access and medications necessary for treating anaphylaxis (adrenalin, normal saline and hydrocortisone).

## Communicating with Parents and Children

The parents must be explained about need, efficacy, safety and cost of vaccines being offered. One-to-one discussion is required. A balanced scientific view needs to be given about the vaccines. The care providers need to be updated on newer developments in rapidly progressing field of immunization. Parents should be imparted enough knowledge about vaccine-related issues to empower them to make informed decisions regarding vaccination. The common expected side effects should be informed in advance so that parents do not become anxious. As mentioned earlier medication for treating fever and pain should be prescribed to be used, if required. Children should also be offered age appropriate information and explained about the administration process. A positive and caring attitude reassures children and makes the inevitable pain more tolerable. This will ensure continued follow-up and reduce incidence of drop out and missed doses.

### IN A NUTSHELL

1. Do not deviate from the recommended route, site and technique.
2. Children should be provided a friendly environment with caring attitude of personnel and measures should be taken to alleviate pain and discomfort.
3. Infection control and safe vaccination practices need utmost attention. Errors can be avoided, if guidelines are strictly followed.
4. Proper documentation of vaccine administered is essential.
5. The paramedical staff should be adequately trained and supervised.
6. Vaccination setup should be well prepared to manage life-threatening events like anaphylaxis.
7. Proper communication regarding need, safety, efficacy and cost is must.



## MORE ON THIS TOPIC

- Atkinson WL, Pickering LK, Schwartz B, et al. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR Recomm Rep*. 2002;51:1-35.
- Kroger AL, Atkinson WL, Pickering LK. General Immunization Practices. In: Plotkin SA, Orenstein WA, Offit PA (Eds). *Vaccines*. 6<sup>th</sup> ed. USA: Saunders Elsevier; 2013. pp. 88-112.
- National Center for Immunization and Respiratory Diseases. General recommendations on immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60:1-64.
- Pandya SV. Vaccination records. In: Vashishtha M, Kalra A. *Pediatric Immunization*. 1<sup>st</sup> ed. Mumbai: Tree Life Media; 2014. pp.184-6.
- Vashishtha VM, Kalra A, Thacker N. *FAQs on Vaccines and Immunization Practices*, 1<sup>st</sup> ed. New Delhi: Jaypee Brothers Medical Publishers; 2011. pp.41-53.

## Chapter 23.3

# Scheduling of Vaccines

Vipin M Vashishtha

Vaccines are life-saving, great public health tools. More and more vaccines are now developed and used worldwide, first in developed countries and later, in poor developing countries. In developing countries, particularly, they are licensed and introduced first in a private market for individual use, and later some of them inducted into national immunization programs for mass use after a *lag period* which is considerably long for poor developing countries than for industrialized, developed nations. Whether used in individual practice or in large scale mass immunization programs, they need to be scheduled in a particular way so that not only the best possible protection is achieved, but the maximum utilization of their other inherent virtues is also ensured.

### DETERMINANTS OF OPTIMAL IMMUNIZATION SCHEDULE

To devise an optimal immunization schedule, various considerations such as appropriate immunologic response to vaccines, epidemiology and burden of vaccine-preventable diseases (VPDs), impact of the vaccination on future epidemiology of VPDs are taken into account. The focus and objectives are different when planning vaccination strategies for a large community and for an individual child. For instance, an optimal and not necessarily best immunological response may be considered appropriate for effective protection at the earliest in a situation where risk of contracting infection at an early age is high. The few key determinants of an optimal immunization schedule include the following:

**Immunological determinants** Minimum age at which vaccine elicits immune response, the total number of doses required for adequate priming, duration of protection, need and timing of boosters, interval between doses, if multiple doses are required, are few examples where immunological principles affect structure of an immunization schedule.

**Epidemiological determinants** Disease burden and age of highest susceptibility for infection and disease, impact of vaccination on age shift of a particular disease, propensity of a vaccine to cause herd effect, determination of ideal coverage to offset disease transmission, force of transmission ( $R_0$ ) of a particular VPD in different geographic regions, impact of vaccination on postvaccination disease epidemiology, are few instances that determine planning and execution of a mass vaccination program.

**Programmatic determinants** Logistic issues including overall financial burden and cost-effective analysis, opportunity to deliver an antigen with other scheduled intervention, increase coverage by limiting the required contacts, transportation and maintenance of vaccines in proper cold chain, training of health staff, gain critical significance whenever a large scale, mass vaccination program is devised.

A fair interplay of the above three determinants ultimately have major impact on the designing of an optimal immunization schedule. Some other key factors such as immune-competence of the individual, age-specific risk for disease, age-specific risk of disease complications, potential interference with maternal antibodies, and interaction with other vaccines in the schedule also affect the scheduling of different vaccines.

### Synergizing Between Immunological and Epidemiological Determinants

Striking a fair balance between immunological principles and epidemiological concerns is the biggest challenge to devise an optimal immunization schedule. Issue like achieving protective immune response prior to the age when children are most vulnerable versus inducing optimal immune response causes greatest concern. Starting late might induce a higher response, but miss the vulnerable age. For example, the current expanded program on immunization (EPI) schedule of 6-10-14 weeks for primary doses of DTP, *Haemophilus influenzae* type b (Hib), and Hepatitis B followed in most developing countries including India, is not ideal immunologically, but considering the epidemiology of these VPDs which affect children at very young age, this schedule is most suitable. Similarly, wider intervals between doses give a better response, but delays induction of immunity, leaving children vulnerable in a crucial period of life. For example, the schedule of 2, 4, 6 months followed in most industrialized countries, is immunologically much superior to EPI schedule but may not be ideal for developing countries having younger age affection of most VPDs. Hence, the disease epidemiology factors in a big way while forming an immunization schedule, particularly at country level. A schedule that is used in one population is not the best for another; hence, the need to individualize and tailor to suit local needs.

### Determinants of Vaccination Schedules for Community Versus Individual Protection

While planning and developing a vaccination program or schedule, a multifactorial approach is preferred in decision making. Vaccination schedules at individual and community level often vary considerably with regard to different attributes as summarized in **Table 1**. Large scale mass vaccination programs are in the best interests of the community and at Government's cost whereas vaccination provided through private health-care is in the best interests of each child. Therefore the cost is to be borne by the family. So epidemiological and economic parameters go into the assessment of the promise and potential of specific vaccines in delivered through public health program. As shown in **Table 1**, for public sector programs usually it is cost first, efficacy next followed by safety. However, at individual level, it is safety first, efficacy next followed by cost. Nevertheless, it must be remembered that what is not in the best interests of the individual cannot be in the best interests of the community and what is in the best interests of the community is also in the best interests of the individual. Therefore, the private health-care and public health programs including vaccination schedules should be complementary and not contradictory regarding immunological basics, ethics and epidemiology.

### Vaccination Schedule for Community Protection

While designing a vaccination schedule for the community, the greatest challenge comes on the programmatic front. Creating synergies between immunological and epidemiological considerations is one of the greatest hurdles to pass. Matching the optimal schedule with programmatic realities in the local population to achieve maximum effect on disease control is the key consideration. Various logistic issues such as predominant modality of vaccine delivery, e.g., fixed sites or outreach, number of contacts required with health systems, exploring options of linking vaccination with delivery of other interventions, exploring best delivery mechanism (such as campaigns, immunization days, etc.) that increase coverage and reach the *hard to reach*

**Table 1** Key differences in the vaccination schedules devised for community and individual protection

Attributes	Community/Public health	Individual/Private health-care
Focus	Community; Vaccination in public health is in the best interests of community	Individual child; Vaccination in health-care is in the best interests of each child
Need	Determined by the epidemiology and disease burden in the community	Determined by the risk (probability of disease) to an individual child
Objective	To control a set of infectious diseases from the community Control = reduce <i>incidence</i> and <i>monitor</i> reduction	To protect the individual who is vaccinated
Ownership	Government	Consulting physician/pediatrician or individual health facility
Volume	Large	Small
AEFI	Mainly <i>coincidental</i> and <i>programmatic</i> since large volume is used	Mainly <i>vaccine reactions</i> and <i>coincidental</i>
Funding	By the government or international donor agencies	Individual parents
Logistic issues	Major determinants	Not so important
Considerations	Cost first, efficacy next, safety last	Safety first, efficacy next, cost last
Examples	EPI and Universal Immunization Program (UIP)	IAP Immunization schedule

areas, are taken into consideration. In a nutshell, the issues related to coverage, cost, compliance, availability, disease burden, competing priorities, funding, and competing interests play major determinants for vaccination schedules for community protection.

### Vaccination Schedule for Individual Protection

Safety and immunological issues override other considerations while a schedule is designed for individual protection. Sharing information with parents is one of the key factors. Here, the *actors* are not many, and they are mainly parents and physicians. Whereas many actors such as Ministry of Health, WHO, finance department, funding agencies, professional academic bodies, play important role in vaccination schedule for community protection. So a vaccination schedule targeting individual child may be closer to established immunological principles, but it should not be contradictory to national vaccination schedule for community protection and should also address the epidemiological concerns.

## NATIONAL IMMUNIZATION PROGRAMS

At country level vaccination programs, there are two main aims, first to prevent serious disease (in absolute numbers, severity or both), and second to reduce spread of infection. Once a disease gets eliminated, the objectives of vaccination against that particular VPD also change as is the case with polio in India. During pre-elimination, endemic phase, the objective was to control disease and prevent paralysis caused by wild poliovirus. Safety concerns of oral polio vaccine (OPV) took backseat and issues such as vaccine-associated paralytic polio (VAPP) were not highlighted. Once the elimination of wild poliovirus is achieved, the objective has shifted to maintain immunity against wild poliovirus and safety issues of OPV came into perspective. **Table 2** summarizes the shifting focus and key objectives in the two stages.

### Requirements of an Ideal Vaccination Schedule

Apart from meeting epidemiological and immunological concerns, an ideal vaccination schedule whether designed for community or individual protection should have provision for *catch-up* immunization for those who missed age-recommended vaccine dose. Further, there is a need to reach age groups beyond infancy with high coverage. Detailed guidelines regarding minimum number of doses in different age groups and minimum intervals between two doses of a vaccine shall facilitate catch-up immunization. Immunization of adolescents at community level is a grossly neglected entity. A separate schedule for adolescents and preadolescents can fill this void.

Immunization is a dynamic and very rapidly evolving subspecialty of science. New developments such as licensing of new vaccines and emergence of new technology on vaccine administration and storage are taking place regularly at short intervals, hence the need to revise recommendations at regular interval. An ideal schedule cannot be static but should be flexible enough to incorporate new developments including new vaccines into the schedule.

*Factors that affect the inclusion of a new vaccine in the national immunization program:*

1. Disease (burden, severity, mortality, national security, risk of importation, competing priorities)
2. Recipient (age, cohort size, politics)
3. Vaccine (local production, availability, cost, efficacy, safety, other vaccines)
4. Cost-effectiveness analysis.

In countries still having a high burden of natural disease, disease prevention and controlling the morbidity and mortality is the most important objective, therefore vaccine with the highest effectiveness is chosen for inclusion in the national program.

**Table 2** Aims and objectives of vaccination programs during various stages of VPD control

	Countries where disease is endemic	Countries where disease has been eliminated
Objective	Disease control	Maintain immunity
Concerns	Medical, political and economic	Importation, outbreaks, bioterrorism
Choice	Vaccine that meets specific criteria (may not always be the safest option)	Vaccine with the highest safety
Example	OPV in Global Polio Eradication Initiative	IPV during polio endgame and posteradication phase

Abbreviations: VPD, vaccine-preventable diseases; IPV, inactivated poliovirus vaccine; OPV, oral polio vaccine.

Whereas, in a country with a low burden of natural disease, the main concerns are low or no side effects of a new vaccine which will decide acceptance of the vaccine. Therefore, a vaccine with a high safety level can only be included in the immunization schedule. As new vaccines are being developed, they are being incorporated in the immunization schedule based on the disease burden and cost-effectiveness of the vaccine.

Strict compliance to *evidence-based review* process while issuing recommendations on vaccination schedule is another key requirement of an ideal vaccination schedule. Most of the reputed international agencies such as WHO, ACIP, etc. have now incorporated *evidence-based review* policy and have also started adopting GRADE (Grading of Recommendations Assessment, Development and Evaluation) system on rating quality of evidence and strength of recommendations.

## VACCINATION SCHEDULES AT GLOBAL, REGIONAL AND NATIONAL LEVEL

There is great heterogeneity in the vaccination schedules of developing and developed countries. Even in these two broad groups, different vaccines and different schedules of same vaccines are noticed based on the availability of licensed products in a particular country and their need based on epidemiology of different VPDs (**Box 1**). There are several reasons why uniform immunization schedule is not possible; some of them include the following:

- *Epidemiologic heterogeneity*: Increasing reports of resistant, emerging and re-emerging infections that challenge vaccination strategies
- *Resource heterogeneity*: Priorities have to be affixed commensurate to affordability
- Variable health systems capacity and research evidence
- Variability in ethics, legal and policy procedures
- Variations in public and political reactions: AEFI, agenda, intensities of resistance and hostility.

### Process of Issuing Global Recommendations

WHO issue recommendations to each country, particularly to developing country on broad framework of their own country-specific vaccination schedule. WHO has formed a specific, highly technical group on immunization, called Strategic Advisory Group of Experts (SAGE) on immunization. SAGE is the principal advisory group to WHO for issuing recommendations on vaccines and immunization related issues that ultimately decide overall global policies and strategies.

The WHO encourages each of its country members to have their own NITAGs (National Immunization Technical Advisory Groups) to decide and chalk out their own national immunization programs and vaccination schedules. Each NITAG is expected to follow WHO-SAGE recommendations on immunization-related issues. The NITAG in India was first established by Ministry of Health, Government of India in August, 2001 and is called as NTAGI (National Technical Advisory Group on Immunization).

#### BOX 1 Different vaccination schedules of few key developing countries

*Vaccination schedules for primary immunizations in developing countries:*

- 6, 10, 14 weeks (India, Kenya, Madagascar, Mozambique, Philippines, Rwanda, South Africa)
- 2, 4, 6 months (Egypt, Chile, Mexico, Thailand, Uruguay, Argentina, Brazil)
- 2, 3, 4 months (Gambia, Indonesia, Turkey, Vietnam)
- 2, 3, 5 months (Malaysia)
- 3, 4, 5 months (China).

NTAGI issues recommendations to Government of India to formulate national immunization schedule and also to make changes based on new developments. There is another vaccination schedule issued by Indian Academy of Pediatrics (IAP) for its members and clinicians in the private sector. The Academy has a specific subcommittee, ACVIP (Advisory Committee on Vaccines and Immunization Practices) that issues recommendations regarding vaccination schedule at periodic intervals. So, in India there are two major vaccination schedules in practice today, one, the vaccination schedule under Universal Immunization Program (UIP) issued by Government of India (**Table 3**), another, by Indian Academy of Pediatrics (**Table 4**).

## NEED OF THE HOUR

There are still many challenges both at planning and execution level as far as national immunization program and UIP schedule is concerned. Many key vaccines are still not part of our national immunization schedule, and on the other end, there is gross heterogeneity of coverage in different states and even in different districts of the existing vaccines. Further, there is inappropriate delivery of vaccines. The states having the highest burden of VPDs are reached in the last owing to poor infrastructure and vaccine delivery system. There is an urgent need of research and analysis to explore more cost-efficient schedules, particularly with new vaccines. There is need to reach age groups beyond infancy with high coverage, to incorporate vaccines for certain *neglected* diseases such as typhoid, rabies, etc., need to national level up scaling of pentavalent vaccines, to develop schedules and strategies to reach the *hard-to-reach* areas, to create links with other programs to achieve synergy and to deliver a package of interventions, etc. The bolstering of *school health programs* to boost adolescent immunization is also urgently needed. In the last, there is growing demand on relook at the existing EPI schedule in India and other developing countries.

### IN A NUTSHELL

1. Proper scheduling of available vaccine is the key to proper utilization of available vaccines and achieving good protection against prevailing VPDs.
2. The few key determinants of an optimal immunization schedule include immunological principles, epidemiological aspects and programmatic issues.
3. There are key differences in the vaccination schedules designed for individual and community protection.
4. While safety and efficacy are the key issues for individual schedule, cost and programmatic issues override all the considerations in schedules planned for community protection.
5. There is marked heterogeneity in the vaccination schedules of different countries.
6. WHO-SAGE gives recommendations to NITAGs of individual country to formulate their national vaccine policies including their schedules.
7. NTAGI in India gives recommendations to Government of India regarding planning of its immunization schedule. ACVIP of IAP devises its immunization schedule for pediatricians working in private sector.
8. Catch-up immunization, adolescent immunization, improvement in coverage, adoption of new vaccine technology, incorporation of new lifesaving vaccines, support to innovation and research and development related to vaccines are few key initiatives urgently needed to improve our existing national immunization schedule.



**Table 3** Vaccination schedule under Universal immunization program (UIP) in India

<i>Vaccine</i>	<i>When to give</i>	<i>Dose</i>	<i>Route</i>	<i>Site</i>
<i>For Pregnant Women</i>				
TT-1	Early in pregnancy	0.5 mL	Intramuscular	Upper arm
TT-2	4 weeks after TT-1*	0.5 mL	Intramuscular	Upper arm
TT-Booster	If received 2 TT doses in a pregnancy within the last 3 years	0.5 mL	Intramuscular	Upper arm
<i>For Infants</i>				
BCG	At birth or as early as possible till 1 year of age	0.1 mL (0.05 mL until 1 month of age)	Intradermal	Left upper arm
Hepatitis B Birth dose	At birth or as early as possible within 24 hours	0.5 mL	Intramuscular	Anterolateral side of mid-thigh
OPV Zero dose	At birth or as early as possible within the first 15 days	2 drops	Oral	Oral
OPV 1, 2 and 3	At 6 weeks, 10 weeks and 14 weeks	2 drops	Oral	Oral
DPT 1, 2 and 3	At 6 weeks, 10 weeks and 14 weeks	0.5 mL	Intramuscular	Anterolateral side of mid-thigh
Hepatitis B 1, 2 and 3	At 6 weeks, 10 weeks and 14 weeks	0.5 mL	Intramuscular	Anterolateral side of mid-thigh
HiB 1, 2 and 3	At 6 weeks, 10 weeks and 14 weeks	0.5 mL	Intramuscular	Anterolateral side of mid-thigh
Measles 1st dose	9 completed months–12 months. (give up to 5 years, if not received at 9–12 months age)	0.5 mL	Subcutaneous	Right upper arm
JE 1st dose**	9 completed months	0.5 mL	Subcutaneous	Left upper arm
<i>For Children and Adolescents</i>				
DPT booster	16–24 months	0.5 mL	Intramuscular	Anterolateral side of mid-thigh
OPV Booster	16–24 months	2 drops	Oral	Oral
Measles 2nd dose	16–24 months	0.5 mL	Subcutaneous	Right upper arm
Rubella ***	16–24 months Adolescent girls	0.5 mL	Subcutaneous	Right upper arm
JE 2nd dose	16–24 months with DPT/OPV booster	0.5 mL	Subcutaneous	Left upper arm
DPT Booster 2	5–7 years	0.5 mL	Intramuscular	Upper arm
TT	10 years and 16 years	0.5 mL	Intramuscular	Upper arm
Vitamin A****				

\*Give TT-2 or Booster doses before 36 weeks of pregnancy. However, give these even if more than 36 weeks have passed. Give TT to a woman in labor, if she has not previously received TT.

\*\*JE Vaccine (SA 14-14-2) is given in select endemic districts, after the campaign is over in that district.

\*\*\* Rubella vaccine will be given as part of Measles 2nd dose.

\*\*\*\*The 2nd to 9th doses of vitamin A can be administered to children 1–5 years old during biannual rounds, in collaboration with ICDS.

Abbreviations: BCG, bacillus Calmette–Guérin; DPT, diphtheria, tetanus and pertussis; Hib, *Haemophilus influenzae* type b; JE, Japanese encephalitis virus.

Source: Multi Year Strategic Plan 2013-17, Universal Immunization Program, Department of Family Welfare, Ministry of Health and Family Welfare, Government of India, New Delhi.

**Table 4** Indian Academy of Pediatrics (IAP) Immunization timetable 2014

I. IAP recommended vaccines for routine use		
Age (completed weeks/months/years)	Vaccines	Comments
Birth	BCG OPV0 Hepatitis B1	Administer these vaccines to all newborns before hospital discharge
6 weeks	DTwP1 IPV1 Hepatitis B2 Hib1 Rotavirus1 PCV1	<b>DTP</b> <ul style="list-style-type: none"> <li>DTaP vaccine/combinations should preferably be avoided for the primary series</li> <li>DTaP vaccine/combinations should be preferred in certain specific circumstances/conditions only</li> <li>No need of repeating/giving additional doses of whole-cell pertussis (wP) vaccine to a child who has earlier completed their primary schedule with acellular pertussis (aP) vaccine-containing products</li> </ul> <b>Polio</b> <ul style="list-style-type: none"> <li>All doses of IPV may be replaced with OPV, if administration of the former is unfeasible</li> <li>Additional doses of OPV on all SIAs</li> <li>Two doses of IPV instead of 3 for primary series, if started at 8 weeks, and 8 weeks interval between the doses</li> <li>No child should leave the facility without polio immunization (IPV or OPV), if indicated by the schedule</li> </ul> <b>Rotavirus</b> <ul style="list-style-type: none"> <li>2 doses of RV1 and 3 doses of RV5</li> <li>RV1 should be employed in 10 and 14 weeks schedule, instead of 6 and 10 week</li> <li>The 10 and 14 week schedule of RV1 is found to be far more immunogenic than existing 6 and 10 weeks schedule</li> </ul>
10 weeks	DTwP2 IPV2 Hib2 *Rotavirus2 PCV2	<b>Rotavirus</b> If RV1 is chosen, the first dose should be given at 10 weeks
14 weeks	DTwP3 IPV3 Hib3 *Rotavirus3 PCV3	<b>Rotavirus</b> Only 2 doses of RV1 are recommended at present. If RV1 is chosen, the 2nd dose should be given at 14 weeks
6 months	OPV1 Hepatitis B3	<b>Hepatitis B</b> The final (third or fourth) dose in the Hepatitis B vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose.
9 months	OPV2 MMR1	<b>MMR</b> <ul style="list-style-type: none"> <li>Measles-containing vaccine ideally should not be administered before completing 270 days or 9 months of life;</li> <li>The 2nd dose must follow in 2nd year of life;</li> <li>No need to give stand-alone measles vaccine</li> </ul>
9–12 months	Typhoid conjugate vaccine	<ul style="list-style-type: none"> <li>Currently, two typhoid conjugate vaccines, Typbar-TCV® and PedaTyph® available in Indian market;</li> <li>PedaTyph® is not yet approved; the recommendation is applicable to Typbar-TCV® only</li> <li>An interval of at least 4 weeks with the MMR vaccine should be maintained while administering this vaccine</li> <li>Should follow a booster at 2 years of age</li> </ul>
12 months	Hepatitis A1	<b>Hepatitis A</b> <ul style="list-style-type: none"> <li>Single dose for live-attenuated H2-strain Hepatitis A vaccine</li> <li>Two doses for all killed Hepatitis A vaccines are recommended now</li> </ul>
15 months	MMR2 Varicella 1 PCV booster	<b>MMR</b> <ul style="list-style-type: none"> <li>The 2nd dose must follow in 2nd year of life</li> <li>However, it can be given at any time 4–8 weeks after the 1st dose</li> </ul> <b>Varicella:</b> The risk of breakthrough varicella is lower, if given 15 months onwards

Contd...

Contd...

Age (completed weeks/months/years)	Vaccines	Comments
16–18 months	DTwP B1/DTaP B1 IPV B1 Hib B1	The first booster (4th dose) may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose. <b>DTP</b> <ul style="list-style-type: none"> <li>First and second boosters should preferably be of DTwP</li> <li>Considering a higher reactogenicity of DTwP, DTaP can be considered for the boosters</li> </ul>
18 months	Hepatitis A2	<b>Hepatitis A</b> 2nd dose for killed vaccines; only single dose for live-attenuated H2-strain vaccine
2 years	Typhoid booster	<ul style="list-style-type: none"> <li>Either Typbar-TCV® or Vi-polysaccharide (Vi-PS) can be employed as booster</li> <li>Typhoid revaccination every 3 years, if Vi-polysaccharide vaccine is used</li> <li>Need of revaccination following a booster of Typbar-TCV® not yet determined</li> </ul>
4–6 years	DTwP B2/DTaP B2 OPV 3 Varicella 2 Typhoid booster	<b>Varicella</b> The 2nd dose can be given at any time 3 months after the 1st dose
10–12 years	Tdap/Td HPV	<b>Tdap</b> It is preferred to Td followed by Td every 10 years. <b>HPV</b> <ul style="list-style-type: none"> <li>Only 2 doses of either of the two HPV vaccines for adolescent/preadolescent girls aged 9–14 years</li> <li>For girls 15 years and older, and immunocompromised individuals 3 doses are recommended</li> <li>For two-dose schedule, the minimum interval between doses should be 6 months</li> <li>For 3 dose schedule, the doses can be administered at 0, 1–2 (depending on brands) and 6 months</li> </ul>
<b>II. IAP recommended vaccines for high-risk* children (Vaccines under special circumstances):</b>		
1-Influenza vaccine 2-Meningococcal vaccine 3-Japanese encephalitis vaccine 4-Cholera vaccine 5-Rabies vaccine 6-Yellow fever vaccine 7-Pneumococcal polysaccharide vaccine (PPSV 23)		

**\* High-risk category of children:**

- Congenital or acquired immunodeficiency (including HIV infection)
- Chronic cardiac, pulmonary (including asthma, if treated with prolonged high-dose oral corticosteroids), hematologic, renal (including nephrotic syndrome), liver disease and diabetes mellitus
- Children on long-term steroids, salicylates, immunosuppressive or radiation therapy
- Diabetes mellitus, cerebrospinal fluid leak, cochlear implant, malignancies
- Children with functional/anatomic asplenia/hyposplenia
- During disease outbreaks
- Laboratory personnel and health-care workers
- Travelers
- Children having pets in home
- Children perceived with higher threat of being bitten by dogs such as hostellers, risk of stray dog menace while going outdoor.

**Abbreviations:** BCG, bacillus Calmette Guérin; DTaP, diphtheria tetanus acellular pertussis; DTwP1, diphtheria tetanus whole-cell pertussis; Hib, *Haemophilus influenzae* type b; HPV, human papillomavirus; IPV, inactivated poliovirus vaccine; MMR, measles-mumps-rubella; OPV, oral polio vaccine; PCV, pneumococcal conjugate vaccine; RV, rotavirus vaccine; SIA, supplementary immunization activities; Tdap, tetanus, diphtheria and pertussis.

**MORE ON THIS TOPIC**

Choudhury P. Scheduling of Vaccine. IAP Text Book of Vaccines, In: Vashishtha VM, Agarwal R, Sukumaran T (Eds). New Delhi: Indian Academy of Pediatrics, Jaypee Brothers Medical Publishers; 2013.

Indian Academy of Pediatrics Committee on Immunization (IAPCOI). Consensus recommendation on Immunization and IAP Immunization Timetable 2012. Indian Pediatr. 2012;49:560.  
Scheduling of Vaccines. In: Vashishtha VM, Choudhury P, Bansal CP, Yewale VN, Agarwal R (Eds). IAP Guidebook on Immunization 2013-2014. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.

## Chapter 23.4

# Vaccine Storage and Cold Chain

Karan Singh Sagar, Manish Jain

Safety and potency are the two key characteristics underlying success of any vaccine resulting in reduction in incidence of vaccine preventable diseases (VPDs) and associated mortality and morbidity. These key characteristics are in most part dependent on and determined by proper management of vaccines and vaccine products, which includes storage in the recommended conditions and handling during transportation, distribution and use. The exposure of vaccines (and vaccine products) to temperature (and light) outside the recommended ranges may lead to reduction in potency and the protection it results after administration to the beneficiaries. This not only leads to improved immunization safety and efficacy but also serves to reduce program costs by preventing high wastage rate.

**Cold chain** It is the system used for storage and transportation of vaccines (and vaccine products) in the recommended conditions and acceptable temperature ranges from point of manufacture until it is administered to the beneficiary (**Fig. 1**). Effective cold chain network is the backbone for ensuring quality immunization services in any country. The key elements of cold chain system include: personnel (for vaccine management, storage and distribution), equipment (for vaccine storage and transportation, both electrical and nonelectrical) and procedures including monitoring (for ensuring vaccine storage and transportation under recommended conditions).

### TERMINOLOGY USED IN COLD CHAIN SYSTEM

**Hold over time of cold chain equipment** It is the time in hours for which all points inside the vaccine compartment of a vaccine

refrigerator remain below  $+10^{\circ}\text{C}$ , at the maximum ambient temperature of the temperature zone for which appliance is rated, after the power supply has been disconnected. For example, the minimum storage temperature of an ice-lined refrigerator (ILR) is  $+2^{\circ}\text{C}$ , so the time taken for cabinet temperature to reach  $+10^{\circ}\text{C}$  would be the hold over time of that ILR. In case of vaccine freezers, the hold over time is the time in hours for which the temperature inside the compartment remains below  $-5^{\circ}\text{C}$ . The hold over time applies to both electrical and nonelectrical cold chain equipment, and for a specific equipment, it depends on the ambient temperature (with inverse relationship), frequency of opening the equipment, quantity of vaccines stored, spacing between vaccine boxes and condition of water-packs (in nonelectrical equipment).

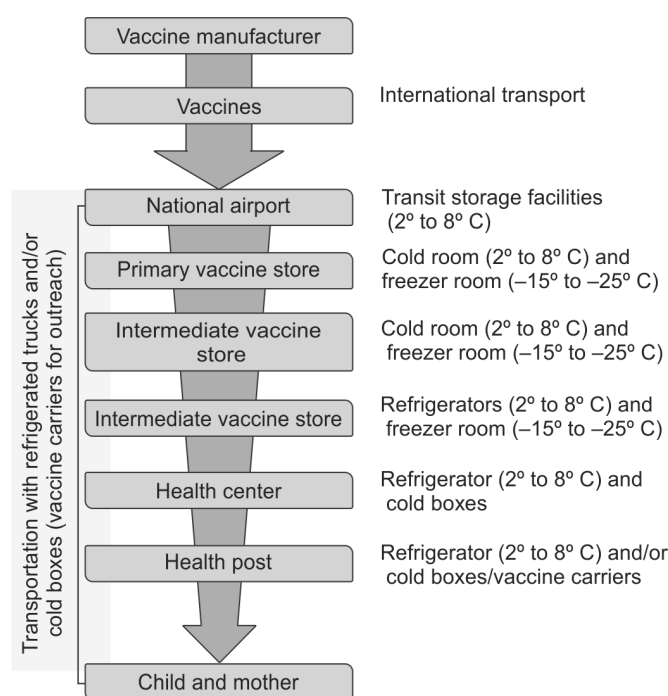
**Vaccine storage capacity** It is the actual volume available inside the equipment (refrigerator, freezer, cold box or vaccine carrier) for the storage of vaccines. This is specified by the equipment manufacturer in the product specifications and can also be measured by physical methods.

**Water-pack freezing capacity** This applies to water-pack freezers and is the maximum weight (kg/24 hour) of water-packs that can be fully frozen, in one batch, within a period of 24 hours.

**Refrigerants and foaming agents [Chlorofluorocarbons (CFC)]** R11 and R12 have been popular refrigerant gases used in compression refrigeration circuits and as foaming agents for the insulation of refrigerators, cold boxes and vaccine carriers. But as these are potent greenhouse gases having depleting effect on stratospheric ozone layer, therefore as per *Montreal Protocol* CFC equipment are condemned for use in industrialized nations (since January 1st, 1996) as well as in the developing nations (since January 1st, 2010). Refrigerants now recommended and which are now being used by manufacturers include hydrofluorocarbon (HFC) 134a and hydrocarbon R600 (isobutene); and the foaming agents that are being used are cyclopentane and R141b. Other gases being investigated for these purposes are HPC-245fa, HFC-365mfc, HFC-234a, isopentane and *n*-pentane.

**Vaccine wastage factor** This indicates how much additional vaccine should be ordered in order to allow for the given wastage rate. The vaccine wastage rate can vary according to session size, session plan, vial presentation, supply management and many other characteristics. Each country should monitor its own vaccine wastage; however, there are indicative wastage levels for different vial sizes for lyophilized (single dose: 5%; 2–6 dose vial: 10%; 10–20 dose vial: 50%) and liquid vaccines (single dose: 5%; 2–6 dose vial: 10%; 10–20 dose vial: 25%). Vaccine wastage can be due to unavoidable and avoidable reasons. Wastage occurring due to discarding reconstituted vaccines at the end of session or after recommended usage time, poor stock management leading to oversupply, wastage due to expiry before use, failure of cold chain leading vaccines to exposure to higher or lower temperature, administering incorrect dosage to the beneficiaries, failure in using multidose vials in correct manner and breakage, etc. are the important avoidable reasons which can be addressed through proper planning and compliance to guidelines.

**Volume per dose** This refers to the volume occupied by each dose of vaccine, including the volume occupied by its packaging (and volume of diluent, if applicable) in the cold chain equipment at time of storage. The volume per dose depends on the type of vaccine and is an important factor to be considered for estimation of vaccine storage requirements.



**Figure 1** Cold chain

Source: Immunization in Practice, Module 3, WHO. (2008)

### VACCINE STORAGE IN COLD CHAIN

Each vaccine is different in terms of its constituents and therefore each one of them have a recommended range of temperature for storage and transportation, clearly specified in the product



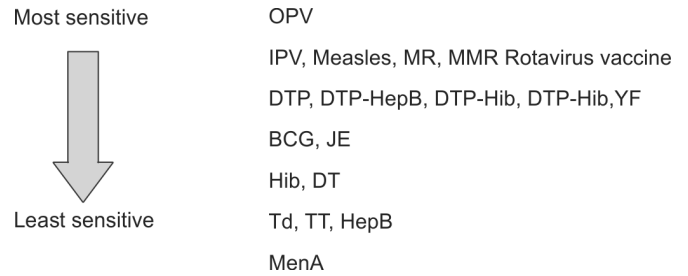
specifications issued by the manufacturer. Temperature ranging from +2°C to +8°C is generally safe for storage of majority of vaccines, except a few which need to be stored at negative temperature between -15°C and -25°C [e.g., oral polio vaccine (OPV)]. Vaccines exposed to temperature above +8°C gradually lose their potency over time. This can be either in form of an exposure to lot of heat over a short period of time (e.g., keeping vaccine in direct sunlight on a summer day) or exposure to small amount of heat over a longer period of time (e.g., frequent opening the lid of storage equipment). Heat-sensitive vaccines are shown in **Figure 2**. There are some vaccines, e.g., “T” series vaccines [e.g. diphtheria tetanus pertussis (DTP), diphtheria tetanus (DT), tetanus toxoid (TT), dT, Td and Hepatitis B], liquid *Haemophilus influenzae* type b (Hib) and liquid pentavalent vaccine, which are damaged by freezing and/or exposure to freezing temperature. Hepatitis B vaccine is most sensitive to the freezing temperature. Freeze sensitivity of vaccines is shown in **Figure 3**.

There are some vaccines which are sensitive to strong light. These vaccines lose their potency overtime followed by exposure to ultraviolet component of sunlight and fluorescent (neon) light. Such vaccines are packaged and supplied in vials having dark-brown glass which gives some protection from damage due to light exposure, but still care must be taken to keep them covered and protected from strong light during storage, transportation and use. Examples of these types of vaccines are bacille Calmette-Guérin (BCG), measles and rubella (MR), measles, mumps, and rubella (MMR) and rubella, which are sensitive to both light and heat.

Diluents used for reconstitution of freeze dried vaccines may be stored outside the cold chain as it may occupy the space inside equipment which is necessary for storage of vaccines but at the same time, it is important that diluents are stored between +2°C to +8°C inside storage equipment/refrigerator at least 24 hours before use, i.e., reconstitution. Same temperature of vaccine and diluent prevents thermal shock to the vaccine, i.e., death of some or all the essential live organisms in the vaccine due to exposure to higher temperature leading to reduction in potency. Besides this, it is essential that only the diluent supplied by manufacturer either bundled with vaccine or separately should be used for reconstituting freeze dried vaccine, because diluents are specifically designed with respect to volume, pH level and chemical properties to suit for the needs of a particular vaccine.

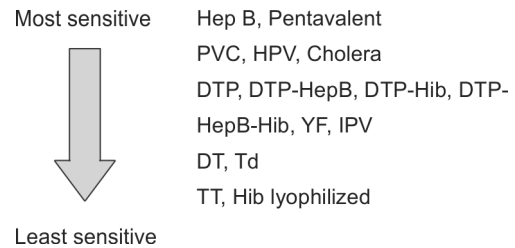
The physical appearance of any vaccine cannot help to decide, if it has been exposed to high or freezing temperature, or to strong light as the appearance of vaccine generally remains unchanged. Once any vaccine gets damaged due to inappropriate temperature exposures, it is not possible to regain its potency. Vaccine vial monitor (VVM) and freeze tags are generally used in cold chain to assess exposure of vaccines to higher or freezing temperature over a period of time. The details of VVM and freeze tags are as follows:

**Vaccine vial monitor (VVM)** This is a tag containing a heat sensitive material and placed on label or on the cap of the vaccine vials (for liquid and freeze dried vaccines respectively). It is designed to register cumulative heat exposure over time during transportation and/or storage. VVM conventionally comprise of an inner lighter square placed within outer darker circle. The combined effects of temperature and duration of exposure cause the inner square of VVM to darken gradually and irreversibly. As long as inner square of VVM is lighter than the outer circle (and the expiry date has not passed) the vaccine is usable; but when color of inner square matches with that of outer circle (known as discard point) or gets darker the vaccine becomes unusable. There are four types of VVM currently in use—types 2, 7, 14 and 30, each number referring to the number of days the VVM takes to reach discard point, if kept at +37°C. Different types of VVM are used to monitor different vaccines depending on their heat sensitivity. For example, VVM



**Figure 2** Heat sensitivity of different vaccines

**Abbreviations:** BCG, bacille Calmette Guérin; DT, diphtheria tetanus; DTP, diphtheria-tetanus pertussis; MR, measles and rubella; MMR, measles, mumps, rubella; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus; OPV, oral polio vaccine; Td, tetanus diphtheria; TT, tetanus toxoid; MenA, meningococcal A; YF, yellow fever.



**Figure 3** Freeze sensitivity of different vaccines

**Abbreviations:** DT, diphtheria tetanus; DTP, diphtheria-tetanus pertussis; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus; Td, tetanus diphtheria; TT, tetanus toxoid; YF, yellow fever.

type 2 is assigned to OPV, which is the most heat sensitive vaccine, while VVM type 14 is assigned to DTP-Hep B, which is much less heat sensitive. VVM, however, have its limitations as it only measures exposure to high temperature and not vaccine potency, safety and exposure to freezing temperature (for freeze sensitive vaccines). Secondly, status of VVM only applies to the vaccine vial on which it is tagged, but is not applicable as a proxy indicator for other vaccines, which may have different temperature sensitivities and storage history. It is important that all workers who manage, handle and administer vaccines are well aware of different stages (usable and unusable) of VVM.

**Freeze indicator** These are electronic and passive phase change type of devices used during internal distribution of freeze sensitive vaccines and for monitoring freezing events in cold rooms and refrigerators. The status of freeze indicator changes from *good* to *alarm* as soon as vaccine is exposed to -0.5°C for more than 60 minutes. These indicators are used to assess status of freeze sensitive vaccines.

Before distributing, opening or using any vaccine, it is important to monitor status of VVM and expiry date. Vaccines whose expiry date has passed should never be used (even if VVM shows no heat damage), and on the other hand, vaccine vials whose VVM has crossed the discard point should not be used even, if they are well within the expiry date. Similarly, usable status of freeze sensitive vaccines can be determined by *Shake test*. This test is not routinely employed and is done only for suspected vaccine vials, to assess whether at any point of time they have been exposed to freezing temperature. *Shake test* compares the *test* vial of the vaccine which is suspected to have frozen during storage or transportation with a *Control* vial of the same type of vaccine and from the same manufacturer and same batch number. *Control* vial is prepared by storing it at -20°C overnight, and later allowed to thaw at normal room temperature. During test both *Test* and *Control* vials are vigorously shaken and placed cap side down on

flat surface undisturbed for 30 minutes. The rate of sedimentation is observed in both the vials. If the rate of sedimentation in *Test* vial is slower than in the *Control* vial shows that the vaccine under test has not been damaged due to freezing. However, if the sedimentation in both vials is same or is faster in the *test* vial than the vaccines has been damaged and should not be used.

Total period of vaccine storage at different levels of entire cold chain system is also an important factor for proper vaccine management. Suggested maximum length of storage of vaccines at national level is 6–12 months and that at subnational and district level stores is 3 months, maximum. At sub-district and health facility levels vaccines should not be stored for period of more than 1 month. **Table 1** lists the recommended ranges of storage temperature for most Expanded Programme on Immunization (EPI) vaccines.

## COLD CHAIN EQUIPMENT

There is a wide range and variety of equipment available as part of cold chain system having different capacities and features to suit the local conditions and needs. Electrical cold chain equipment includes Walk-in-Coolers (WIC), Walk-in-Freezers (WIF), Deep Freezers (DF), Ice-lined Refrigerators (ILR) and domestic refrigerators; while nonelectrical cold chain equipment are cold boxes, vaccine carriers and water-packs. There are also solar refrigerators for areas with poor or no electricity supply. Refrigerated trucks and vaccine vans are also part of cold chain system and are used for transportation in the recommended temperature ranges, which help to ensure vaccine potency from manufacturer till health facilities, outreach sessions and beneficiaries.

## Electrical Cold Chain Equipment

**Walk-in-freezers** These are installed at large stores at national and subnational levels and are used to store bulk quantity of vaccine for longer period (3 months or more), maintaining temperature around  $-20^{\circ}\text{C}$ . Generally, these are used for storing OPV and for preparing frozen water-packs to be used during transportation, campaigns, etc. These are available in different sizes and are provided with two cooling units and an auto-start generator for maintaining temperature in case of power failure/interruption. Along with this, WIF also have automatic temperature recording system and emergency alarm which sets on if the temperature crosses a safe range.

**Walk-in-coolers** These are installed at national and subnational level stores and are used to store bulk quantity of vaccines at  $+2^{\circ}\text{C}$  to  $+8^{\circ}\text{C}$  for a longer period (3 months or more). These are used to store vaccines such as pentavalent, PCV, Rota, DTP, DT, TT, measles, BCG and Hepatitis B, etc. and similar to WIF, these also have two cooling units, autostart generator, automatic temperature recording system and emergency alarm.

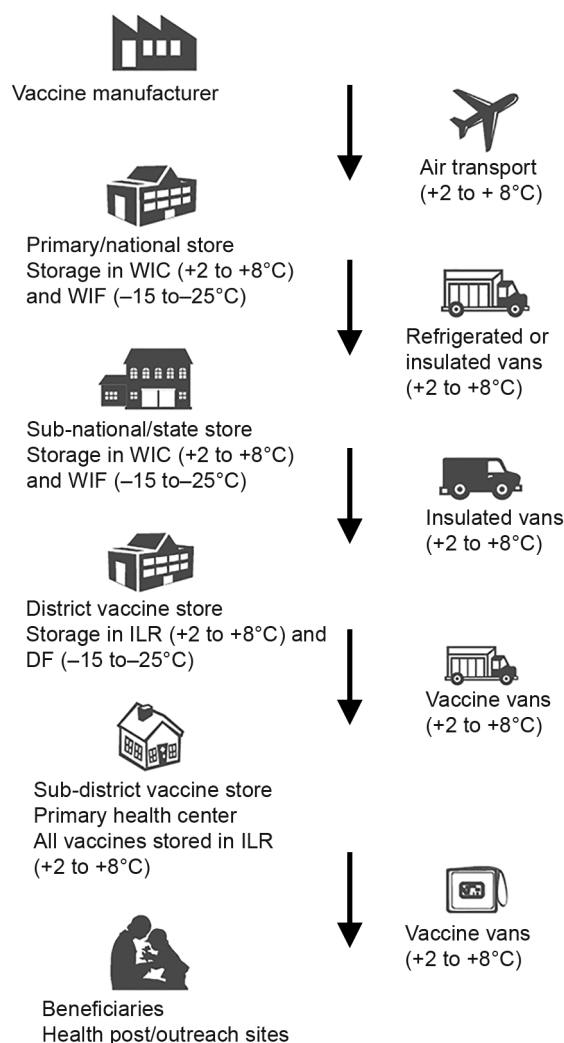
**Deep freezers** These are used at district and sub-district level and are used for storing vaccines (mostly OPV) and for preparing/freezing water-packs. In immunization program, different sizes of top-opening freezers are supplied as they are able to retain cool air inside better than the front opening refrigerators. Deep freezers maintain a cabinet temperature in the range between  $-15^{\circ}$  and  $-25^{\circ}\text{C}$ . In cases of power failure, which is very common in subdistrict level remote and rural health facilities, the special insulation of these freezers can maintain the cabinet temperature in the range of  $-15^{\circ}$  to  $-25^{\circ}\text{C}$  for a period up to 18 and 26 hours at external ambient temperatures of  $42^{\circ}$  and  $32^{\circ}\text{C}$  respectively, if not opened.

**Ice-lined refrigerators** These are top opening electrical cold chain equipment available in different sizes and are used to store vaccines at district and sub-district level facilities at  $+2^{\circ}$  to  $+8^{\circ}\text{C}$  storage temperature (**Fig. 4**). These are internally lined with water containers (water-packs or tubes in different models) fitted around the walls in form of a frame. The water in these containers freeze when the ILR is functioning (or when power supply is available), and in case of power failure/interruption this ice or cold water in the containers maintain the storage temperature within the recommended range for at least 20 hours (hold over time), if not opened. This characteristic feature of ILR makes it suitable for vaccine storage even in the areas having electricity supply of as less as 8 hours. For areas with no power supply, ILRs are designed to run using kerosene, gas and also solar energy. The bottom part of the ILR is the coldest part internally and therefore vaccines which can get damaged by freezing or exposure to low temperature should not be kept in this part, especially directly on floor (Remember—freeze-sensitive vaccines should *never* be stored within 150 mm of the base). The top part maintains the recommended temperature range and all vaccines can be stored safely in this part. As a safety measure, it is necessary to ensure during storage that none of the vaccine vials comes in direct contact with the walls or floor which can lead to freeze damage.

**Table 1** Recommended ranges of storage temperature for vaccines

Vaccines	National level stores	State and district level stores	Health facility level
	Maximum duration of storage: 6–12 months	Maximum duration of storage: 3 months	Maximum duration of storage: 1 month
OPV	Store at $-15^{\circ}\text{C}$ to $-25^{\circ}\text{C}$ OPV is the only vaccine that can be safely be frozen and unfrozen repeatedly		Store at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$
BCG, measles, MMR, MR, yellow fever, Hib lyophilized, meningitis, JE	These lyophilized vaccines are to be stored at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$ Under exceptional circumstances, these can be temporarily stored at $-15^{\circ}\text{C}$ to $-25^{\circ}\text{C}$ (e.g., if there is temporary shortage of storage space) Diluent never to be frozen		Store at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$
HepB, DTP-HepB, DTP-HepB-Hib liquid, Cholera, Hib liquid DTP, DT/TT/Td Pneumococcal, Rotavirus, HPV, Pneumococcal, Rabies, Influenza, IPV		Store at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$ Never freeze	

**Abbreviations:** BCG, bacillus Calmette Guérin; DT, diphtheria tetanus; DTP, diphtheria-tetanus pertussis; MR, measles and rubella; MMR, measles, mumps, rubella; HPV, human papillomavirus; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus; JE, Japanese encephalitis; OPV, oral polio vaccine; Td, tetanus diphtheria; TT, tetanus toxoid.



**Figure 4** Cold chain system

**Domestic refrigerators** This can also maintain a temperature within the recommended ranges but the hold over time of these refrigerators is as little as four hours, and their capacity to freeze water-packs is also limited due to which they are generally not recommended in the immunization program. These are mostly used for vaccine storage in small health facilities and by private service providers in the urban settings where continuous power supply can be ensured. In settings where the domestic refrigerators are used for storing vaccines, it is necessary to ensure that other supplies (e.g., drugs, ointment, pathological samples, food articles and drinks) are not placed inside it and that they are exclusively used and labeled for storage of vaccines, diluents and water-packs only. Secondly, the vaccines must not be stored in the door shelves (which are relatively warmer and gets exposed to environment temperature every time when door is opened) and in the freezer compartment (which should be used only for freezing and storing water-packs). Vaccines should be arranged in shelves from top to bottom in order of their heat sensitivity, i.e., vaccines which are more heat sensitive (e.g., OPV and measles) should be placed just below the freezer compartment, while more freeze-sensitive vaccines (e.g., Hepatitis B and T series vaccines) should be in the lower shelves. Diluents should also be placed next to the vaccines for which they are supplied so that they both are at the same temperature at time of distribution and this minimizes any chances of mixing up with diluents for other vaccines.

**Sure chill vaccine refrigerators** These are new type of refrigerators which are specifically designed to maintain temperature range of 4°C–5°C for vaccines and avoid any chances of freezing and exposure to higher temperature. These are now available in two types—one running on electricity (requiring just 2½ hours of power supply per day) and the other solar *direct drive* model (with no requirement of batteries to maintain cooling performance overnight). These refrigerators can keep vaccines safe for up to 10 days at 32°C ambient, and even longer at lower temperature.

**Solar refrigerators** These are freezer cum refrigerators with two separate compartments, one having basket for storing vaccines (maintains temperature at +2°C to +8°C) and other for freezing water-packs (with temperature at -15°C to -25°C). These refrigerators run on the same principle as normal compression refrigerators but involve low voltage DC compressors and motors (12V or 24V). Normally, the batteries can store solar energy for 5 days. It is important to clean the solar panel on a periodic basis for removing dirt, soot, smog and debris, as shading of as less as 10% of panel area with dirt or bird droppings can reduce power output by 50% (similar to that of a cloudy day).

**Automatic voltage stabilizer** This is an important part of cold chain system, which corrects the fluctuations in the main voltage and maintains it in range of 220 ± 10 V, which is necessary for ensuring correct storage temperature. Each electrical refrigeration equipment should necessarily be connected to a separate dedicated mains supply via a separate functional stabilizer at all levels of the cold chain. Different types of voltage stabilizers used in cold chain system are as follows: *servo-mechanical voltage stabilizers* recommended for areas with mains voltage range variation up to 50%; *electronic voltage stabilizers* for equipment requiring extremely fast correction speed and those located in hostile climatic conditions; and *tap changing voltage stabilizers* recommended for less sensitive equipment.

### Nonelectrical Cold Chain Equipment

**Cold boxes** These are big insulated boxes mainly used for transportation of vaccines (and diluents) and also for storing vaccines in case of power failure or equipment breakdown. These are available in different sizes such as 5, 8, 20 and 22 liters depending on the storage capacity and are supplied with requisite number of water-packs. A 5 and 8 liter cold box can store 1,500 and 2,400 doses of mixed antigens respectively. Vaccines are placed in cartons or polythene bags inside the cold box and while arranging vaccines either for storage or transportation it is essential to ensure that OPV and single antigen lyophilized vaccines (those packed with frozen water-packs) are placed separately from freeze sensitive and multivalent vaccines (those packed with cool water-packs). After placing vaccines, frozen/cool water-packs are arranged over top of vaccines and diluents and covered with plastic sheet for ensuring full hold over time. Freeze indicator should also be placed inside cold box to monitor that the storage temperature has not dropped below 0°C. In order to maintain proper functioning of cold boxes, it is essential that after every use they are examined both internally and externally for any cracks, rubber seal around the lid is checked, hinges and locks are lubricated periodically and are kept unlocked and opened while not in use.

**Vaccine carriers** These are insulated boxes used to carry small quantities of vaccines and diluents (approximately 16–20 vials) to immunizations sessions in the outreach areas. These are supplied with four water-packs and a foam pad to cover vaccines from top and maintain the storage temperature. Vaccine carriers should be packed with mix of vaccines and diluents with cool water-packs in order to prevent damage to freeze sensitive vaccines. The diluents (and droppers as for OPV) should be packed with vaccines for



transportation to outreach sites, taking care that diluents does not come in direct contact with the frozen/conditioned water-packs. Vaccine carriers should be wiped and cleaned dry both from inside and outside each time after use and stored with lid opened.

**Water-pack (Ice-pack)** These are flat plastic containers, filled with fixed quantity of water (0.3 L, 0.4 L and 0.6 L depending on size and manufacturer) and are prepared as *frozen water-pack* (for storage and transportation of OPV and single antigen freeze dried lyophilized vaccines), *cool water-pack* (for transportation of liquid vaccines other than OPV) or a *warm water-pack* (stabilized at room temperature between +10°C and +24°C and used for transportation of freeze-sensitive vaccines for a period up to 8 hours). The water-packs frozen inside deep freezer have a surface temperature of -15°C to -25°C, which can cause freeze damage particularly to freeze-sensitive vaccines during transportation. Therefore, before packing frozen water-packs, they are kept in open at room temperature until the ice within it which is in contact with the walls melts. This process is known as conditioning of water-packs and the time required for melting some ice depends on the ambient temperature and can take up to 30 minutes.

## MONITORING OF COLD CHAIN

Monitoring of cold chain is an indispensable part of entire cold chain system and it helps to ensure that adequate number of type of cold chain equipment are available and functioning, vaccine supply is timely and adequate, storage temperatures and other conditions are as recommended and that all vaccines are potent and safe to use.

### Temperature Monitoring Devices

**Fixed dial thermometer** These are used to measure temperature inside ILR and DF and can show the temperature in the range of -50°C to +50°C. Bimetallic dial thermometers are no longer used because they easily lose their calibration.

**Alcoholic stem thermometer** These thermometers are more sensitive and accurate than dial thermometers and can record the same temperature range. These can be used in all types of refrigerators and freezers; however, since they do not provide a continuous record of vaccine temperature exposure therefore they should not be used as primary temperature monitoring device.

**Electronic data logger** This is an electronic device which is placed within the vaccine vials and record temperature for a period of 30 days. This is equipped with alarm system which alerts the handlers whenever the storage temperature crosses the safe range. These are specifically designed to be used in ILRs and WICs which are required to maintain the temperature between +2° and +8°C.

### Vaccine Management: Storage and Distribution

It is necessary to ensure that at any point of time, sub-district level cold chain facility has adequate quantity of vaccines estimated as per requirement for the catchment area for a particular period of time. In addition to monthly requirement, a designated buffer stock of each vaccine (25% of monthly requirement) should also be available to meet extra demand or any delay in supply. Estimate of requirements for each different vaccine should be done for the catchment area on periodic basis and the quantity of any particular vaccine should be requested/indented depending on the number of beneficiaries in the area, number of doses required for a vaccine by one beneficiary to complete immunization schedule and the wastage factor for that vaccine. General guidelines for storage of vaccines are as follows:

- All vaccines stored in ILR should be placed in baskets (supplied with equipment) in separate labeled boxes for easy identification and with adequate space between them for air

circulation (2 cm space on all sides and between boxes). The boxes should also have holes to facilitate good access to cool air.

- In case basket is not available vaccine boxes should be kept over two layers of empty water-packs placed to prevent direct contact with the floor (also prevents boxes to get wet by water collected at bottom).
- Every cold chain equipment should have one thermometer placed in basket with vaccines or between the vaccine boxes for twice daily monitoring of storage temperature. Care should be taken that thermometer is placed in contact with the walls.
- Freeze sensitive vaccines and those with close expiry should be kept on top in ILR basket (and front in front opening refrigerators) so that they are utilized first.
- Diluents should not be frozen or stored inside deep freezer as these ampoules are not designed for freezer storage and can crack.
- Food items, drinks, other drugs and vaccines not included in national immunization program should not be stored in equipment (electrical or nonelectrical) in which vaccines are stored.
- Cold chain equipment should be plugged directly into the wall outlets, with a label *Do not unplug*. Alternatively, plug guards or safety-lock plugs can be used to prevent inadvertent unplugging of the equipment.
- Every equipment should be defrosted and cleaned at least once every month or when the frost on inner walls is more than 0.5 mm. At time of defrosting vaccines should be shifted to other equipment or in cold boxes with adequate number of cool water-packs.
- Proper record keeping is crucial for ensuring quality cold chain system and separate date-wise records of vaccine receipts, distribution and balance sheets should be available for each type of vaccine and vaccine product. Other information to be recorded and updated include the date of receipt, name of manufacturer, batch number, manufacture and expiry date, VVM status and any other information available for ensuring the quality and potency of vaccines and vaccine products.

**Vaccine inventory control** For ensuring adequate and effective immunization coverage in an area, it is important that availability of vaccine stock is ensured at all times. A vaccine inventory should be conducted on monthly basis to ensure adequate supply for meeting demand. Diluents are also a part of inventory and it is essential that they are available in adequate supply. Factor which determine the requirement of vaccines and diluents are projected demand, storage capacity, and current vaccine supply.

Problems generally encountered with respect to stock position include—inadequate stock (amount available is less than the buffer stock, i.e. 25% of monthly requirement), stock out (when a particular vaccine or vaccine product is not available) and excess stock (when available stock is more than 1 month requirement and buffer stock, i.e. more than 125%), which leads to vaccine wastage or outdated vaccines in hand.

## GUIDELINES FOR USE OF OPENED MULTIDOSE VIALS

Earlier it was generally followed that all vaccine vials opened for an immunization session were discarded at the end of session, irrespective of the type of vaccine or the remaining number of doses. However, for vaccines including OPV, DTP, TT, DT, Hepatitis B and liquid Hib revised policy has been instituted by WHO provided that these vaccines meet WHO requirements for potency and temperature stability, are packaged according to ISO standards and contain and appropriate concentration of preservative (e.g.



thiomersal for injectable vaccines only). For these vaccines revised policy states that:

Multidose vials of OPV, DTP, TT, DT, Hepatitis B and liquid formulations of Hib vaccines from which one or more doses of vaccines have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 4 weeks, only when the following conditions are met:

- The expiry date has not passed
- The vaccines are stored under appropriate cold chain conditions
- The vaccine vial septum has not been submerged in water
- Aseptic technique has been used to withdraw all doses
- VVM (if attached) has not reached the discard point.

The revised policy does not change recommended procedures for handling vaccines that require reconstitution, i.e. BCG, measles, yellow fever and some formulations of Hib vaccine. These vaccines once reconstituted, vials must be discarded at the end of immunization session or at the end of recommended period of use whichever comes first. As per WHO guidelines, reconstituted vaccines should not be used beyond 6 hours of time of reconstitution. In India's Universal Immunization Programme, BCG, measles and Japanese encephalitis (JE) are the vaccines which require reconstitution, out of these reconstituted BCG and measles are not to be used beyond 4 hours and Japanese encephalitis (JE) vaccine not beyond 2 hours from the time of their reconstitution.

**Vaccine disposal** There are situations when the vaccine vials and other vaccine products need to be terminally disposed and there are specific guidelines for disposal of unopened unexpired vials, expired vials, opened vials with unused doses, doses drawn but not administered and potentially compromised vaccines resulting due to inappropriate storage conditions. To dispose vaccines in these different forms medical waste disposal procedures outlined in national level policies and guidelines must be followed.

### IN A NUTSHELL

1. Effective cold chain network is most essential to ensure quality immunization services.
2. Temperature ranging from +2°C to 8°C is generally safe for storage of nearly all the vaccines.
3. Sunlight and fluorescent (neon light) can also cause loss of potency of the vaccines.
4. A wide range of equipment is available for the cold chain system having different capacities and features to suit different local conditions and needs.
5. It is important to monitor the expiry date and VVM (where applicable) before distributing, opening or using these vaccines.
6. All vaccines stored in the cold chain equipment should have separate labeled boxes for easy identification and adequate space between them for air circulation.
7. Proper record-keeping is crucial for ensuring quality cold chain system.

### MORE ON THIS TOPIC

- CDC. Vaccine Storage and Handling; Epidemiology and Prevention of VPDs. Atlanta: CDC; 2011.
- Handbook for Vaccine and Cold Chain Handlers. New Delhi: Ministry of Health & Family Welfare, Government of India; 2010.
- WHO. PQS Devices Catalogue, Pre-qualified equipment for the Expanded Programme on Immunization. Geneva: WHO; 2014.
- WHO. The use of opened multidose vials of vaccine in subsequent immunization sessions. WHO Policy Statement. Geneva: World Health Organization; 2000.
- WHO. Training for Mid-level Managers, Module 1: Cold Chain, vaccines and safe injection equipment management. Geneva: WHO/IVB, World Health Organization; 2008.

## Chapter 23.5

## Adverse Events Following Immunization

Ajay Kalra

An adverse event following immunization (AEFI) is defined as medical incident that takes place after immunization, causes concern, and is believed to be caused by immunization. The event can be a true adverse event or an event coincidental to the immunization. AEFIs are classified into the categories given in **Table 1**.

## VACCINE REACTIONS

The vaccine can cause adverse events due to its inherent properties. They are usually of two types: (a) Minor reactions and (b) Serious reactions. Most vaccine reactions are minor and settle down on their own.

*Minor reactions* are more common. They can be local like pain swelling and/or redness at injection site or systemic such as fever, vomiting, malaise which can result from the normal immune response to the vaccine.

*Serious reactions* are rare. They can be in the form of seizures, encephalopathies [as in pertussis and measles, mumps, and rubella (MMR) vaccines], hypotonic, hyporesponsive episode (pertussis) severe allergic reactions (all vaccines) anaphylaxis (all vaccines), suppurative lymphadenitis, osteitis, disseminated infection [all with *Bacillus Calmette–Guérin* (BCG) vaccine], brachial neuritis, thrombocytopenia.

## PROGRAMMATIC ERRORS

Program errors result from errors and accidents in vaccine preparation, handling, or administration (**Table 2**). Programmatic errors are the most common causes of serious adverse events and deaths following vaccination. The identification and correction of these errors are of great importance as they are preventable and detract from the overall benefit of the immunization program. The most common program error is an infection as a result of nonsterile injection. The infection can manifest as a local reaction (e.g. suppuration, abscess), systemic effect (e.g. sepsis or toxic shock syndrome), or blood-borne virus infection [e.g. human immunodeficiency virus (HIV), hepatitis B or hepatitis C].

A program error may often be suggested by a cluster of events associated with immunization. A cluster of AEFIs is defined as two or more cases of the same adverse event related in time, place or vaccine administered. These clusters are usually associated with a particular provider, or health facility, or even a single vial of vaccine that has been inappropriately prepared or contaminated.

## INJECTION REACTION

This event is from anxiety about or pain from the injection itself rather than the vaccine. Syncope due to pain of injection in an adolescent girl is the best example of this category.

*Coincidental* The event that happens after immunization but not related to it, is a chance association. Sudden infant death syndrome following vaccination is known event which is coincidental.

*Unknown* The event for which cause cannot be determined.

Besides the above-defined reactions, there are situations which are vaccine scare related due to theories of a causal link which are not actually established. These vaccine scare-related adverse events have no established causal link and are most often

**Table 1** Classification of adverse events following immunization (AEFI)

Type of AEFI	Definition	Example
Vaccine reaction	An event caused or precipitated by the active component or one of the components of the vaccine	Anaphylaxis due to measles vaccine
Program error	An event caused by an error in vaccine preparation, handling or administration	Bacterial abscess due to unsterile injection
Injection reaction	Event from anxiety about, or pain from the injection itself rather than the vaccine	Syncopal attack in a teenager after immunization
Coincidental	An event that occurs after immunization but is not caused by the vaccine. This is due to a chance association	Acute gastroenteritis 5 days after DPT immunization
Unknown	Events cause cannot be determined	

**Table 2** Programmatic errors leading to adverse events following immunization (AEFI)

<i>Nonsterile Injection</i>	
<ul style="list-style-type: none"> <li>Reuse of disposable syringes or needles</li> <li>Improperly sterilized syringes or needles</li> <li>Contaminated vaccines or diluents</li> <li>Reuse of reconstituted vaccine at subsequent session</li> </ul>	<ul style="list-style-type: none"> <li>Local suppuration at injection site, abscess, cellulitis</li> <li>Systemic infection</li> <li>Sepsis</li> <li>Toxic shock syndrome</li> <li>Transmission of blood-borne infections such as HIV, Hepatitis B, Hepatitis C, malaria, etc.</li> </ul>
<i>Vaccine administered at improper site</i>	
<ul style="list-style-type: none"> <li>SC instead of ID BCG</li> <li>Hepatitis B and Anti-Rabies vaccine given on gluteal region</li> <li>DPT such as vaccine not given by deep IM route</li> </ul>	<ul style="list-style-type: none"> <li>BCG adenitis</li> <li>Ineffective vaccine or poor immunologic response</li> <li>Local reactions such as induration, nodule formation</li> </ul>
<i>Incorrectly prepared vaccine</i>	
<ul style="list-style-type: none"> <li>Vaccine reconstituted with incorrect diluent</li> <li>Drugs substituted for vaccine or diluent</li> <li>Storage and transportation of the vaccine incorrectly</li> <li>Contraindication ignored</li> <li>Avoidable vaccine reactions</li> </ul>	<ul style="list-style-type: none"> <li>Local reaction or abscess formation</li> <li>Effect of drug used such as insulin, muscle relaxant</li> <li>Ineffectiveness of the vaccine</li> <li>Increased local reactions from frozen vaccines</li> </ul>

hypothetical. An example of this is MMR and autistic spectrum disorder or inflammatory bowel disease. Review of all currently available evidences does not support any casual relationship between MMR vaccine and autism or inflammatory bowel disease. Thiomersal (50% ethyl mercury), a preservative in inactivated vaccines particularly in multidose vials, has been linked in the past to autistic spectrum disorders and neurodevelopmental disorders. Consequently, most of the vaccine preparations available in the developed nations are thiomersal free. Systemic review of evidences, however, has not supported any casual association between thiomersal and neurotoxic effects. Therefore, in developing nations, where multidose vials significantly bring down vaccine costs and cold chain space requirement, the benefits of thiomersal far outweigh any possible risks. Asthma, sudden infant death syndrome, chronic fatigue syndrome, immune deficiency, leukemia, autoimmune diseases, learning disorders, etc., are other diseases of unknown or only partially understood etiology which are also linked with vaccines.

AEFIs due to individual vaccines are listed in **Box 1**.

## MANAGEMENT OF COMMON AEFI

A summary of management guidelines of some commonly encountered AEFI are outlined in **Table 3**.

### Anaphylaxis

Severe allergy or anaphylaxis occur rarely following vaccination, with a frequency of 1 per 1,000,000 vaccine doses. They may present as generalized urticaria, hives, wheezing, swelling of mouth and throat, difficulty in breathing, hypotension and shock. As occurrence of anaphylaxis cannot be predicted, all those who have received a vaccine should be observed for at least 15 minutes postvaccination. There should be availability of all resuscitative equipment and emergency drugs at the place of vaccination.

- Place child in recumbent position and elevate feet
- Clear airway, establish breathing (oxygen, bag and mask) and maintain circulation

#### BOX 1 Adverse effects following specific vaccines

##### *Bacillus Calmette-Guérin (BCG) vaccine*

Persistent discharging sinus at the site of vaccination, secondary infection at the vaccination site, BCG adenitis and cold abscess formation, disseminated BCG infection (especially in immunocompromised children), osteitis, tuberculous osteomyelitis

##### *Diphtheria-Pertussis-Tetanus (DPT) vaccine*

Local pain, erythema and induration at injection site, fever, persistent inconsolable crying (> 3 hours), febrile convulsions, hypotonic hyporesponsive episode (HHE), anaphylactic reaction, encephalopathy

##### *Oral Polio Vaccine (OPV)*

Almost none, rarely vaccine associated polio paralysis (VAPP)

##### *Inactivated Poliovirus vaccine (IPV)*

Local pain, erythema, induration at injection site, hypersensitivity to streptomycin or neomycin (used as preservatives)

##### *Measles vaccine*

Mild fever, coryza, rash, dissemination of tuberculosis (especially in immunocompromised children), encephalitis, toxic shock syndrome (TSS) due to contamination of measles vaccine by *S. aureus*, thrombocytopenia. Rarely subacute sclerosing pan encephalitis (SSPE)

##### *Measles, Mumps and Rubella (MMR) vaccine*

Mild fever, rash, encephalopathy, parotid swelling, aseptic meningitis, Guillain-Barré syndrome (due to mumps component), arthralgia, lymphadenopathy (due to rubella component)

##### *Hepatitis B vaccine*

Soreness at the site of injection, mild fever, myalgia, arthralgia, rarely anaphylaxis

##### *Hepatitis A vaccine*

Soreness, induration at injection site, headache, nausea, loss of appetite

##### *Typhoid vaccine (Vi antigen vaccine)*

Pain and induration at injection site, fever

##### *Tetanus toxoid (TT)*

Repeated TT injections after trial injuries can lead to reduced immunogenicity, hypersensitivity, hemolytic anemia, etc.

##### *Haemophilus influenzae type b (Hib) vaccine*

Local pain, redness and swelling at injection site

##### *Varicella vaccine*

Local reactions such as pain, redness and swelling at vaccination site, fever systemic varicella such as rash in around 5%, herpes zoster

##### *Human papillomavirus (HPV) vaccines*

Pain, erythema and swelling at the site of vaccination, fever. No deaths have been reported casually associated with HPV vaccines

##### *Pneumococcal vaccine*

Pain, erythema and swelling at injection site, fever

##### *Rotavirus vaccine*

No increased risk of intussusception

##### *Rabies vaccines*

Pain, redness and swelling at vaccination site, fever, headache, dizziness and gastrointestinal side effects. Systemic hypersensitivity reactions have been reported with human diploid culture vaccine (HDCV)

##### *Influenza vaccines*

Fever, rash. No extra risk of Guillain-Barré syndrom (GBS)

##### *Yellow fever vaccine*

Encephalitis, ADEM, GBS, yellow fever mimicking illness (may be fatal).

**Table 3** Management guidelines of common AEFI at health facility

No.	Adverse events	Vaccine	Symptoms	Management
1.	Anaphylaxis	Any vaccine	Within minutes 1. Acute decompensation of circulatory system 2. Hypovolemic shock 3. Laryngospasm/edema 4. Acute respiratory distress	1. Adrenaline 2. Cardiopulmonary resuscitation 3. IV volume expanders 4. Hydrocortisone 5. Dopamine/Dobutamine
2.	Hypotensive-hyporesponsive episode (HHE)	DTP	1. Acute paleness 2. Transient decreased level or loss of consciousness 3. Decrease or loss of muscle tone	1. IV fluids 2. Oxygen
3.	Inconsolable cry	DTP	1. Within 48–72 hours of Immunization 2. Excessive inconsolable crying	1. Sedation with Triclofos-50 mg/kg 2. Paracetamol (10–15 mg/kg/per dose) 3. Feeding advice
4.	Toxic shock syndrome	Contamination of Measles vaccine by <i>S. aureus</i>	1. Within 30 minutes to few hours 2. Mounting fever 3. Vomiting 4. Diarrhea 5. Septic shock	1. IV fluids 2. Antimicrobials cloxacillin 50–100 mg/kg/day 3. Steroids 4. Supportive therapy
5.	Lymphadenitis	BCG	Within 2–6 months Firm to soft axillary lymphadenitis 1.5–3 cm size	1. If firm, no treatment 2. If soft and fluctuant, aspiration/surgical excision 3. Anti-tubercular therapy not indicated
6.	Seizure(s) with fever (rare)	DTP, measles	Always generalized	1. Anticonvulsants 2. IV fluids (if need be)
7.	Bacterial abscess	Any vaccine	After days to weeks fluctuant or firm	1. Antibiotics 2. Antipyretics 3. Drainage
8.	Moderate-to-severe local reaction	Any vaccine	Nonfluctuant swelling/redness 3–10 cm size at the injection site	1. Paracetamol

Source: Adapted from Science of Vaccinology Module, Indian Academy of Pediatrics, 2012.

- Administer epinephrine (1:1,000 solutions) in the dose of 0.01 mL/kg (max 0.5 mL) IM/SC, may be repeated every 3–5 minutes, if required
- If child is hypotensive, setup IV access and give volume expanders. Normal saline or ringer lactate 20 mL/kg over 10–15 minutes. Two to three boluses can be repeated to get response, if required.
- Injection hydrocortisone (IM or slow IV) in the dose of 25 mg in children less than 6 months, 50 mg in 6 months to 6 years, 100 mg in 6–12 years and 200 mg in above 12 years age.
- Oral antihistaminics may be given to ameliorate skin symptoms. Intravenous antihistaminics are not recommended
- Monitoring of vitals is essential.

## PREVENTION OF AEFI

It is mandatory for the person administering the vaccine to have sufficient knowledge regarding the vaccines, proper technique of administering the vaccine and expected adverse events. Parents should be explained in detail regarding vaccine and its possible adverse effects. The equipment for resuscitation in a case of severe AEFI like anaphylaxis should be kept available at the place of vaccination. The functioning of the equipment should be confirmed. The vaccines should be kept at the recommended temperature and cold chain should be maintained. Vaccines must only be reconstituted with the diluent supplied by the manufacturer. Reconstituted vaccines must be discarded at the

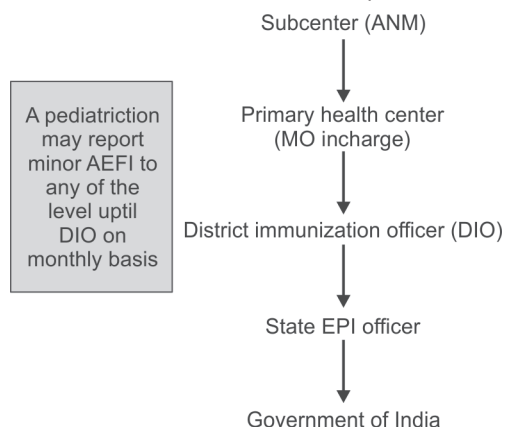
end of each immunization session and should never be retained. No other drugs or substances should be stored in the refrigerator of the immunization center.

## REPORTING OF AEFI

Reporting should be done as quickly as possible so that an immediate decision on the need for action and investigation can be made. This is called the first information report (FIR). Private practitioners should also report events that come to their notice. The minor AEFIs should be reported every month to the subcenter or the primary health center (PHC) or the district immunization officer (DIO) who sends reports to the state EPI officer. Eventually, the report reaches the Central Government (**Flow chart 1**). The serious AEFIs should be referred without any loss of time especially within 24 hours. In these cases, the FIR can be sent to the PHC, community health center (CHC) or the district health authorities. The district authorities forward these reports within 24 hours to the state and central health authorities. The report should contain the description of the event, timing of the event in relation to immunization, vaccines given, batch number and other details of the vaccine, identifying details of the patient, etc. The peripheral health worker or supervisor in the periphery should report all AEFIs to the higher center or the district authority. The medical officer (MO) at the PHC or the DIO should conduct a preliminary investigation and send the report (PIR) to the state and central health agencies within 7 days. A detailed report is to be sent by AEFI



**Flow chart 1** Routine monthly reporting of 'Minor' AEFI cases (How, Whom and When to report)



investigation team within 90 days. **Table 4** provides a summary of the formats and timelines of reporting serious AEFI cases. The vaccination program should be continued while awaiting the completion of the reporting and investigation. The media play an important role in public perception. Key messages should be prepared before the media contact.

**Table 4** Reporting of serious AEFI cases (formats and timelines)

Type of report	Responsible	Timeline
<i>FIR</i> First Information Report	Pediatrician/Private Practitioner/MO	48 hours
<i>PIR</i> Preliminary Investigation Report	MO/DIO	7 days
<i>DIR</i> Detailed Investigation Report	AEFI investigation team	90 days

## IN A NUTSHELL

1. Most adverse events are minor and self-limiting and can be easily managed.
2. Proper management, reporting and investigation of the significant (albeit rare) adverse events are important to prevent recurrences.
3. With universal vaccine usage, risks and adverse effects receive much higher priority from the public and needs to be addressed so as to not offset the benefits of universal immunization.

## MORE ON THIS TOPIC

- Centers for Disease Control and Prevention. Update: vaccine side effects, adverse reactions, contraindications, and precautions: Recommendations of the Advisory Committee on Immunisation Practices (ACIP). *MMWR*. 1996;45(No.RR-12):1-35.
- Ghosh TK, Kundu R, Ganguly N, et al. Controversies Answered: A Monograph on Vaccinology. Infectious Diseases. Mumbai: IAP; 2007.
- Global Programme for Vaccines and Immunisation. Surveillance of adverse events following immunisation (WHO/EPI/TRAM/93.02REV.1). Geneva: World Health Organization; 1997.
- Prajapati BS, Prajapati RV, Sharma S, et al. Adverse events following immunization (AEFI). In: Vashishtha VM, Kalra A (Eds). Vaccine Safety & Misinformation Against Vaccination. Mumbai: Tree Life Media; 2014. pp.131-46.
- Rao IM. Adverse events following immunization. In: Thacker N, Shah NK. Immunization in Clinical Practice. New Delhi: Jaypee Brothers Medical Publishers; 2005. pp.37-46.
- Rao IM. Adverse events following immunization. *Indian J Pediatr*. 2006;8:208-19.
- Reis EC, Jacobson RM, Tarbell S, et al. Taking the sting out of shots: control of vaccination associated pain and adverse reactions. *Pediatr Ann*. 1998;27:375-86.
- Standard Operating Procedures for investigation of AEFI. Department of Family Welfare, Ministry of Health and Family Welfare, Govt of India. [online] Available from [www.jacob.puliyel.com/download.php?id=258](http://www.jacob.puliyel.com/download.php?id=258). [Accessed November, 2014.]
- Yewale V, Choudhury P, Thacker N. IAP Guide Book on Immunization Edition 2011, Mumbai: Indian Academy of Pediatrics; 2009.

## Chapter 23.6

# BCG Vaccine

Sangeeta Sharma

Bacille Calmette-Guérin (BCG) is the deliberate administration of a suspension of live attenuated *Mycobacteria bovis*-Calmette and Guérin strain to produce immunity against tuberculosis (TB). In 1908, Edmond Nocard first isolated a strain of *Mycobacteria bovis* from a cow with tuberculous mastitis, known as Lait Nocard strain. Over a span of 13 years, until 1921, Calmette and Guérin performed successive 231 subcultures to the attenuate these bacilli, to produce the BCG strain. This strain was later lyophilized at the Pasteur Institute and distributed to various countries. Different ways of sequential culture performed in different countries led to the origin of different substrains due to eight genetic mutations over a 40-year period. The substrain brought by Julio Elvio Moreau to Uruguay in 1925, known as *Moreau strain*, had already undergone two mutations while the BCG vaccine brought by Arlindo de Assis to Brazil in 1927 was actually a daughter strain of the *Moreau strain*, the BCG vaccine brought by Moreau. This was therefore named as BCG *Moreau-Rio de Janeiro, Brazilian strain*, the most immunogenic strain known. World Health Organization (WHO) has recognized 12 vaccine substrain preparations till now, which are currently available.

Presently, BCG vaccine is being produced by several laboratories around the world. Although the preparations are made from attenuated *M. bovis*, they are not identical due to the different genotypic and phenotypic characteristics of the substrains. As a result, depending on the substrain, they have different viability, immunogenicity, reactogenicity, residual virulence, potency and efficacy. The number of particles cultivated per dose is also different, e.g., varies from 37,500 to 500,000 in the Pasteur substrain and from between 200,000 and 3,200,000 in the Copenhagen substrain. Recent genomic studies have shown that different BCG vaccine substrains differ in the genetic code.

BCG vaccine was extensively used in Europe between 1920 and 1930 as an oral BCG vaccine. In 1929 in Lubek, Germany, an oral BCG vaccine lot caused 72 deaths among 251 children vaccinated. Although it was later found to be due to an unintentional contamination of the vaccine with a virulent TB strain, this led to a big question mark on the routine immunization practices with BCG. Intradermal BCG vaccination and multiple puncture technique were introduced in 1927 and 1939, respectively. Currently, BCG vaccination covers 85% of newborn infants all over the world. Developing countries of Africa, Southeast Asia and the Western Pacific have lower vaccination rates.

## TYPES OF BCG VACCINE

### Liquid Vaccine

It loses potency very quickly with rapid deterioration occurring within 2 weeks if exposed to light or temperature fluctuation.

### Freeze Dried Vaccine

The solution harvesting the bacilli is frozen. It can be stored at room temperature (with 1% sodium glutamate as preservative). It remains viable for 12 months.

## TECHNIQUES OF ADMINISTRATION

### Intradermal Technique

It is the most common technique with 0.1 mL of BCG vaccine injected into the left arm at deltoid insertion, leading to a wheal formation of 5–7 mm, which later transforms into a papule in

1 week and ulcerates at 3–4 weeks, finally healing by scar formation in 3 months.

### Oral Vaccine

BCG was introduced for the first time as an oral vaccine in France. There are many disadvantages of this technique like large dose requirement, and sensitivity to temperature. Cervical adenitis is also more common.

### Multiple Puncture Technique

The vaccine is given intradermally using multiple punctures. It is not suitable for mass immunization as it requires a large dose.

### Jet Injections

The vaccine is given intradermally using jet syringe and needle but it is also not suitable for mass immunization.

## PROTECTIVE EFFICACY

In several case-control studies and clinical trials conducted worldwide reported the protective efficacy rate of BCG range between 0 and 80% depending on the geographic area and the study design. Protection against tuberculous meningitis and miliary tuberculosis was consistently higher (> 50%) in all these studies. The wide variation in the protection levels so obtained could be attributed to the differences in some aspects of these studies, for instance, the age of the cases included in the analysis, proportion of different clinical forms of TB, source of controls, selection criteria for controls and sample size, etc., which may influence the results so obtained. The largest clinical trial carried out by the Indian Council of Medical Research (ICMR) in Chingleput, Chennai showed no protection against TB.

Three meta-analyses conducted by Rodrigues et al. (1993), and Colditz et al. (1994, 1995) have analyzed the studies on BCG vaccine for preventing TB. The results were homogeneous for the protective efficacy of BCG vaccine against tuberculous meningitis and miliary TB, ranging between 72% and 100%, with a summary estimate of 86%. Summary estimates of the protection afforded by BCG vaccine against all forms of TB were similar for randomized clinical trials (RCT) and case-control studies (51% and 50%, respectively). Nevertheless, the protective efficacy of BCG vaccine against pulmonary TB was quite heterogeneous, as several RCTs revealed rates ranging between 8% and 79%. A recent study from Turkey carried out on children exposed to domestic contact with TB cases using the enzyme-linked immunospot (ELISpot) test suggested a protective effect of 40% against the primary infection. The BCG vaccine can also prevent the infection from becoming an active illness.

## Reasons for Heterogeneity

Many factors have been implicated for the heterogeneity in the protective efficacy of BCG, especially with regard to pulmonary TB:

- Biological variability of BCG vaccine of different strains and stability of vaccine.
- Studies using the same BCG strain in different countries report different levels of protection due to frequent exposure to environmental mycobacteria (EM) which may influence the recipient's *BCG take*, thus interfering with the efficacy of BCG vaccine. Clinical trials carried out with populations from countries located far away from the equator, with low or no prevalence of EM, had high efficacy rates (greater than 70%), while in a study conducted in southern India the low protective efficacy observed is consistent with exposure to EM. A meta-analysis revealed that 41% of the discrepancy in the estimated efficacy is due to latitude, which may represent exposure to EM.

- **Route of infection:** The vaccine protects against progression of primary complex (e.g., meningitis and disseminated TB), while there is a low protective efficacy against reinfection. If this hypothesis were true, there would be low protective efficacy in those populations at high-risk for infection and reinfection.
- Differences in the virulence of the *M. tuberculosis*, high-risk of reinfection; viability, dose and route of vaccine administration also play a role.
- Host-related factors like nutritional status, other coexisting infections and genetic make-up also influence the protective response to the vaccine.

## DURATION OF PROTECTION

The length of the protective efficacy of BCG vaccine plays an important role in the establishment of vaccination policies. According to the literature, the protection provided by BCG vaccine decreases with time, i.e., 10–15 years. In Great Britain, the Medical Research Council conducted a study between 1950 and 1970, including 54,239 participants aged 14 and 15 years to assess the length of protective efficacy of BCG vaccine. The analysis carried out every 5 years revealed that protection decreased from 84% in the first 5 years to 59% between 10 years and 15 years, showing a reduction in protective efficacy. A study based on a placebo-controlled clinical trial including American Indians and Alaska Natives has been recently published revealed a decline in efficacy at the beginning of the follow-up period (1935–1947) from 77% to 52% during a six-decade follow-up (period from 1948 to 1998). A study of the RCT control group on the efficacy of the second dose of BCG vaccine in Brazilian school-aged children demonstrated that the protective efficacy of neonatal BCG against all forms of TB lasts for 15–20 years.

## BCG REVACCINATION

### Protection

Revaccination was given to children and adolescents in Hungary from 1959, when high incidences of TB were found, with levels comparable to a serious epidemic. Revaccination was administered to tuberculin-negative children and adolescents with the second dose of the BCG vaccine. It was found to provide no protection. These results acted in support of the decision to suspend the Brazilian revaccination program against TB.

### Repeated Vaccination

Russia, Portugal, Chile and Hungary, use repeated doses of BCG vaccine against pulmonary TB, on the assumption that the protection provided by the vaccine decreases with time. Most of the evidence regarding the second dose of BCG vaccine is based on observational studies. After the second dose of BCG vaccine was discontinued in purified protein derivative (PPD)-nonreactive children, the number of cases did not increase, compared to the cohort of children revaccinated with BCG vaccine. The WHO recommends the use of one dose of BCG vaccine against TB, given the lack of evidence supporting the use of additional doses.

In some of these countries, the use of BCG vaccine has been discontinued in order to safeguard the diagnostic value of PPD as an indicator of previous MTB infection. Countries with a low incidence of TB like USA, United Kingdom have focused on the identification and treatment of infected individuals in order to prevent transmission of disease and occurrence of new cases. In other countries, such as Brazil, revaccination has recently been discontinued and BCG vaccine is now given at birth only. Other control measures include early diagnosis, treatment of TB cases, and chemoprophylaxis of contacts.

## ADVERSE EVENTS

BCG vaccine is a fairly safe vaccine. Adverse events resulting from the vaccination are infrequent with local adverse events like accelerated ulceration, axillary lymphadenopathy occurring in 0.01–6.0 per 1,000 livebirths. Adverse events that involve the generalized spread of the BCG vaccine infection usually 6–12 months after receipt of the vaccine are rare but can occur in immunocompromised children.

## CONTRAINDICATIONS

- Dermatological infection in the area where the vaccine is to be administered
- Children on immunosuppressant drugs
- Congenital immunodeficiency
- Children with acquired immune deficiency syndrome (AIDS).

## BCG VACCINE IN HIV-POSITIVE CASES

Case-control studies performed in human immunodeficiency virus (HIV) positive children did not provide any evidence of the protective efficacy of BCG vaccine against pulmonary and extrapulmonary TB. The use of live attenuated vaccines may pose risks to HIV-positive individuals. In 1987, the WHO concluded that the benefits of providing the BCG vaccine to all children in high incidence countries are greater than the risks of adverse events occurring among HIV-positive groups. In these countries, vaccination is recommended for HIV-positive children except those with AIDS. Countries with low prevalence of TB do not give BCG vaccine to these groups. In 2004, the recommendation was revised to include the proposal that vaccinated children to HIV-positive mothers, should be monitored to for the occurrence of possible adverse events like localized reaction, occurrence of lymphadenitis, or the spread of the BCG infection.

## STRATEGIES FOR BCG VACCINATION AROUND THE WORLD

### First Dose of BCG Vaccination

As per WHO recommendations, most national immunization programs of various countries recommend a single dose of BCG for all newborn babies. In high endemic regions, additional doses have mainly been adopted in order to protect against the spread of very serious forms of the infection especially in young children and adolescents, though there is lack of evidence of its extra efficacy.

BCG vaccine is not recommended for newborn babies in seven European countries namely Luxembourg, Andorra, Austria, Germany, Spain, Belgium and Denmark. In the last two countries of this group, the vaccine is only recommended for children who move from high incidence countries. East European countries give the BCG vaccine to newborn babies. France, Norway, United Kingdom, Malta, Greece, Holland and Slovenia vaccinate children when they are adolescents, i.e., 12–13 years old. Low incidence countries like USA, Sweden and Canada vaccinate only high-risk groups such as health professionals working in endemic areas, children who have been exposed to multi-resistant TB and homeless people.

### Second Dose of BCG Vaccination

Hungary and Russia administer multiple doses of BCG, on the basis that the protection diminishes over time. In Thailand and Japan, school children who do not develop a scar receive a second vaccine, while in Turkey, a second dose is recommended for school children, irrespective of scarring or PPD. In Slovakia, the Czech Republic, Poland and Bulgaria, school children are revaccinated

when the result of their PPD test is negative. Brazil has recently suspended the use of the second dose of the BCG vaccine in school children due to lack of evidence of its efficacy.

## NEWER TUBERCULOSIS VACCINES

The current BCG vaccine is not very effective in preventing pulmonary TB, the most common and most infectious form of the disease. Efficient drug therapy exists, but the treatment is long and case detection rates are low, making the development of a better vaccine an important goal. Cochrane database analyses have shown that BCG vaccine being used today can only protect against development of severe and disseminated forms of tuberculosis amongst children, i.e., tubercular meningitis and miliary tuberculosis and is not very effective at preventing primary complex. Also, the conventional BCG does not boost the immune response to a level that it can prevent reactivation/reinfection TB. Therefore, revaccination with a second dose of BCG is fast losing ground due to loss of efficacy.

An ideal TB vaccine should therefore not only prevent the progression of primary TB disease but should also be able to prevent the primary infection, its transmission and reactivation, should be safe, should not interfere with the diagnosis and if required also be used as an adjunct to chemotherapy. Therefore, it should work either before or after primary infection but with a long standing, preferably lifelong immunity, without need for frequent boosters. It should also have a low cost.

## Difficulties in Development of the Newer BCG Vaccine

Animal studies/models provide limited information as these cannot be extrapolated on potential human vaccine candidates due to lack of good *protective markers*. Moreover, most human beings have either already been immunized with BCG or exposed to atypical

environmental mycobacteria. Therefore, it may not be possible to find a clean catch human population for the trial of a new vaccine. Also, as the level of immunity cannot be increased any further in these already immunized or environmental mycobacteria exposed individuals, the new vaccine might not seem to give the expected results in these cases. Induction of a strong immune response in some infected persons may produce immunopathology. The newer vaccines are shown in **Table 1**.

Deoxyribonucleic acid (DNA) subunit vaccines (recombinant, natural, synthetic), virus vector vaccines or recombinant protein vaccines are capable of carrying one or more immunodominant antigens of the *M. tuberculosis*. These may possibly be used to substitute the BCG vaccine and include:

- MVA85A (recombinant modified vaccinia Ankara expressing antigen 85A) is recombinant virus vector vaccine (attenuated vaccinia virus) expressing antigen 85 A in the *M. tuberculosis*. This is considered to be safe and displayed good results in a population of noninfected and also previously BCG received guinea-pigs. In 2003, phase 2 of the study began in South Africa.
- rBCG30—recombinant vaccine (antigen 85 B).
- Mtb72F—recombinant vaccine that includes polyproteins, obtained by combining two antigens (Mtb32 and Mtb39) that are recognized by the immune system of the infected patient. In 2004, phase 1 of studies began in the United States.
- ESAT6 and Ag85B—recombinant vaccines that express polyproteins. In 2005, phase 1 of studies began in Europe.

## Current Status of New BCG Vaccines

Results of the phase I trial of a leading new TB vaccine MVA85A have shown it to be an effective, safe, and immunogenic in the BCG-vaccinated individuals without any induction of immunopathology. This is the first subunit TB vaccine to enter clinical trials in *M. tuberculosis*-infected subjects.

**Table 1** Selected promising tuberculosis (TB) vaccines

Vaccine candidate	Example	Comment	Current status	Reference
<i>Subunit vaccine</i>				
Antigen and Adjuvant	Mtb 72 F	Skewed Ag profile	Ph I clinical trial in healthy volunteer	J Immunol 2004
	Fusion protein: Ag85 – ESAT-6	Mild side effects	GMP production	Infect Immun 2001
Naked DNA	Ag85 Mtb 72F	CD4 and CD8 stimulation, safety concern	Clinical Ph II started	Nat Med 1996
Recombinant carrier expressing antigen	r-MVA expressing Ag85	CD4 and CD8 stimulation, safety concern	Chemical Ph I trial	Nat Med 2004
<i>Viable mycobacterial vaccine</i>				
Mtb deletion mutant	PhoP/PhoQ – Mtb	CD4 and CD8 stimulation, Safety concern	Ph I trial completed	Nature 2000
Auxotrophic mutants	Met, leu, ilv – BCG	Improved safety, Reduced efficacy	Used in HIV patients	Nat Med 1996
Recombinant BCG expressing cytolysin	Δurease r-BCG expressing listerolysin	CD4 and CD8 stimulation, Safety concern	Clinical Ph I started	Curr HIV Res 2004
Recombinant BCG over expressing Ag	r-BCG – Ag85	Improved antigenicity esp CD4 cells	Clinical Ph I ongoing	Proc Natl Acad Sci 2000
<i>Prime boost vaccination</i>				
Based on BCG prime	BCG/protein (Ag85)/r-MVA(Ag85)/Leprae	Improve efficacy of BCG prime		Infect. Immun 2001
Naturally Attenuated NTM	<i>M. vaccae</i> , <i>M. microti</i> , <i>M. smegmatis</i>		Heat-inactivated used in HIV patients	Indian J Pediatr 2000
Non Mtb vector	<i>Salmonella</i> , Vaccinia and Adeno virus	Improve efficacy of BCG prime		Int J Tub Lung Dis 1999

Abbreviations: BCG, Bacille Calmette-Guérin; HIV, human immunodeficiency virus; Ag, antigen; MVA, modified vaccinia Ankara; Ph, phase.



In 2012, at least six different TB vaccine candidates both live and subunit vaccines, have completed initial phase I clinical trials, three are currently in phase II trials. Most of the new vaccines will at least initially be given as booster doses on top of a priming BCG vaccination. A virus vectored booster vaccine candidate has recently entered an early efficacy (phase IIb) trial and we would soon know if this vaccine provides an advantage over BCG. In an optimistic scenario, i.e., assuming that at least one of the first generation candidates successfully completes phase III (efficacy) evaluation, licensure of a new TB vaccines is anticipated around 2014–15. Until that time, extensive resources are needed to conduct reliable clinical trials in developing country settings. As with other vaccines targeting diseases of poverty, particular efforts in the areas of financing, production capacity logistics, etc., must be made to ensure that once a new TB vaccine is available it can be implemented rapidly with high coverage rates.

### MORE ON THIS TOPIC

- Colditz GA, Berkey CS, Mosteller F, et al. The efficacy of Bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analysis of the published literature. *Pediatrics*. 1995;96:29-35.
- Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA*. 1994;271:698-702.
- Grange JM, Gibson J, Osborn TW, et al. What is BCG? *Tubercle*. 1983;64:129-39.
- Rodrigues LC, Pereira SM, Cunha SS, et al. Effect of BCG revaccination on incidence of tuberculosis in school aged children in Brazil: the BCG-REVAC cluster randomised trial. *Lancet*. 2005;366:1290-5.
- Sharma S. Newer TB vaccines. In: Vashishtha VM, Kalra A, Thacker N (Eds). *FAQs on vaccines and immunization practices*, 1<sup>st</sup> ed. New Delhi, India: Jaypee Brothers Medical Publishers; 2011.

Sharma S, Sarin R, Khalid UK, et al. The DOTS strategy for treatment of pediatric pulmonary tuberculosis in south Delhi, India. *Int J Tuberc Lung Dis*. 2008;12:74-80.

Tuberculosis Prevention Trial. Trial of BCG vaccines in south India for tuberculosis prevention. *Indian J Med Res*. 1980;72:1-74.

Vashishtha VM, Choudhury P, Bansal CP, et al. BCG vaccines. In: *IAP Guidebook on Immunization 2013–2014*. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.

### IN A NUTSHELL

1. Conventional BCG vaccine is a part of universal immunization program.
2. It is given intradermal in dose of 0.1 mL at insertion of left deltoid.
3. Scar visually develops by 3 months. However, absence of scar does not indicate absence of immunity.
4. Conventional BCG vaccine does not prevent primary TB infection.
5. BCG has a definite predictive role against disseminated TB disease.
6. It also prevents serious forms of TB like tuberculous meningitis and miliary tuberculosis.
7. Immunity lasts for 10–15 years.
8. Revaccination is not indicated.
9. Efficacy is hindered by environmental mycobacteria like atypical mycobacteria.
10. Limitations of conventional BCG vaccine have reconstructed research on development of newer vaccines.

## Chapter 23.7

# Poliovirus Vaccines

Puneet Kumar, Vipin M Vashishtha

Inactivated poliovirus vaccine (IPV) and live oral poliovirus vaccine (OPV) are the two effective vaccines against poliomyelitis that have ensured remarkable decline in the global burden of disease in last five decades. India reported its last case of wild poliovirus (WPV) on January 13, 2011. Both these vaccines are complementary to each other and have unique roles to play, both at individual and community level. This chapter would describe both of these in brief, with special focus on Indian scenario.

## ORAL POLIOVIRUS VACCINE

Oral poliovirus vaccine consists of live attenuated strains of polioviruses (called vaccine polioviruses or Sabin viruses) grown in monkey kidney cell cultures and stabilized with magnesium chloride. These vaccine strains were developed in 1950s by Albert Sabin in Cincinnati in the USA. Of note, Sabin never patented these strains and in fact, donated these strains to Soviet Union in 1959, then to Pasteur Institute of India in Coonoor (Tamil Nadu) in 1974 and finally donated them along with *proprietary ownership* to the World Health Organization (WHO) in 1979. Initially, monovalent OPV (mOPV) was developed and later, trivalent OPV (tOPV) was developed containing all the three types (types 1, 2 and 3) of polioviruses. When tOPV was formulated, it was found that type 2 strain inhibits immune response to types 1 and 3. Thus, it was *balanced* by including maximum virus particles [1,000,000 cell culture median infectious dose (CCID<sub>50</sub>) of type 1, minimum (100,000 CCID<sub>50</sub>) of type 2 and intermediate number (300,000 CCID<sub>50</sub>) of type 3, i.e., ratio of 10:1:3. WHO revised this ratio to 10:1:6 by increasing type 3 virus particles (600,000 CCID<sub>50</sub>) in 1980s. Since then all tOPV that is manufactured anywhere has the same constitution. Since WHO *owns* the Sabin viruses, every manufacturer needs to take WHO approval regarding the constitution of OPV. This is unlike all other vaccines, where it is the manufacturers who decide the formulation and the dose content of the vaccines they make.

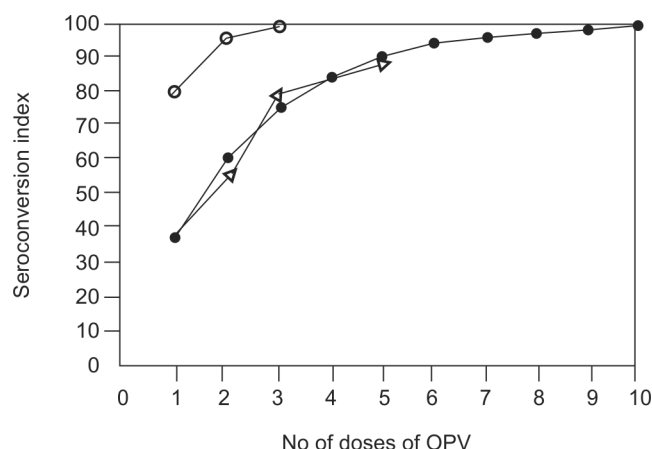
## Immunogenicity and Efficacy

### Global

Vaccination with tOPV results in type-specific immunity to the type that is *taken* by the intestinal mucosa. There is no cross-protection between types. Moreover, unlike most other vaccines (including IPV), its immunogenicity shows marked variation in various regions of the world and even within the country. In temperate countries with high degrees of sanitation, its efficacy is very high.

### Tropical Countries including India

In tropical and subtropical countries with poor sanitation, the efficacy is low. Data from the composite of Vellore studies in 1970s and 1980s suggest that seroconversion rates after three doses of OPV average 65%, 95% and 67% for types 1, 2 and 3, respectively. Using this data, it was calculated that in order to reach near 100% seroconversion using tOPV, it would need about 13–15 doses for types 1 and 3, while only five doses are sufficient to reach that level for type 2 poliovirus. Thus, it is not surprising that we have achieved eradication of type 2 WPV globally in as early as 1999, while the feat is not yet achieved for type 1. **Figure 1** depicts comparative immunogenicity of OPV in developed and developing (tropical) countries.



**Figure 1** Immunogenicity of oral polio vaccine (OPV) in developed and developing (tropical) countries

The incremental responses to sequential doses of OPV shown as "seroconversion index (SI)". Seroconversion Index (SI): (No. of seroconverted to types 1+2+3 × 100)/(No. seronegative to types 1+2+3 before immunization);

The top curve shows the pattern of developed countries. SI is fixed at 80 for first dose and also for subsequent doses. SI after two doses 96, after three doses 99. The curve below with triangle shows SI to OPV in children in developing countries (example Vellore, TN, India). SI after first dose 37, two doses 54, three doses 78, and after five doses 87.

The curve with dark dots shows the SI calculated arithmetically for subsequent doses using SI 37 for each dose. For example, SI after two doses =  $37 + [37(100-37)]/100 = 60$ ; SI after three doses =  $60 + [37(100-60)]/100 = 75$ , SI after four doses 84, after five doses 90, after six doses 94, after seven doses 96. Response to sequential doses increases by "arithmetic proportion" principle—Decreasing numbers respond to each additional dose; titres remain low to moderate—Small proportions always fail; we have confirmed wild virus polio after 10, 18, even 24 doses

(Reproduced with permission from John TJ. Immunization against polioviruses in developing countries. Rev Med Virol. 1993;3:149-60.)

Even within India, there is a large variation in its efficacy across different regions. While the per-dose vaccine efficacy has been found to be about 30% in Vellore, it was just around 10% in some regions of Uttar Pradesh and Bihar, the two *hotspots* of polio in India. It has also been shown that the vaccine efficacy of a geographical location remains stable over decades. The poor immunogenicity in some states is not just due to poor routine immunization (RI) coverage and breaks in cold chain, as previously thought. Many experts believe that the reason for poor immunogenicity in certain areas is some unknown defect in gut-related immunity; however another school of thought is just the opposite: It has been suggested that *good* mucosal immunity, that remains on *high alert* on account of frequent enteric infections prevents infection by vaccine viruses (vaccine virus *take*), an essential first step before the immune response can be expected. Another reason cited for poor efficacy in some regions of India includes high incidences of diarrhea, malnutrition and high population density. Presence of other nonpolio enteroviruses inhibits proper *uptake* of Sabin polio viruses contained in OPV. Thus, both *failure of the vaccine* as well as *failure to vaccinate* results in poor efficacy epidemiologically.

### Mucosal Immunity

Being an oral live vaccine, OPV induces mucosal immunity also, i.e., it induces production of secretory immunoglobulin A (IgA) locally in the mucosa. Thus, OPV is capable of providing *better* herd immunity as compared to IPV and is capable of

preventing infection with WPV (*breaking the transmission chain*) in addition to offering personal protection against paralytic poliomyelitis. However, the mucosal immunity is short lived unlike long-term systemic immunity and is not as *solid* as humoral immunity. Thus, while humoral immunity fully protects an individual from disease (paralytic poliomyelitis), possibly for life, but mucosal immunity is not 100% dependable in protecting against repeat infection and breaking the transmission chain.

### Herd Immunity and Contact Immunity

*Herd immunity* should not be confused with *contact immunity*, a related concept wherein a vaccinated individual can *pass on* the vaccine to another individual through contact. Not all vaccines possess this virtue which is mainly the quality of certain live, attenuated vaccines that shed very efficiently either through gut or nasal mucosa though still producing *herd effect* and contributing in generation of *herd immunity*. OPV has got this unique quality and provides efficient *contact immunization*. On the other hand, IPV despite providing *herd immunity* and *herd effect*, does not provide *contact immunity*. The greater the transmissibility of a vaccine organism, the higher the contact immunization or contact immunity.

### Onset and Duration of Protection

Oral poliovirus vaccine has a much faster onset of action as compared to IPV, making it the vaccine of choice for outbreak control. Being a live vaccine, it is expected to offer lifelong protection. However, data from developed countries show there is gradual decline in the humoral antibodies level amongst vaccinees and they decline sometimes to almost undetectable levels after decades. However, these individuals continue to remain protected for lifelong against the paralytic disease despite having very low level of antibodies. There is no data from developing countries on duration of protection.

*Monovalent OPVs (mOPVs) and bivalent OPV (bOPV, for types 1 and 3)* are more efficacious than tOPV, as the inhibitory effect of type-2 is eliminated. In addition, elimination of type-2 also eliminates the risk of vaccine-associated paralytic poliomyelitis (VAPP) due to type-2 virus and reduces the risk of vaccine-derived polioviruses (VDPV) (*vide infra*) remarkably, since over 90% of cases of VDPV are due to type-2 virus only. Thus, mOPV for types 1 and 3 were introduced in India in 2005 and bOPV (developed and tested in India) is being used for pulse immunization since 2010. Their induction in the sub-National immunization days (SNIDs) and other supplementary immunization activities (SIAs) was amongst the main reasons behind disappearance of paralytic polio from India.

### Safety

OPV is well tolerated without any gastrointestinal side effects. However, it is associated with a rare, but well recognized serious adverse effect, VAPP.

### Vaccine-associated Paralytic Poliomyelitis

Vaccine-associated paralytic poliomyelitis is defined as those cases of acute flaccid paralysis (AFP) which have residual weakness 60 days after the onset of paralysis and from whose stool samples, vaccine-related poliovirus but no WPV is isolated. Clinically, it is indistinguishable from WPV polio. It is caused by deattenuation of the vaccine viruses during replication in the gut. It may occur in the vaccine recipient (recipient VAPP) or close contact of the vaccine recipient (contact VAPP). Conventionally, it is believed that the type-3 virus is the most common cause of

recipient VAPP and type-2 is the most common cause of contact VAPP. However, the epidemiology of polio in recent times revealed that type-2 was mainly responsible for VAPP in India and elsewhere.

The risk of developing VAPP also shows geographic variations. In developed nations the risk of VAPP is higher with the first dose of OPV and the risk decreases sharply (> 10-fold) with subsequent OPV doses, whereas in developing countries this decline is more gradual, probably as a consequence of lower vaccine effectiveness. Most of VAPP cases in India were associated with subsequent OPV dose, not first dose. The incidence of VAPP has been estimated at 4 cases per million birth cohort per year in countries using OPV. The incidence of VAPP in developed countries, such as USA, has been reported to be 1 per 2.4 million doses distributed and 1 per 750,000 with first dose. The risk of VAPP in India has been estimated to be 1 per 4.1–4.6 million doses distributed and 1 per 2.8 million first dose, and subsequent-dose recipient risk is found around 1 case per 13.9 million. This comparatively lower risk of VAPP has been attributed to maternal antibodies, birth dose of OPV, early immunization with OPV and most importantly lower *take* of the vaccine (as only the vaccine that takes up can cause VAPP). Nevertheless the absolute numbers of VAPP are high and it is estimated that 181 cases of VAPP occurred in India in 1999. Moreover, if the risk of VAPP is calculated *per-million birth cohort* (rather than *per-million doses distributed*), the risk is then higher in India than in Western world, simply because our babies are getting more number of OPV doses every year as compared to West in OPV era: thus our babies are at higher risk!

### Vaccine-derived Poliovirus

Viruses causing VAPP have low transmissibility despite being neurovirulent. The fact that this property of low transmissibility of Sabin viruses can also revert along with regaining neurovirulence was predicted long back by an Indian scientist. However, it was not well understood by the experts, until the year 2000 when one such virus resulted outbreak of polio in children in the Hispaniola Island (Haiti and Dominican Republic); such reverted Sabin-derived virus causing polio outbreak was named VDPV. Since then, over 18 outbreaks of VDPVs have been reported from 16 countries, affecting 699 children. India has reported 37 cases. Type 2 virus is the cause of VDPV in 85–90% cases. Currently, VDPVs are classified into three groups: (1) circulating VDPV (cVDPV)—VDPV with evidence of virus circulation in the population causing two or more paralytic cases; (2) iVDPV—VDPV in the immunodeficient person; and (3) VDPV of ambiguous origin (aVDPV)—VDPV isolated from environmental sources or evidence of circulation not established.

### INACTIVATED POLIOVIRUS VACCINE

Inactivated poliovirus vaccine consists of poliovirus grown in monkey kidney cell/human diploid cells and killed by formaldehyde. It was developed by Jonas Salk in 1950s in the USA. In the *first generation IPV* polioviruses were grown in primary monkey kidney cell cultures and had water-in-oil emulsion as adjuvant. It was very immunogenic having 80–90% efficacy against paralytic disease and 70% against any disease after two doses. Because of presence of adjuvant, the *old IPV* was very painful. Thus, *second generation IPV* was developed without adjuvant, but it required three doses for adequate seroconversion. The modern-day, *third generation IPV* [also called as enhanced IPV (eIPV)] was developed by Dutch scientist Anton von Wezel in 1978 which was not only more potent but was more refined

too. *eIPV* is the current vaccine in use all over the globe now. In this, Vero cell line replaced the monkey kidney cells. Moreover, the virus was purified before inactivation and vaccine potency was standardized in experimental laboratory animals. Currently available IPV is this third generation IPV (*eIPV*), containing 40, 8 and 32 D antigen units of type 1, 2 and 3 respectively without any adjuvant.

Very recently, *fourth generation IPV* has also been developed. In this, Sabin virus strains are used instead of laboratory maintained WPVs, and thus is called Sabin-IPV. This has an obvious advantage in the event of laboratory leak of viruses from the manufacturing sites. Thus, manufacturing such vaccine would require less strict biosafety mechanisms and could be more freely manufactured all over the world including in developing countries. Japan is the only country that is already using this Sabin-IPV, while Chinese manufacturers are also conducting trials of similar vaccine.

Most of the brands of IPV available are stand-alone IPV. However, many different combinations (and even hexavalent: DTaP/Hib/IPV/HBV) are available and are in use in some countries. There is no DTwP-IPV combination anywhere in the world, although India and France did develop one such IPV that could be mixed with DTwP and was even manufactured in India in early 1980s. Currently available preparations of IPV do not contain any adjuvant but do contain thiomersal as preservative. Since thiomersal affects IPV potency, in combination products with DTP it is either avoided or replaced with 2-phenoxy-ethanol.

### Immunogenicity and Efficacy

Inactivated poliovirus vaccine is one of the most immunogenic vaccines, and since it is known that virus neutralizing antibody in the blood stream is highly protective against paralytic polio, immunogenicity parallels protective vaccine efficacy in case of polio vaccines. Studies have shown that just two doses at 2 months interval achieve nearly 100% seroconversion to all the three serotypes. However, if the vaccination is started at 6 weeks of age [as in Expanded Program on Immunization (EPI) schedule], then there is some interference with maternal antibodies and thus, three doses are required. Further, since the interval between the second and third dose is 1 month rather than ideal gap of 2–4 months, a booster is needed at 15–18 months for optimum results. **Table 1** shows impact of maternal antibodies on seroconversion of IPV during two trials of IPV (old and enhanced) in India. IPV was licensed in USA, Canada and several European countries in 1955; wherever it was systematically used in children polio incidence declined by over 95%.

**Table 1** Impact of maternal antibodies and interval between doses on seroconversion of inactivated poliovirus vaccine (IPV)

Vaccine	Maternal antibodies	Interval between doses (weeks)	
		4 weeks	8 weeks
Old IPV (3 doses)	Present	66%	95%
	Absent	95%	99%
<i>eIPV</i> (2 doses)	Present	87%	87%
	Absent	96%	96%

Abbreviations: IPV, inactivated poliovirus vaccine; *eIPV*, enhanced potency inactivated poliovirus vaccine.

Adapted from John TJ. The golden jubilee of vaccination against poliomyelitis. Indian J Med Res. 2014;119(1):1–17.

Conventionally, it is believed that IPV does not induce strong mucosal (intestinal) immunity. Hence, it is not suitable for interruption of wild virus transmission especially in tropical countries. OPV is considered a *vaccine of choice* by virtue of possessing an excellent mucosal immunity. However, it has been found that IPV also induces intestinal mucosal immunity which results from transudation or *spillover* of serum antibodies (IgM, IgG and nonsecretory IgA) on mucosal surfaces and secretions. Nevertheless, since secretory IgA is not induced, this is often labeled as *mucosal protection* rather than *mucosal immunity*. It has also been suggested that there may be some other mechanisms other than IgA to induce mucosal immunity. In fact, contrary to the conventional wisdom, studies have shown that IPV also induces excellent *herd effect*. This has been demonstrated in large national-level vaccine programs like in Finland where paralytic disease disappeared with even a modest 51% of national coverage with three doses of IPV in 1961 without ever using OPV. Many experts argue now that *mucosal immunity* may not be as important in overall protection against the disease as believed so far, and it is the *humoral immunity* that ultimately determines protection against wild disease.

### Duration of Protection

Information on the duration of IPV-induced protection originates only from industrialized countries. Circulating antibody persist for decades (possibly for life), but antibody titers decrease overtime, so some adults may lack detectable antibody; typically they first lose antibody to type-3 poliovirus. However, as with OPV, these individuals remain protected against paralytic disease. There is no data from developing countries on this attribute.

### Safety

IPV (all generations) has an exceptionally clean record of safety. As it is unadjuvanted vaccine, local injection site reactions and pain are minimal, if any. The purification processes get rid of cell debris and cellular deoxyribonucleic acid (DNA), etc. IPV contains trace amounts of streptomycin, neomycin and polymyxin B, allergic reactions may be seen in individuals with hypersensitivity to these antimicrobials. There is no risk of VAPP or VDPV with this vaccine. A detailed comparative evaluation of both the polio vaccines is provided in **Table 2**.

### POLIO “END GAME” STRATEGIES

Since India has fully interrupted the WPV transmission and has been declared a polio-free country by the WHO, the time to withdraw OPV is approaching fast, considering the safety issues (VAPP and VDPV) associated with continuation of OPV in post-eradication scenario. The process of gradual withdrawal of OPV synchronously from all over the world without exposing children to the risk of wild or vaccine-derived polio is the greatest concern to the global polio eradication initiative (GPEI). This process and strategies involved in the transition from OPV to IPV all over the globe is referred as *end game* in polio parlance. The recently launched, *Polio Eradication and Endgame Strategic Plan, 2013–2018* provides strategic framework for the sequential cessation of Sabin strains, starting with Sabin type 2. For Sabin type 2, cessation means that tOPV must be replaced with bOPV in a synchronized manner globally. For risk mitigation, the framework includes at least one dose of IPV included in the routine EPI (starting >6 months before switch from tOPV to bOPV). Hectic preparations



**Table 2** Comparative evaluation of oral polio vaccine (OPV) and inactivated poliovirus vaccine (IPV)

Attributes	OPV	IPV
<b>Efficacy issues</b>		
Potency	Low (needs 4 or more doses)	High (needs 2 or 3 doses)
Systemic immunity	Variable (high in industrialized countries; low in tropical countries)	High
Predictability of immune responses	Low, variable	Highly predictable
Mucosal immunity	Excellent (both pharyngeal and intestinal)	Low (low intestinal but good pharyngeal)
Contact immunization	Yes (community protection)	No (individual protection)
Onset of action	Faster	Comparatively slower
Duration of protection	Long, possibly life-long	Long
<b>Safety issues</b>		
Risk of VAPP	Yes	No
Risk of cVDPV	Yes	No
Risk of use in bioterrorism	No	Yes (produced with wild virus seeds)
Requirement of Biosafety measures	Less stringent	Stringent (BSL-3)
<b>Administration issues</b>		
Extra injection	No	Yes (in stand-alone preparation is used)
Possible combination vaccine	No	Yes
Injection safety issues	No risk	A risk
Compliance	Excellent	May be reduced if used as stand-alone preparation
Suitability for large scale campaigns	Yes	No
<b>Other issues</b>		
Cost	Low	High
Availability	Good (many manufacturers even in developing countries)	Scarce (only two major manufacturers)

Abbreviations: VAPP, vaccine-associated paralytic poliomyelitis; cVDPV, circulating vaccine-derived polioviruses; BSL, biosafety level.

are going on to introduce at least one dose of IPV at the time of third dose of DTP in the Universal Immunization Program (UIP) in India at the earliest.

## SCHEDULES OF POLIO VACCINES

### Dose

The dose of OPV is two drops orally: for routine vaccination, supplementary vaccination as well as for travelers. The dose of IPV is 0.5 mL to be administered intramuscularly/subcutaneously. All the currently available brands of IPV in India are packaged in prefilled syringe.

## National Immunization Schedule

The national immunization schedule (UIP schedule) has not introduced IPV as of now. As per UIP schedule, OPV is given at birth, 6, 10 and 14 weeks followed by booster at 15–18 months. It is planned to introduce IPV in national schedule somewhere around first quarter of 2015. In addition to RI, all OPV doses (mono-, bi- or trivalent) offered through supplemental immunization activities (SIAs: *pulse polio*), should also be given to all children below 5 years of age, regardless of previous RI.

## The Indian Academy of Pediatrics Schedule for Office Practice

The Indian Academy of Pediatrics (IAP) has recommended *sequential IPV-OPV schedule* in its 2012 and 2013 guidelines as a step before complete withdrawal of OPV. This is in accordance with strong evidence that sequential schedules that provide IPV first, followed by OPV can prevent VAPP while maintaining the critical benefits conferred by OPV (i.e., high levels of gut immunity). As per this schedule, OPV is to be administered at birth, three primary doses of IPV at 6, 10 and 14 weeks, followed by two doses of OPV at 6 and 9 months, another dose (booster) of IPV at 15–18 months and OPV at 5 years. IAP continues to recommend the birth dose of OPV, since giving OPV dose at a time when the infant is still protected by maternally-derived antibodies may, at least theoretically, also prevent VAPP. Though OPV at birth is not immunogenic, it enhances seroconversion of subsequent polio vaccines, both OPV and IPV considerably. A birth dose of OPV is considered necessary in countries where the risk of poliovirus transmission is high.

If IPV is started after 8 weeks, then only two doses at 2 months interval are sufficient as primary doses, since there is no interference from maternal bodies that occurs when it is started at 6 weeks; booster is recommended at 15–18 months of age. For any unimmunized child less than the age of 5 years, IPV can be offered as *catch-up* vaccination. The schedule in such a case is two doses at 2 months interval followed by booster 6 months after the last dose.

In case, IPV is unavailable or unaffordable, the primary series must be completed with three doses of OPV given at 6, 10, and 14 weeks. Boosters of OPV are recommended at 15–18 months of age and at 5 years of age.

OPV is contraindicated in immunodeficient patients (especially humoral immunodeficiencies) and their household contacts.

Countries using IPV only in their schedules usually recommend three doses (at 2/4/6 months or 2/3/5 months of age) followed by booster at 4 years of age.

Since India is now a *polio free* country, IAP has specific recommendations for travelers to polio-endemic countries or areas:

- For those who have previously received at least three doses of OPV or IPV should be offered another dose of polio vaccine as a once-only dose before departure.
- Nonimmunized individuals should complete a primary schedule of polio vaccine, using either IPV or OPV. Primary series includes at least three doses of either vaccine.
- For people who travel frequently to polio-endemic areas but who stay only for brief periods, a one-time only additional dose of a polio vaccine after the primary series should be sufficient to prevent disease.

Government of India has made it mandatory for all travelers to and from polio endemic countries (Afghanistan, Nigeria and Pakistan) and countries with wild polio virus circulation following importation (Ethiopia, Kenya, Somalia and Syria) to take one dose of OPV at least 4 weeks prior to departure to or from these countries. OPV vaccination certificate issued after such additional dose remains valid for 1 year. This additional dose is must for

travelers of all ages, even adults. This is because of the fact that even adults can acquire infection with poliovirus and transmit WPV to others, even though paralytic polio is rare in children above 5 years of age. These requirements are effective for all travels from March 2014. Similar recommendations on a global level have been issued by the WHO under the International Health Regulations on May 5, 2014. The WHO lists Cameroon, Equatorial Guinea and Israel also as polio-infected countries in addition to seven countries named earlier.

### MORE ON THIS TOPIC

Consensus recommendations on immunization and IAP immunization timetable 2012. Indian Academy of Pediatrics Committee on Immunization (IAPCOI). Indian Pediatr. 2012;49:549-64.

Global Polio Eradication Initiative. From <http://www.polioeradication.org>. Accessed November 4, 2014.

John TJ, Samuel R. Herd immunity and herd effect: new insights and definitions. Eur J Epidemiol. 2000;16:601-6.

John TJ, Vashishtha VM. Eradicating poliomyelitis: India's journey from hyperendemic to polio-free status. Indian J Med Res. 2013;137:881-94.

John TJ, Vashishtha VM. Eradication of vaccine viruses: why, when and how? Indian J Med Res. 2009;130:491-4.

John TJ. Immunisation against polioviruses in developing countries. Rev Med Virol. 1993;3:149-60.

John TJ. Inactivated Poliovirus vaccine. In: Vashishtha VM (Ed). IAP textbook of Vaccines, 1<sup>st</sup> ed. New Delhi: Jaypee Brothers Medical Publishers; 2014.

John TJ. The golden jubilee of vaccination against poliomyelitis. Indian J Med Res. 2004;119:1-17.

Ministry of Health and Family Welfare, Govt. of India. Requirements of Polio vaccination for international travelers between India and Polio infected countries. From <http://www.mohfw.nic.in/showfile.php?lid=2634>. Accessed November 4, 2014.

Thacker N, Vashishtha VM. Polio vaccines. In: Vashishtha VM, Choudhury P, Bansal CP (Eds). IAP Guidebook on Immunization 2013-2014. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.

World Health Organization. Polio vaccines and polio immunization in the pre-eradication era: WHO position paper. Wkly Epidemiol Rec. 2010;85:213-28.

World Health Organization. Polio vaccines: WHO position paper. Wkly Epidemiol Rec. 2014;89:73-92.

### IN A NUTSHELL

1. Inactivated poliovirus vaccine (IPV) and live oral poliovirus vaccine (OPV) are highly efficacious vaccines against poliomyelitis.
2. Initially, monovalent OPV (mOPV) was developed and later, trivalent OPV (tOPV) was developed containing all the three types (types 1, 2 and 3) of polioviruses.
3. OPV shows marked variation in its immunogenicity in various regions of the world and even within the country. Its efficacy is highest in industrialized, temperate countries whereas lowest in tropical, developing countries.
4. OPV induces excellent gut mucosal immunity and thus provides better *herd immunity* as compared to IPV. It also produces good *contact immunity* by contact immunization.
5. Monovalent OPVs (mOPVs) and bivalent OPV (bOPV, for types 1 and 3) are more efficacious than tOPV, as the inhibitory effect of type-2 is eliminated. Induction of these *new* OPVs greatly facilitated wild poliovirus elimination in India.
6. Vaccine associated paralytic poliomyelitis (VAPP) and vaccine-derived poliovirus (VDPV) are two serious side effects of OPV.
7. Original Salk's IPV developed in 1950s was highly immunogenic having 80–90% efficacy against paralytic disease and 70% against any disease after two doses.
8. The modern-day, third generation IPV, *enhanced IPV (eIPV)* is not only more potent but more refined too. It is the current vaccine in use all over the globe now. Studies have shown that just two doses started at 2 months of age and at 2 months interval achieve nearly 100% seroconversion to all the three serotypes.
9. The greatest virtue of IPV is its predictable immunogenicity, without being affected much by geographic locations, and extreme safety free from serious side effects like VAPP and VDPV of OPV. IPV also induces good pharyngeal and some useful intestinal mucosal immunity. Studies have also shown that IPV also induces excellent *herd effect*.
10. The process and strategies involved in the transition from OPV to IPV all over the globe is referred as *end game* in polio parlance. The *new endgame* strategies include *parallel* rather than *sequential* risk management.

## Chapter 23.8

# Diphtheria, Tetanus and Pertussis Vaccines

Puneet Kumar, Vipin M Vashishtha

Introduction of diphtheria, tetanus and pertussis (whooping cough), DTP or DPT or DTwP (DTwP is a type of DTP vaccine) vaccine in 1940s and subsequent adoption in expanded program on immunization (EPI) leading to increased global coverage made tremendous impact on morbidity and mortality due to diphtheria, tetanus and pertussis. While tetanus has virtually disappeared, diphtheria as a childhood disease remains fairly well controlled (with some evidence of an epidemiological shift affecting adolescents and adults). Pertussis, on the other hand, has resurfaced in highly immunized populations in the recent years and is now under intense scrutiny. Coverage with three doses of the whole cell vaccine (DTwP vaccine) in India is still low (71.5%) and only 41.4% children in the age group of 18–23 months had received first DTWp booster. The need of completing the schedule and boosters should be stressed upon by the pediatrician. This chapter would briefly describe all the vaccines against these infections, with special focus on Indian scenario.

### DTwP VACCINE

It is composed of 20–30 Lf of diphtheria toxoid, 5–25 Lf of tetanus toxoid (TT) and inactivated whole cell pertussis bacilli adsorbed on insoluble aluminum salts as adjuvant.

### Immunogenicity and Efficacy

For diphtheria and tetanus, the protective levels of their respective antitoxins have been defined as more than 0.1 IU/mL and more than 0.01 IU/mL, respectively. Studies have demonstrated immunogenicity as well as clinical efficacy (in outbreak settings) of three properly spaced doses of the vaccine to be above 95% for these two infections. Disease may occur in vaccinated individuals but is milder.

In contrast, the scenario of pertussis is complex. First, unlike *C. diphtheriae* and *C. tetani*, *B. pertussis* has multiple virulence factors, viz., pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), fimbriae (FIM) type 2 and type 3, adenylate cyclase toxin (ACT), tracheal cytotoxin (TCT), BrkA (Bordetella resistance to killing genetic locus, frame A), lipooligosaccharide and *B. pertussis* endotoxin. Second, the bacillus alters its phenotypic state depending upon environmental conditions, and may show different expression of virulence factors under different conditions. Third, the exact pathogenesis of pertussis is incompletely understood even today: this makes the relative role of various virulence factors to be unclear. Thus, there is no single absolute or surrogate correlate of protection known for pertussis disease and vaccines till date. Antibody levels against PT, PRN and FIM can be used as markers of protection, but no established protective antibody levels are known. Hence, it is difficult to define *immunogenicity* of pertussis vaccines accurately.

Assessment of clinical efficacy of pertussis vaccine is equally complex, since laboratory diagnosis of pertussis is difficult and the facilities are virtually absent in the developing world. The diagnosis invariably remains clinical and the sensitivity and specificity varies with the case definition used. Accordingly, the efficacy estimates also vary considerably with different case definitions used in different studies. This also makes the comparison between different studies difficult. The efficacy estimates have varied from 83% to 98% in higher efficacy trials to as low as 36–48% in lower efficacy trials. According to a 2003 systematic review, the pooled efficacy of wP vaccine against pertussis in children was 78%, but efficacy varied significantly among vaccines. The efficacy of wP alone ranged from

61% to 89%, and the efficacy of combination DTWp vaccines ranged from 46% to 92%. Further evidence of the efficacy of wP vaccine is provided by the observation that the reported incidence of pertussis disease varies inversely with vaccine acceptance rates. There is no data on the effectiveness of wP vaccines among older age groups since pertussis was previously perceived as a problem only of young children, and the reactogenicity of wP vaccine was thought to be too high to permit routine use in older children, adolescents and adults.

### Duration of Protection

Immunity against all three components has been documented to wane over 6–12 years and hence regular boosting is recommended for all three antigens.

### Adverse Effects

Most adverse effects are due to the pertussis component. Minor adverse effects like pain, swelling and redness at the local site, fever, fussiness, anorexia and vomiting are reported in almost half the vaccinees after any of the three primary doses. Serious adverse effects have been reported with DTWp vaccines but are rare. The frequency of these side effects/1,000 doses is 0.2–4.4 for fever more than 40.5°C, 4–8.8 for persistent crying, 0.06–0.8 for hypotonic hyporesponsive episodes (HHE), 0.16–0.39 for seizures and 0.007 for encephalopathy. The frequency of systemic reactions reduces and that of local reactions increases with increasing number of doses. Children with history of a reaction following vaccination are more likely to experience a reaction following future doses. Catastrophic side effects such as sudden infant death syndrome (SIDS), autism, chronic neurologic damage, infantile spasms, learning disorders and Reye's syndrome were attributed to use of the wP vaccines in the past. It has now been proved beyond doubt that the wP vaccine is not causally associated with any of these adverse events.

### Contraindications and Precautions

Absolute contraindications to any pertussis vaccination (including DTWp vaccine) are history of anaphylaxis or development of encephalopathy within 7 days following previous DTWp vaccination. In case of anaphylaxis, further immunization with any diphtheria/tetanus/pertussis vaccine is contraindicated as it is uncertain which component caused the event. For patients with history of encephalopathy following vaccination, any pertussis vaccine is contraindicated and only diphtheria and tetanus vaccines may be used. Events such as persistent inconsolable crying of more than 3 hours duration/hyperpyrexia (fever >40.5°C)/HHE within 48 hours of DTWp administration and seizures with or without fever within 72 hours of administration of DTWp are considered as precautions but not contraindications to future doses of DTWp because these events generally do not recur with the next dose and they have not been proven to cause permanent sequelae. Progressive/evolving neurological illnesses, is a relative contraindication to first dose of DTWp immunization. However, DTWp can be safely given to children with stable neurologic disorders.

### DTaP VACCINES

Good coverage of DTWp vaccines in developed countries led to remarkable decline in incidence of all the three infections in second half of the last century. With only few cases being reported, the frequent local side effects of the vaccine became increasingly unacceptable to the society leading to decline in coverage of the vaccine in some of the developed countries and resurgence of these infections, especially pertussis. This led to the development of less reactogenic acellular pertussis containing DTaP (*a* for acellular) vaccines starting with Japan in 1981 and then by 1996 in USA.

DTaP vaccines contain at least one of the separately purified antigens PT, FHA, PRN, and fimbrial hemagglutinins 1, 2 and 3 (FIM type 2 and type 3), in addition to diphtheria and tetanus toxoids as

in DTwP vaccines. Although DTaP vaccines contain only a subset of 1–5 antigens, in contrast to DTwP vaccines that contain entire complement of approximately 3,000 antigens, the *concentration* of the antigens in DTaP vaccines is much higher. Hence, while DTwP vaccines can be considered as vaccines with *broad coverage* but low titers, DTaP vaccines have *narrow coverage* but high titers. Among different DTaP vaccines also there is lot of variations. They differ from one another not only in the number and quantity of antigen components, but also with regard to the bacterial clone used for primary antigen production, methods of purification and detoxification, incorporated adjuvants, and the use of preservatives, such as thiomersal. Nearly two dozen DTaP vaccines have been designed and tested, but direct comparison between these products is almost impossible due to several variables listed earlier. Further, the exact contribution of the different aP antigens to protection is not clear and thus there is no consensus as yet about the antigenic composition of an ideal aP vaccine, although it is clear that PT is the most important antigen. Among the DTaP vaccines that are licensed in India, Pentaxim® is 2-component DTaP [in combination with inactivated polio vaccine (IPV) and reconstituted with *Haemophilus influenzae* type b (Hib) conjugate vaccine], Infanrix® is 3-component, while Tripacel® is 5-component DTaP vaccine.

### Efficacy

This is the topic being hotly debated globally in view of outbreaks of pertussis in highly vaccinated countries like USA, Australia, New Zealand and some European countries which have been using DTaP in their national programs for more than a decade. The efficacy trials conducted in Europe and Africa have brought out variable results and are not strictly comparable due to lot of variation between different DTaP vaccines tested, variation in the DTwP products with which former have been compared and variations in case definition used. Moreover, no study has evaluated a multicomponent vaccine directly against versions of itself that contain alternate components or different quantities of each component. Although these limitations have precluded a formal meta-analysis of the efficacy data, a recent Cochrane Review has suggested that the efficacy of multicomponent ( $\geq 3$ ) vaccines varied from 84% to 85% in preventing typical whooping cough (characterized by 21 or more consecutive days of paroxysmal cough with confirmation of *B. pertussis* infection by culture, appropriate serology or contact with a household member who has culture-confirmed pertussis), and from 71% to 78% in preventing mild pertussis disease (characterized by seven or more consecutive days of cough with confirmation of *B. pertussis* infection by culture or appropriate serology). In contrast, the efficacy of one- and two-component vaccines varied from 59% to 75% against typical whooping cough and from 13% to 54% against mild pertussis disease. Multicomponent acellular vaccines are more effective than low-efficacy whole-cell vaccines, but may be less effective than the highest-efficacy whole-cell vaccines.

Recent studies have also suggested that the efficacy of DTaP vaccines is especially low when they are used in primary series of the vaccination. Children *primed* with whole cell pertussis vaccine were better protected from pertussis during the recent outbreaks in comparison to those who received acellular pertussis vaccines throughout. Those who received even one (first dose) of whole cell pertussis vaccine, followed by acellular vaccine in subsequent doses were found to be better protected, and this difference was statistically significant in many studies conducted as a part of retrospective analyses in USA and Australia after the recent outbreaks. Recent analysis of epidemiological data of 54 countries has also clearly demonstrated that there is a statistically significant correlation between use of DTaP vaccine used as the first (priming) dose and resurgence of pertussis in the respective countries in last two decades. Thus, it is being suggested that the immune response to acellular and

whole-cell priming might be different. The lesser protection provided by acellular pertussis vaccines, both as the initial vaccine or full primary course, may be due to *linked epitope suppression*, when the initial exposure locks in the immune response to certain epitopes and inhibits response to other linked epitopes on subsequent exposures. It has also been shown that in contrast to DTwP vaccines that induce immune response with Th1 and Th17 bias, DTaP vaccines induce predominantly Th2 (antibody producing) immune response. This might also be in some way be involved in different *priming* when DTaP vaccine is used as the first dose.

Recent animal studies have also shown that the immune response to currently available DTaP vaccines is much less effective in preventing infection/colonization with *B. pertussis* than current DTwP vaccines. It is also less effective in mucosal clearance of pertussis infection. These two factors make current DTaP vaccines less effective in reducing transmission of infection as compared to currently available DTwP vaccines, even though the difference might be less in preventing pertussis. This *might* be the missing link explaining the recent resurgence/outbreaks.

### Duration of Protection

Data from developed countries suggests that protection after DTaP vaccination wanes after 4–12 years. Similar data from developing countries is lacking as on date.

### Adverse Effects

The incidence of minor adverse effects (pain, swelling and redness at the local site, fever, fussiness, anorexia and vomiting) is about 66% less than with DTwP vaccine, but incidence and severity of local adverse effects increases with each successive dose of DTaP vaccine, as with DTwP vaccines. The incidence of severe adverse effects (persistent crying, hypotonic hyporesponsive episodes, seizures and encephalopathy) is same as with DTwP vaccines. Contraindications and precautions are same as with DTwP vaccines.

### DT VACCINE

This vaccine comprises of diphtheria and tetanus toxoid in similar amounts as in DTwP/DTaP, but lacks the pertussis component totally. It is recommended in children below 7 years of age where pertussis vaccination is contraindicated.

### Td AND Tdap VACCINES

Good coverage with DTP vaccines in a population breaks the transmission cycle and reduces natural circulation of these infections in young children. Moreover, the immunity to all the three infections is known to wane after 6–12 years after last booster (more rapidly with DTaP vaccines). This results in pooling of susceptible adolescents and adults in these populations. Thus, infrequent *natural boosting* and rapid waning of immunity acquired from childhood vaccination increases the incidence of these *childhood infections* (diphtheria and pertussis) in adolescents and adults. Secondly, the partly protected adolescents and adults also act as *reservoirs* as a disease transmission to unvaccinated/partially vaccinated young infants. Third, when childhood vaccination programs break down as happened in the former Soviet Union in the early 1990s, massive outbreaks of diphtheria involving primarily adults have occurred. Recent outbreaks of pertussis in several countries have also affected adolescents majorly. Thus it is desirable to regularly boost adult immunity against diphtheria and pertussis in addition to tetanus every 10 years. In addition, vaccination against diphtheria and tetanus is also needed for catch-up vaccination in unimmunized/partially immunized children. Vaccinating pregnant women with diphtheria and pertussis vaccine (in addition to tetanus) can also protect their newborn babies against these infections before the age



of 6–8 weeks when routine immunization begins. However, DTP vaccines (both DTwP and DTaP) and DT vaccines have increased reactogenicity in older children and are thus not recommended in children above 7 years of age. Thus, tetanus-diphtheria (Td) and tetanus-diphtheria-pertussis (Tdap) vaccines were developed. Td contains the usual dose of TT and only 2 Lf units of diphtheria toxoid (instead of 20–30 Lf in childhood vaccines) and is available in India as SII Td-vac<sup>®</sup>. Tdap vaccines contain standard quantity TT and reduced quantity diphtheria and acellular pertussis vaccine. The two brands available in India are Boosterix<sup>®</sup> and Adacel<sup>®</sup>.

### Efficacy and Effectiveness

Tdap vaccine was licensed first time in May 2005. The coverage of this vaccine in the USA was 40.8% in 2008 which has increased to 84.6% in 2012. Hence, the efficacy and effectiveness data is also limited. This limited data suggests only modest efficacy (in the range of 65–75%) of the pertussis component of Tdap. The preliminary data suggest effectiveness wanes very rapidly (within 3–4 years) among aP vaccine recipients and there was no evidence of herd immunity.

### Adverse Effects

The most common side effect with Tdap is pain at the local injection site in about 70% of vaccinees, followed by other local adverse effects like redness and swelling. Systemic side effects like fever, headache and fatigue are rarely seen. Serious adverse events have not been reported.

### Precautions and Contraindications

The Tdap vaccine needs to be used with caution in following conditions:

- Moderate or severe acute illness;
- History of an Arthus reaction following a previous dose of TT and/or diphtheria toxoid containing vaccine, including meningococcal conjugate vaccine;
- Guillain-Barré syndrome (GBS) within 6 weeks of previous dose of TT containing vaccine; and
- Progressive or unstable neurological disorder or uncontrolled seizures, until these are stabilized with medical therapy.

The contraindications are serious allergic reaction to any component of the vaccine or history of encephalopathy not attributable to an underlying cause within 7 days of administration of a vaccine with pertussis component.

### TT VACCINE

Regular boosting of immunity against tetanus *lifelong* is strongly recommended to remain protected from the ubiquitous bacteria, *Clostridium tetani*. TT was developed as early as 1914 and adsorbed TT was first licensed in USA in 1937. It contains 5 Lf of toxoid with aluminum hydroxide as adjuvant. It is very efficacious vaccine and has helped in near elimination of tetanus in most parts of the world. Tetanus is exceedingly rare in well-immunized individual. The local reactions like local pain, erythema and mild swelling are frequent but serious adverse events are exceedingly rare. Repeated doses at frequent intervals are, however, associated with profound immune complex mediated reactions like swollen limbs and fever (Arthus type 2 reactions).

## RECOMMENDATIONS FOR USE OF ALL DTP VACCINES (DTwP/DTaP/DT/TDaP/Td/TT VACCINES)

### Routine Vaccination

Indian Academy of Pediatrics (IAP) recommends three primary doses of DTP vaccines at 6, 10 and 14 weeks and two boosters at

15–18 months and 4–6 years of age. Only DTwP should be used in primary series. DTaP vaccines may be preferred to wP vaccines only in those children with history of severe adverse effects after previous dose/s of wP vaccines or children with neurologic disorders, if resources permit. The parents should be counseled about the probable efficacy related disadvantages of using aP vaccines for the primary series. In booster doses, DTaP can be considered, considering reactogenicity of DTwP vaccines. However, DTwP is preferable even for booster doses. Whenever DTaP is chosen, the vaccine with at least 3 aP components should be chosen, the more the better. DT vaccine is recommended only when pertussis vaccine is contraindicated. Under Universal Immunization Program (UIP), only DTwP is available with almost similar schedule.

In its latest update of October 2014, IAP has recommended that children who have received the prior doses of DTaP instead of DTwP should be offered DTwP for all subsequent doses. There is no need of repeating or giving additional doses of wP vaccine to boost immunity, as more doses may be associated with a risk of adverse reactions.

Globally, most of the developed countries start routine immunization at 2 months of age. Different countries follow different schedules: either 2, 3, 4 months or 2, 4, 6 months or 2, 3, 5 months schedule for primary series and boosters at 16–18 months and at 4–6 years of age. Some countries like Australia do not recommend booster at 18 months of age.

Tdap vaccine is recommended at 10 years of age by IAP, followed by Td vaccine every 10 years (lifelong). At 10 years of age, Td can replace Tdap vaccine if Tdap is not available or not affordable; TT can be used if Td is also not available. For subsequent doses also, TT can be used if Td is not available. Only TT is available under National Immunization Program of India. TT is to be given at 10 years and 16 years of age under the program.

### Vaccination in Specific Circumstances

#### Catch-up Vaccination

For unimmunized children *below 7 years of age*, three doses of DTwP/DTaP should be used (preferably DTwP) at 0, 1 and 6 months interval. The second childhood booster is not required if the last dose has been given beyond the age of 4 years. It is essential to immunize even those recovering from pertussis as natural disease does not offer complete protection.

For children *above 7 years of age*, the first dose should be of Tdap and subsequent doses of Td vaccine. This is followed by Td vaccine every 10 years. If Td is not available, then TT can be used. These children do not require Tdap vaccine dose at 10 years of age.

For adolescents/adults who have never received Tdap vaccine in past must be given single dose of the vaccine. Tdap can be given regardless of time elapsed since the last vaccine containing TT or diphtheria toxoid.

#### Pregnancy

Classically, TT vaccine has been recommended in pregnancy to protect the newborn from tetanus. For unimmunized pregnant woman, the first dose should be administered at the time of first contact/as early as possible and the second dose of TT should be administered 1 month later and at least 2 weeks before delivery. A single dose of TT would suffice for subsequent pregnancies that occur in the next 5 years; thereafter, 2 doses of TT would again be necessary. The WHO has recommended replacement of TT with Td in a phased manner.

Maternal immunization, particularly of pregnant women, may be an effective approach to protect very young infants and neonates from pertussis also. It has been shown that among several strategies to protect newborns/young infants from pertussis like immunization of pregnant women, postpartum immunization, cocooning and

neonatal immunization, immunization during pregnancy is possibly the best strategy today. Thus, in 2011, the Advisory Committee on Immunization Practices (ACIP) in USA recommended a dose of Tdap to all pregnant women after 20 weeks gestation to provide protection for both the mother and her newborn during the infant's earliest weeks of life. IAP, in its latest guidelines in November 2013 has also recommended immunization of pregnant women with a single dose of Tdap during the third trimester (preferred during 27–36 weeks gestation) regardless of number of years from prior Td or Tdap vaccination. Tdap has to be repeated in every pregnancy irrespective of the status of previous immunization (with Tdap). Even if an adolescent girl who had received Tdap 1 year prior to becoming pregnant will have to take it since there is rapid waning of immunity following pertussis immunization.

However, under UIP only TT vaccine is available as of now.

### Wound Management

All patients presenting with skin wounds/infections should be evaluated for tetanus prophylaxis. Cleaning of the wound, removal of devitalized tissue, irrigation and drainage is important to prevent anaerobic environment which is conducive to tetanus toxin production. The indications for TT and tetanus immunoglobulin (TIG) are given in **Table 1**. Again, replacement of TT with Td/Tdap is recommended.

**Table 1** Tetanus prophylaxis in wound management

	Doses of TT	Clean, minor wounds	All other wounds <sup>#</sup>	Given in past
	TT	TIG*	TT	TIG*
Unknown, < 3 doses, immunodeficient	Yes	Yes	Yes	Yes
≥ 3 doses	No**	No	No***	No

(Source: IAP Guidebook on Immunization, 2013–14.)

Abbreviations: TIG, tetanus immunoglobulin; TT, tetanus toxoid.

<sup>#</sup>Including, but not limited to, wounds contaminated with dirt, feces, soil, saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.

\*TIG: Tetanus immunoglobulin (250–500 IU IM)

\*\*Yes, if more than 10 years since last dose

\*\*\*Yes, if more than 5 years since last dose

### MORE ON THIS TOPIC

- Choudhary SK, Vashishtha VM. Diphtheria, Tetanus and Pertussis. In: Vashishtha VM (Ed). FAQs on Vaccine and Immunization Practices, 1<sup>st</sup> ed. New Delhi: Jaypee Brothers Medical Publishers; 2011. pp. 122–36.
- Diphtheria, Tetanus and pertussis vaccines. In: Vashishtha VM, Choudhury P, Bansal CP (Eds). IAP Guidebook on Immunization 2013–2014. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.
- Edwards KM, Berbers GA. Immune responses to pertussis vaccines and disease. *J Infect Dis*. 2014;209(1):S10–5.
- Edwards KM, Decker MD. Pertussis vaccines. In: Plotkin S, Orenstein W, Offit P, (Eds). Vaccines, 5<sup>th</sup> ed. Philadelphia: Saunders; 2008. pp. 467–517.
- Jackson DW, Rohani P. Perplexities of pertussis: recent global epidemiological trends and their potential causes. *Epidemiol Infect*. 2014;142:672–84.
- Jefferson T, Rudin M, Di Pietrantonj C. Systematic review of the effects of pertussis vaccines in children. *Vaccine*. 2003;21:2003–14.
- Liko J, Robison SG, Cieslak PR. Priming with whole-cell versus acellular pertussis vaccine. *N Engl J Med*. 2013;368:581–2.
- Sheridan SL, Ware RS, Grimwood K, Lambert SB. Number and order of whole cell pertussis vaccines in infancy and disease protection. *JAMA*. 2012;308:454–6.
- Vashishtha VM, Bansal CP, Gupta SG. Pertussis vaccines: position paper of Indian Academy of Pediatrics. *Indian Pediatr*. 2013;50:1001–9.

Vashishtha VM. IAP Textbook of Vaccines. 1<sup>st</sup> ed. New Delhi: Jaypee Brothers Medical Publishers; 2014.

Vashishtha VM, Choudhury P, Kalra A, et al. IAP Recommended Immunization Schedule for Children aged 0–18 years India 2014 and update on immunization. *Indian Pediatr*. 2014;51:785–800.

Warfel JM, Zimmerman LJ, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proc Natl Acad Sci USA*. 2014;111:787–92.

Witt MA, Arias L, Katz PH, et al. Reduced risk of pertussis among persons ever vaccinated with whole cell pertussis vaccine compared to recipients of acellular pertussis vaccines in a large us cohort. *Clin Infect Dis*. 2013;56:1248–54.

World Health Organization (WHO). (2014). Weekly epidemiological record, May 23, 2014. [online] Available from <http://www.who.int/wer/2014/wer8921.pdf?ua=1>. Accessed November 5, 2014.

Zhang L, Prietsch SO, Axelsson I, Halperin SA. Acellular vaccines for preventing whooping cough in children. *Cochrane Database Syst Rev*. 2012;3:CD001478.

### IN A NUTSHELL

1. The morbidity and mortality due to diphtheria, tetanus and pertussis has reduced significantly in India since introduction of the DTwP vaccines in EPI.
2. The overall coverage with primary and booster doses of the DTwP is still quite unsatisfactory.
3. Pertussis incidence is increasing in industrialized countries like US, Australia and many European countries using acellular pertussis vaccines in their national programs.
4. Immunity against all three components has been documented to wane over 6–12 years and hence regular boosting is recommended for all three antigens.
5. DTaP vaccines contain at least one of the separately purified antigens pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbrial hemagglutinins 1, 2 and 3 (FIM type 2 and type 3), in addition to diphtheria and tetanus toxoids as in DTwP vaccines.
6. There is now consensus that aP vaccines are not as efficacious as wP vaccines in providing the *primary induction* and *durability of immune response* (faster waning).
7. The only advantage where aP vaccines score over wP is *safety*, i.e., less reactogenicity.
8. Multicomponent (> 3) aP vaccines are more effective than 1- and 2-component aP vaccines.
9. Most adverse effects of DTP are due to the pertussis component. The mild adverse effects are considerably low with DTaP vaccines than with DTwP vaccines. Serious adverse effects are a rarity even with DTwP vaccines.
10. Absolute contraindications to pertussis vaccination are history of anaphylaxis or development of encephalopathy within 7 days following previous DTP vaccination. These are applicable to DTaP vaccines too.
11. Only DTwP should be used in the primary series. DTaP vaccines may be preferred to DTwP vaccines only in children with history of severe adverse effects after previous dose/s of DTwP vaccines or with neurologic disorders.
12. For booster doses, DTaP can be considered, considering reactogenicity of DTwP vaccines. However, DTwP is preferable even in booster doses.
13. Whenever DTaP is chosen, the vaccine with at least 3 aP components should be chosen, the more the better.
14. Tdap vaccine is recommended at 10 years of age by IAP, followed by Td vaccine every 10 years (lifelong).
15. Maternal immunization, particularly of pregnant women, is an effective approach to protect very young infants and neonates from pertussis.

## Chapter 23.9

# Hepatitis B Vaccine

Ajay Kalra

Prevention of hepatitis B is aimed at preventing chronic carriage of the Hepatitis B virus. Though these carriers are often asymptomatic but are at an increased risk of developing cirrhosis and hepatocellular carcinoma. Carriers can also infect others over long periods of time. Further, chronic infection with hepatitis B virus (HBV) occurs in 80–90% of infants infected perinatally, in 30% of children infected before the age of 6 years; and in less than 5% of infections occurring in adults. Hence universal immunization with this vaccine is important and should begin at the earliest opportunity in life.

## THE VACCINE

The currently available vaccine which contains surface antigens of hepatitis B is a recombinant vaccine derived from the *Sacharomyces cervisiae* yeast and adjuvanted with aluminum salts and lipid A. Both thiomersol preserved and thiomersol free vaccines are available. The vaccines are available as single and multidose vials. They need to be stored at 2–8°C. The single pediatric dose vial of vaccine contains 10 µg of antigen and that for adult use contains 20 µg. Multidose vial contains 20 µg. Vaccines from different internationally reputed manufacturers are immunologically comparable and can be used interchangeably. The vaccine is available as monovalent formulation or in fixed combination with other vaccines such as diphtheria, pertussis (whooping cough), and tetanus (DPT) vaccine.

## Immunogenicity and Efficacy

Serum titers of anti-HBs (more than 10 mIU/mL) are considered as protective. This develops in 95–98% of healthy infants and children who receive a series of three intramuscular (IM) doses. In carefully conducted field trials, efficacy has been estimated to be up to 95%. The recommended series of three IM doses of hepatitis B induces a protective antibody response in more than 90% of healthy adults younger than 40 years of age. After the age of 40 years, the cumulative age-specific decline in immunogenicity drops to less than 90%, and by age 60 years, only 65–70% vaccines develop protective antibody level. Therefore, the earlier the vaccination starts, the better it is. Besides age, other factors, which decrease immunogenicity to hepatitis B vaccination, include obesity, smoking, presence of chronic disease and human immunodeficiency virus (HIV) infection, leukemia in whom the response is as poor as 20–40%. These patients need to be protected by hepatitis B immune globulin (HBIG) prophylaxis. Genetic non-responders and injection given in the gluteal region also elicit decreased immune response.

Some of the nonresponders will respond to doubling the dose like the immune compromised patients or to additional 1–3 doses. Genetic nonresponders will not respond to pure surface antigen vaccine and may respond to experimental vaccines containing preS1/preS2 antigen containing vaccines. Most of the old plasma derived hepatitis B vaccines contained some amount of preS1/preS2 antigens besides the hepatitis B surface antigen (HBsAg). Patients with chronic renal failure have been shown to respond to use of the vaccine along with cytokines like GCSF/GMCSE.

## Duration of Protection

Hepatitis B vaccine has been shown to induce long-term protection for 20 or more years. Although antibody level declines after 15–20 years of age, anamnestic reaction develops after a challenge with HBV and the person develops enough antibodies for protection. Therefore, booster doses are not routinely recommended.

## SCHEDULE OF ROUTINE VACCINATION

Hepatitis B vaccine can be given in any of the following schedules. Immunogenicity of the vaccine is not generally altered, provided at least 1 month interval between the two doses is adhered to.

- Birth, 1 and 6 months
- Birth, 6 and 14 weeks
- 6, 10 and 14 weeks [followed in Universal Immunization Program (UIP), India]
- Birth, 6 weeks, 6 months
- Birth, 6 weeks, 10 weeks, 14 weeks (followed in UIP, India for institutional births)

Three doses are recommended in all the schedules. The classical schedule is 0, 1 and 6 months. The dose is 10 µg for children less than 10 years and 20 µg for children above 10 years age or adults. Seroconversion rates are more than 90% after a three-dose schedule. Since seroconversion rates are lower in the elderly, the immunocompromised and those with renal failure, a four-dose schedule of 0, 1, 2 and 12 months of double dose is needed in these patients. While routine boosters are not needed in healthy children and adults, these may be needed in the immunocompromised children and those with chronic renal disease, whenever the anti HBsAg levels drop below the protective levels.

It is preferable to start vaccination within 12 hours of birth especially as routine antenatal screening for HBsAg is not practiced in India. Any schedule starting at 6 weeks age [tailored to be stitched with the other expanded program on immunization (EPI) vaccine starting at this age] carries the disadvantage of not preventing vertical transmission which is responsible for 18–40% of chronic cases in India. When used to conform to schedules for other childhood vaccines, the third dose should have a minimum gap of 8 weeks after the second dose and at least 16 weeks after the first dose. For infants, it should be at least 24 weeks of age.

The route of vaccination is intramuscular. The site of vaccination is anterolateral thigh in neonates and infants; deltoid in children and adults. Vaccination given by any other route than intramuscular or any other site than anterolateral part of thigh or deltoid should not be considered as valid. Intradermal administration of hepatitis B vaccine reduces the cost tremendously as the dose consists of 0.1 mL. But it has not been found to result in protective antibody titers in all recipients.

## Catch-up Vaccination

Catch-up vaccination with hepatitis B vaccine in a 0, 1, 6 months schedule should be offered to all children/adolescents who have not been previously vaccinated with hepatitis B vaccine. Prevacination screening with anti HBsAg antibody is not cost-effective and is not recommended. Catch-up vaccination is particularly important for contacts of HBsAg positive patient. Prevacination screening for HBsAg should be done in these contacts. If there is a gap of up to 6 months between the first and second dose or a gap of up to 1 year between second and third dose, there is no need to restart vaccination. Complete the remaining doses as per the original schedule. However, such delays are not desirable, as the person remains unprotected till the schedule is completed.

## Adolescent Vaccination

Routine hepatitis B vaccination is recommended for all children through age 18 years. All children not previously vaccinated with hepatitis B should be vaccinated at 11 years or 12 years age with 20 µg. The usual schedule for adolescents is 0–1–6 months. If an accelerated schedule is needed, the minimum interval between the second and third doses should be 8 weeks, but the first and third dose should be separated by at least 16 weeks.



## Reasons for Vaccine Failure

Improper storage of vaccine and failure to maintain cold chain are the most important causes of vaccine failure. Immuno-compromised individuals (those on chemotherapy etc.) may also fail to respond. Surface mutants of HBV may be able to cause infection even in vaccinated children. In addition, there are individuals who do not respond to the vaccine for no apparent reason. However, half of the people who do not develop anti-HBs antibodies after a three-dose series will do so after additional dose(s).

## Adverse Effects and Contraindications

Adverse effects of hepatitis B vaccine consist primarily of local reactions or low-grade fever. Serious reactions like anaphylaxis are very rare but can occur as with any other vaccine.

Persons with a history of serious adverse events, including anaphylaxis, after receipt of hepatitis B vaccine should not receive additional doses. As with other vaccines, vaccination of persons with moderate or severe acute illness, with or without fever, should be deferred until the illness improves. Vaccination is not contraindicated in persons with a history of multiple sclerosis, Guillain-Barré syndrome, or autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis.

## Special Situations

### *Schedule for Immunocompromised Children*

These include advanced HIV infection, chronic renal failure, chronic liver disease, celiac disease and diabetes. It is estimated that 10% of the 40 million people infected HIV infection worldwide are coinfecting with HBV; the presence of HIV markedly increases the risk of developing HBV associated liver cirrhosis and hepatocellular carcinoma. This increase risk for developing chronic HBV may because of enhanced viral replication and ineffective immune clearance.

In immunocompromised hosts double the recommended dose for that age should be used. They may also require additional doses in case they do not show seroconversion following three doses. In situations where early seroconversion is required, one may use accelerated schedule of doses at 0, 1, 2 and 12 months. Despite this, it has been shown that not more than 30% of children with leukemia undergoing chemotherapy show seroconversion. In such cases, it may be better to use regular passive prophylaxis with HBIG. For hemodialysis patients the need for booster doses should be assessed by annual testing for antibody levels and booster doses should be provided when antibody levels decline below 10 mIU/mL.

### *Vaccination in Preterm and Low Birthweight Infants*

Preterm infants born to HBsAg positive women and women with unknown status must receive immunoprophylaxis with hepatitis B vaccine and HBIG beginning at shortly after birth. Preterm infants with birth weight less than 2,000 g have a decreased response to hepatitis B vaccine administered before 1 month of age. However, by chronological age 1 month, preterm infants, regardless of initial birth weight or gestational age, are likely to respond as adequately as full terms infants. Since the HBsAg status of most mothers is usually not known in our country, it is advisable to give the vaccine as recommended above within 12 hours. The next dose given at 1 month age will take care of the immunological incompetence if any of the preterm baby.

## Post-vaccination Testing

Routine post-vaccination testing for immunity is not necessary. It may be done in infants born to HBsAg positive mothers; chronic hemodialysis patients, children infected with HIV, immunocompromised patients, and those occupationally at risk. Testing should be done 1-2 months after administration of last

dose of vaccine using a method that allows for determination of a protective concentration of anti-HBs ( $\geq 10$  mIU/mL).

## HEPATITIS B VIRUS MUTANTS

As compared to other deoxyribonucleic acid (DNA) viruses, the HBV has a higher frequency of mutations. This is because the virus replicates via a ribonucleic acid (RNA) intermediate where the reverse transcriptase appears without a proof reading function. Mutations have been most well recognized in the pre-C/C gene, the polymerase gene and the pre S/S gene. While the Pre-C/C gene mutants are associated with fulminant hepatitis and severe chronic liver disease and the polymerase gene mutants with resistance to treatment with nucleoside analogs, the S gene mutants (surface mutants) are important from the vaccination point of view. The "a" domain containing 124-127 amino acids is major determinant of immune response. The HBV mutates at the 145 amino acid of the surface antigen, which is a very important site for the epitope and recognition by the anti-HBsAg antibody. These mutants might allow replication of HBV in the presence of vaccine induced anti-HBs or anti-HBs contained in the HBIG. Hence they are also called vaccine escape mutant. Also, these mutants may escape being detected in the blood bank testing. It is feared that high hepatitis B vaccination may lead to high level of surface mutant virus and replacement of the wild virus with the surface mutant virus may be in over a long period of time.

## HEPATITIS B IMMUNE GLOBULIN

Hepatitis B immune globulin provides immediate passive immunity and is recommended in situations where there has been acute exposure to HBsAg positive blood. HBIG does not interfere with the development of antibody response to hepatitis B vaccine and hence a person with accidental exposure should be given combined passive-active immunization. The dose in children is 32-48 IU/kg body weight. This should be administered within 7 days (preferably within 48 hours) of exposure. Postexposure prophylaxis with HBIG is recommended for newborn babies born to HBsAg positive mothers. 100-200 IU should be administered within 5 days (preferably within 24 hours). Another dose may be repeated after 2-3 months.

Postexposure prophylaxis with HBIG is also recommended for health personnel who suffer from accidental needle stick injury and for patients who receive HBsAg positive blood inadvertently. Pre-exposure passive prophylaxis with HBIG is needed for individuals failing to respond to vaccine (e.g., immunocompromised children), or in children with disorders that preclude a response (e.g., agammaglobulinemia), when they are likely to be exposed to the risk of acquiring HBV infection.

### *Postexposure Prophylaxis to Prevent Hepatitis B Infection*

*Prevention of perinatal HBV infection* In India where routine HBsAg screening is not possible, all infants born should be vaccinated within 12-24 hours of birth. In definitive situations where an infant is born to HBsAg positive mother, it should receive three doses of hepatitis B vaccines, first dose starting at birth (preferably within 12 hours) and then as per National guidelines. The baby also should receive HBIG 0.5 mL intramuscularly concurrently at different site along with the first dose at birth. In situations where HBIG could not be administered, hepatitis B vaccine alone has been found to be protective in over 90% cases. The cases are to be followed-up strictly for vaccination compliance and at 9-15 months of age anti-HBs and HBsAg titer should be determined. Infants found to be negative for anti-HBs should be revaccinated with complete schedule of three doses.



**Prevention in accidental percutaneous/permucosal exposure to blood** After a percutaneous (needle site, laceration, bite) or permucosal (ocular, mucous membrane) exposure to blood that contains or might contain HBV, obtain a blood sample from the source person to determine the HBsAg status. The vaccination and anti-HBs status of the exposed person is reviewed. **Table 1** depicts the postexposure prophylaxis regimen. The dose of HBIG is 0.06 mL/kg intramuscularly given as 1–2 doses.

## High-risk Approach vs. Universal Immunization Approach for Prevention of HBV Infection

Considering the high cost of vaccination, initially high-risk approach was followed. However, these failed to have any impact on the size of carrier pool in the population. Universal immunization targets every newborn, child and adult, thereby eliminating all modes of transmission. It also raises the possibility of ultimate eradication of this dreaded virus, as humans are the only reservoirs.

**Table 1** US Centers for Disease Control and Prevention (CDC) recommendations for postexposure prophylaxis against hepatitis B

Vaccination and antibody response status of exposed persons <sup>1</sup>	Treatment			
	Source is HBsAg positive	Source is HBsAg negative	Source is unknown or not tested	
			High-risk	Low-risk
Unvaccinated	HBIG <sup>2</sup> (1 dose) and begin a hepatitis B vaccine series	Begin a hepatitis B vaccine series	Begin a hepatitis B vaccine series	Begin a hepatitis B vaccine series
Known responder <sup>3</sup>	No treatment	No treatment	No treatment	No treatment
Not revaccinated	HBIG (1 dose) and begin a revaccination series	Begin a revaccination series	HBIG (1 dose) and begin a revaccination series	Begin a revaccination series B vaccine series
After revaccination <sup>4</sup>	HBIG (2 doses) <sup>5</sup>	No treatment	HBIG (2 doses) <sup>5</sup>	No treatment
Antibody response unknown	Test for anti-HBs <sup>6</sup> . If adequate <sup>3</sup> no treatment; if inadequate, HBIG x1 and vaccine booster	No treatment	Test for anti-HBs <sup>6</sup> ; If adequate <sup>3</sup> , no treatment, If inadequate, give vaccine booster and check anti-HBs in 1–2 months	

**Abbreviations:** HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immune globulin.

**Note:**

1. Person known to have has HBV infection in the past or who are chronically infected do not require HBIG or vaccine.
2. Hepatitis B immune globulin (0.06 mL/kg) administered IM.
3. Adequate response is anti-HBs of at least 10 mIU/mL after vaccination.
4. Revaccination—additional three-dose series of hepatitis B vaccine administered after the primary series.
5. First dose as soon as possible after exposure and the second dose 1 month later.
6. Testing should be done as soon as possible after exposure.

**Source:** The table is adapted from "Updated US PHS Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis." MMWR. 2001;50(RR-11):1-67.

## MORE ON THIS TOPIC

- Beasley RP, Hwang LY, Lee GCY, et al. Prevention of perinatally transmitted Hepatitis B virus infections with hepatitis B immunoglobulin and hepatitis B vaccine. *Lancet*. 1983;2:1099-102.
- Damme PV, Ward J, Daniel Shouval D, et al. Hepatitis B vaccines. In: Plotkin SA, Orenstein WA, Offit PA (Eds). *Vaccines*. 6th ed. Philadelphia: Saunders Elsevier; 2013. pp. 205-34.
- Dutta AK. Immunization against Hepatitis B. In: Thacker N, Shah NK (Eds). *Immunization in Clinical Practice*. New Delhi: Jaypee Brothers Medical Publishers; 2005. pp. 109-18.
- Goldfarb J, Baley J, Medendorp SV, et al. Comparative study of the immunogenicity and safety of 5 microgram and 10 microgram dosage of recombinant hepatitis B vaccine in healthy children. *Pediatr Infect Dis J*. 1996;15:768-77.
- Gomber S, Sharma R, Ramachandran VG, et al. Immunogenicity of Hepatitis B vaccine incorporated into Expanded Program of immunization schedule. *Indian Pediatr*. 2000;37:411-13.
- Kumar TS, Abraham P, Raghuramana S, Cherian T. Immunogenicity of indigenous recombinant Hepatitis B vaccine in infants following 0, 1, 2 month vaccination schedule. *Indian Pediatr*. 2000;37:75-80.
- Mittal SK, Rao S, Kumari S, et al. Simultaneous administration of Hepatitis B vaccine with other EPI vaccine. *Indian J Pediatr*. 1994;61:183-8.
- US Centers for Disease Control and Prevention. Hepatitis B. In: *Atkinsons W, Wolfe S, Hamborsky J (Eds). Epidemiology and Prevention of Vaccine Preventable Diseases*. 12th ed. Washington DC: Centre for Diseases Control and Prevention; 2013. pp. 115-38.

Vashishtha VM, Choudhury P, Bansal CP, et al. IAP Guidebook on Immunization 2013–2014. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.

World Health Organization. WHO position paper on Hepatitis B. *Wkly Epidemiol Rec*. 2009;84:405-20.

## IN A NUTSHELL

1. Prevention of hepatitis B is necessary to prevent chronic carrier stage. Therefore, it should begin at the earliest opportunity of life, i.e., within 24 hours of birth.
2. Hepatitis B vaccine has been shown to give long-term protection for more than 20 years.
3. Booster doses are not recommended.
4. Different vaccination schedules have at least three doses, all having a comparable excellent immunogenicity.
5. The classical schedule is 0, 1 and 6 months giving seroconversion rate of more than 90%. The National Program of Immunization in India recommends three doses at 6, 10, 14 weeks with an additional zero dose at birth for institutional deliveries.
6. In immunocompromised hosts, the recommended dose is double the one for that age and an additional dose may also be required.
7. Adverse effects of the hepatitis B vaccine are very rare.

## Chapter 23.10

# *Haemophilus Influenzae*

## Type B (HIB) Vaccines

AK Patwari

*Haemophilus influenzae* type b (Hib), one of the six serotypes of capsulated *H. influenzae*, is an important invasive pathogen causing diseases such as meningitis, bacteremia, pneumonia, cellulitis, osteomyelitis, septic arthritis and epiglottitis. Most of the invasive Hib disease occurs in children in the first 2 years of life before natural protective immunity is acquired by the age of 3–4 years. Noncapsulated Hib disease causing bronchitis, otitis media, sinusitis and pneumonia is not amenable to prevention at present and can occur at all ages.

### HIB POLYSACCHARIDE VACCINE

*Haemophilus influenzae* type b capsular polysaccharide polyribosylribitol phosphate (PRP) was the first Hib vaccine to be developed. Earlier PRP vaccine studies demonstrated good immunogenicity in older children but limited immune response in young children. Efficacy studies suggested that the vaccine has waning protection over time and does not induce good immunological memory. The vaccine was introduced in United States as a single dose at 24 months in all children or at 18 months in children at high risk of invasive Hib disease. The vaccine was found to be safe, with few serious side effects. However, with the development of Hib conjugated vaccines, the use of Hib-PRP vaccine was discontinued.

### HIB CONJUGATE VACCINES

*Haemophilus influenzae* type b conjugate vaccines (Hib-CVs) have been developed during last two decades to improve the immune response in young children and to provide better memory response. These vaccines have conjugated PRP to diphtheria toxoid (PRP-D), the outer membrane protein group B *Neisseria meningitidis* (PRP-OMP), tetanus toxoid (PRP-T), and a nontoxic mutant diphtheria toxin (HbOC). HbOC and PRP-T vaccines show only a marginal increase in antibody levels after the first dose with a marked increase after the second dose and even better response after the third dose. On the other hand, PRP-OMP shows an increase in antibody level after the first dose itself with only marginal increases after the second and third doses. The onset of protection with PRP-OMP is thus faster. Additionally, while three doses of HbOC and PRP-T are recommended for primary vaccination, only two doses of PRP-OMP are recommended for this purpose. Hib-CV has been found to be highly immunogenic in Indian children.

### Immunogenicity

Efficacy trials have demonstrated 90–100% efficacy against culture proven invasive Hib disease for 1 year after vaccination. A trial in Gambian infants has shown 21% protection against episodes of severe pneumonia. The serologic correlate of protection at the time of exposure has been fixed at 0.15 µg/mL and that for long-term protection as 1 µg/mL. Even though immunological responses of these vaccines after each immunization have been reported to be variable in different population studies, the mean geometric concentration of anti-PRP antibodies in the children studied after three doses was greater than 1.0 µg/mL, the titer necessary for long-term protection, regardless of the formulation.

Indirect protection to the unimmunized susceptible children as a result of diminished Hib transmission (~50% of children exhibited anti-PRP titers  $\geq 5.0$  µg/mL; a level that impedes Hib upper respiratory carriage) has also been observed while conducting serological assessment of the Hib immunization program. Only HbOC and PRP-T are currently available in India. The vaccines should be stored at 2–8°C and the recommended dose is 0.5 mL intramuscularly.

### COMBINATION VACCINES

Over the years the combination of multiple vaccines into a single product has been a major advancement in improving compliance and protecting children from vaccine preventable diseases (VPDs). Hib vaccines have also been successfully produced as combination vaccines with diphtheria, tetanus, whole cell pertussis (DTwP) and hepatitis B (Hep B) antigen. These vaccines have been found to be as safe and effective as their noncombination counterparts. Side effects are mild and usually local.

### CURRENT STATUS OF HIB VACCINES

Developed countries where Hib vaccine was introduced for universal immunization have witnessed virtual elimination in Hib disease with no serotype replacement. The vaccine has also been shown to impart herd protection by reducing nasopharyngeal carriage. A notable exception in the Hib success story was an increased incidence of Hib disease in vaccinated children between the years 1999 and 2003 in the UK occurring after a remarkable initial decline in Hib disease in the early 1990s. Most of the cases of invasive Hib disease occurred in the late 2nd year of life. The major factor responsible for this phenomenon was omission of the 2nd year booster.

Hib vaccine induced immunity wanes overtime and reduced carriage of the organism in the environment compounds the problem by lack of natural boosting. It is also recognized now that immunological memory is insufficient for protection against Hib disease. Hence a booster dose is mandatory for sustained protection. Primary immunization with either pentavalent vaccine is reported to induce an excellent immunity lasting till the 2nd year of life. A booster dose with DTwP-Hib vaccine effectuated a good anamnestic response to all vaccine components, being especially strong for Hib in children previously vaccinated with pentavalent vaccine.

### Safety of Hib Vaccines

In India, after Hib vaccine was introduced in office practice of pediatricians for over a decade, 42% pediatricians ever observed any side effects or adverse event following immunization (AEFI). A meta-analysis of Hib combination vaccines found no increase in serious side effects when the Hib-combination vaccines was given as part of a combination or separately. However, a slight but significant increase in number of minor side effects like redness and pain at the injection site have been observed with combination vaccines as compared to separate vaccines. Based on the available data from Indian studies on vaccine safety, National Technical Advisory Group on Immunization (NTAGI) in India has concluded that the vaccine is safe and efficacious.

### RECOMMENDATIONS FOR USE

Hib-PRP conjugate vaccines are recommended as a separately administered vaccine or given as a part of combination vaccines to protect children from Hib disease. Different formulations of Hib-combination vaccines have been reported to have similar efficacy: HbOC (95–100%), PRP-OMP (95% in one study), PRP-T (88–100%). The only exception is PRP-D which has a wide variability in

efficacy ranging from 35% to 94% depending upon the population in which it was studied. Assessment of relative efficacy of one or the other Hib-combination vaccines and impact of any single vaccine has been difficult to ascertain because more than one Hib-combination vaccines has been used in many countries. However, the overall high reduction in the proportion of disease across countries suggests that the formulations of Hib vaccine currently in use provide excellent protection against invasive Hib disease.

The Government of India initially introduced pentavalent vaccine in the Universal Immunization Program (UIP) schedule in Tamil Nadu and Kerala and later on seven more states have included it in their immunization programs. It is hoped that with increasing awareness regarding the need for protection against Hib and safety of pentavalent vaccine other states will follow.

### Schedule and Doses

The vaccination schedule for Hib consists of three doses when initiated below 6 months, two doses between 6 months and 12 months and one dose between 12 months and 15 months, with a

booster at 18 months. For children aged more than 15 months a single dose may suffice. The interval between two doses should be at least 4 weeks. As Hib disease is essentially confined to infants and young children, catch-up vaccination is not recommended for healthy children above 5 years. However, the vaccine should be administered to all individuals with functional/anatomic hyposplenism irrespective of age.

Hib vaccines are now used mostly as combination vaccines with DTwP/DTaP/Hep B/IPV. Pentavalent vaccine introduced in India contains DTwP, Hep B and Hib, and is recommended to be given as per the schedule of DTP immunization in UIP. Indian Academy of Pediatrics (IAP) recommends three doses of Hib vaccine at 6, 10 and 14 weeks of age and a booster between 12 months and 18 months.

### Catch-up Vaccination for Hib Vaccines

When infants and children under-5 years of age have missed scheduled vaccine doses or start of Hib vaccination has been delayed, a catch-up schedule should be commenced (**Table 1**).

**Table 1** Recommended catch-up schedule when start of *Haemophilus influenzae* type b (Hib) vaccination has been delayed

Vaccine	Trade name	Age now			
		3–6 months	7–11 months	12–14 months	15–59 months
PRP-OMP <sup>1,2</sup> Hib (PRP-OMP)-hepB	PedvaxHIB Comvax	2 doses, 1–2 months apart and booster at 12 months	2 doses, 1–2 months apart and booster at least 2 months later, at 12–15 months	1 dose, and booster at least 2 months after previous dose <sup>4</sup>	Single dose <sup>3,4</sup>
HbOC <sup>3</sup> PRP-T <sup>3</sup>	HibTITER Hiberix ActHIB	3 doses, 2 months apart, and booster at 12 months	2 doses, 2 months apart, and booster at 12 months and at least 2 months after previous dose	1 dose, and booster at 18 months	Single dose <sup>3,4</sup>

<sup>1</sup> Extremely preterm babies (<28 weeks or <1,500 grams) who commence catch-up Hib vaccination with PRP-OMP between 3 months and 11 months of age require a 3-dose primary series (not 2 doses). The third dose should be given 1–2 months after the second dose of PRP-OMP. The booster dose should be given at 12 months as usual.

<sup>2</sup> Where possible, use the same brand of Hib vaccine throughout the primary course.

<sup>3</sup> When a booster is given after the age of 15 months, any of the 3 available conjugate Hib vaccines can be used.

<sup>4</sup> Depending on the combination used, further doses of hepatitis B or IPV are required.

Abbreviation: IPV, inactivated polio vaccine.

### MORE ON THIS TOPIC

- Bar-On ES, Goldberg E, Fraser A, et al. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis. Hepatitis B and *Haemophilus influenzae* B (HIB). Cochrane Database Syst Rev. 2009;3:CD005530.
- Gupta M, Prinja S, Kumar R, Kaur M. Cost-effectiveness of *Haemophilus influenzae* type b (Hib) vaccine introduction in the universal immunization schedule in Haryana State, India. Health Policy Plan. 2013;28:51–61.
- Hutter J, Pasetti MF, Sanogo D, et al. Naturally acquired and conjugate vaccine-induced antibody to *Haemophilus influenzae* type b (Hib) polysaccharide in Malian children: serological assessment of the Hib immunization program in Mali. Am J Trop Med Hyg. 2012;86:1026–31.
- Invasive Bacterial Infections Surveillance (IBIS) Group of the International Clinical Epidemiology Network. Are *Haemophilus influenzae* infections a significant problem in India? A prospective study and review. Clin Infect Dis. 2002;34:949–57.
- NTAGI Subcommittee Recommendation on *Haemophilus influenzae* type b (Hib) introduction in India. Indian Pediatr. 2009;46:945–54.
- Sharma H, Yadav S, Lalwani S, et al. Antibody persistence of two pentavalent DTwP-HB-Hib vaccines to the age of 15–18 months, and response to the booster dose of quadrivalent DTwP-Hib vaccine. Vaccine. 2013;31:444–7.
- Vashishtha VM. IAP recommended immunization schedule for children 0–18 years (with range), 2013. IAP Textbook of Vaccines. 1<sup>st</sup> ed, New Delhi: Jaypee Brothers Medical Publishers; 2014. pp. 610–7.
- Walker CL, Rudan I, Liu L, et al. Global burden of childhood pneumonia and diarrhea. Lancet. 2013;381:1405–16.
- World Health Organization. WHO Position Paper on *Haemophilus influenzae* type b conjugate vaccines. Wkly Epidemiol Rec. 2006;81:445–52.

### IN A NUTSHELL

- Most of invasive Hib disease occurs in children in the first 2 years of life before natural protective immunity is acquired.
- H. influenzae*, causes many invasive diseases such as meningitis, bacteremia, pneumonia, cellulitis, osteomyelitis, septic arthritis and epiglottitis.
- In India, the burden of Hib disease is underestimated owing to lack of culture facilities, and difficulty to grow organism on usual culture media. Nevertheless, the burden is sufficiently high to warrant prevention by vaccination.
- Highly safe and efficacious Hib-conjugate vaccines, PRP-T and HbOC are available in India. Efficacy trials have demonstrated 90–100% efficacy against culture proven invasive Hib disease for 1 year after vaccination.
- Hib vaccines are also available as combination vaccines with diphtheria, tetanus, whole cell pertussis (DTwP), acellular pertussis (DTaP), IPV and hepatitis B (Hep B) antigen.
- Indian Academy of Pediatrics (IAP) recommends three doses of Hib vaccine at 6, 10 and 14 weeks of age and a booster between 12 months and 18 months. A booster dose of Hib vaccine is mandatory for sustained protection.
- Catch-up vaccination with Hib vaccine is recommended till 5 years of age.

## Chapter 23.11

# Measles Vaccine

Sumit Mehndiratta, AP Dubey

Measles vaccine is a part of Universal Immunization Program (UIP) of India. Most measles vaccines use the derivative of original strain (Edmonston) isolated in 1954 which include Schwartz, Edmonston-Zagreb, Edmonston-B, AIK-C and Moraten strains. Following measles vaccines are available: (1) monovalent measles vaccine; and (2) combination vaccines—measles containing vaccine (MCV): MR (measles, rubella), MMR (measles, mumps, rubella), MMRV (measles, mumps, rubella, varicella).

## ROUTINE IMMUNIZATION

Measles vaccine is a live attenuated vaccine with each dose (0.5 mL) containing at least 1,000 infective units (TCID<sub>50</sub>). It is available in a frozen state in single dose and multidose vials. The vaccine is administered subcutaneous/intramuscularly in upper arm/ anterolateral part of thigh. Strain used in India is usually formulated from Edmonston-Zagreb strain grown on human diploid cells or purified chick embryo cells. The vaccine is to be reconstituted with the diluent provided. It is kept at 2–8°C and away from light. It has to be used within 4–6 hours of reconstitution as it does not contain any preservatives. Hence, there are chances of bacterial contamination (*Staphylococcus*) and development of toxic shock syndrome (TSS) due to its exotoxin.

As per National immunization schedule, the measles vaccine (MCV) is administered at 9 months or 270 completed days. But in case of an outbreak, as per Indian Academy of Pediatrics (IAP) recommendation, the vaccine can be administered to children aged 6–11 months. However, these children should be revaccinated with two doses of MCVs, the first at ages 12–15 months and at least 4 weeks after the previous dose, and the second at ages 4–6 years.

## Vaccine Failure

Primary vaccine failure rate is around 15%. Therefore, a second dose of measles vaccine is recommended by National Technical Advisory Group on Immunization (NTAGI). Secondary vaccine failure is rare.

## Contraindications

Severe immunocompromised conditions; past history of severe allergic reaction to vaccine; and pregnancy.

## Adverse Reactions

Mild pain and tenderness at injection site; fever (>103°F in 5–15% recipients between 7th and 12th day); febrile seizures; transient rash (in 5% recipients between 7th and 10th day and lasts 1–3 days); thrombocytopenic purpura; depression of cell mediated immunity; rarely anaphylactic reactions (1 case per 3.5 million doses); encephalitis (1 case per million doses); and toxic shock syndrome (TSS) due to staphylococcal contamination.

## Immune Responses

The vaccine induces both humoral and cellular immune response just like the natural infection. Measles virus-specific antibodies and the circulation of measles virus-specific CD4+ and CD8+ T lymphocytes confer protection against disease. Due to interference from passively transmitted antibodies from mother, the rates differ according to age. It is around 80–85% when administered at 9 months of age. The antibodies develop in around 98% cases of children immunized at 15 months of age. The immunity

is long lasting. The immunogenicity of vaccine is lower in immunocompromised states.

## Second Dose of Measles Containing Vaccine

In India, the overall vaccine coverage is around 70%. Assuming 85% effectiveness, there is buildup of substantial number of susceptible children over a period of time. With an annual birth cohort of 26 million children in India, every 2–3 years the population of susceptible children reaches epidemic threshold. Thus the rationality for providing second opportunity for measles vaccination is two-fold. Firstly, it will cover the primary vaccine failures, and secondly, it will cover those children who missed the first dose of routine immunization. The NTAGI has recommended the implementation strategy of second dose of measles containing vaccine (MCV2) at the state level on the basis of the underlying performance of the routine immunization (RI) program.

In total, 14 states with measles coverage less than 80% (Arunachal Pradesh, Assam, Bihar, Chhattisgarh, Gujarat, Haryana, Jharkhand, Madhya Pradesh, Manipur, Meghalaya, Nagaland, Rajasthan, Tripura and Uttar Pradesh) will introduce MCV2 through catch-up vaccination campaigns. In the remaining 21 states with better performing routine immunization systems (i.e., 80% routine measles coverage), 17 states will introduce MCV2 for children aged 16–24 months through the routine program. The remaining four states and union territories (Delhi, Goa, Puducherry and Sikkim) already use a second dose of measles vaccine in their RI program (as mumps-measles-rubella vaccine) financed with state resources.

## IMMUNIZATION IN SPECIAL CIRCUMSTANCES

- *Asymptomatic human immunodeficiency virus (HIV) infected children:* Yes (at 9 months age).
- *Symptomatic HIV infected children:* Yes (at 9 months age if CD4 count >15%).
- *Patients who have received corticosteroids—prednisolone 2 mg/kg/day or its equivalent for more than 14 days should not be administered measles vaccine for 1 month.*
- *Children with congenital immunodeficiency:* Vaccine can be given but will be ineffective due to concomitant immunoglobulin therapy.
- *The children with severe egg allergy* can be safely given Measles vaccine.
- *The children who had received antibody containing products* like whole blood, packed red cells, plasma, and immunoglobulin should not be given live attenuated vaccines and these products should be avoided for at least 2 weeks after receipt of these vaccines.

## IAP RECOMMENDATIONS ON MEASLES VACCINATION

- The first dose of vaccine is to be administered at 9 months (270 days) completed age.
- In view of the fact that around 15% cases of primary vaccine failure, an additional dose of MCV preferably MMR should be administered at 15 months age.
- The second dose of MMR (third dose of MCV) at 4–6 years of age, just before school entry. The second dose of MMR can be given at any time 4–8 weeks after the first dose.
- Catch-up vaccination beyond 12 months should be with MMR. Recent (2014) recommendations of IAP have substituted stand-alone measles vaccine with MMR at 9 months. The MCV2 would also be MMR at 15 months. The second dose of MMR at 4–6 years of age has been scrapped. This revision is influenced by Government of India's proposal to introduce MR vaccine at 9 and 16–24 months of age in its UIP schedule.



## PASSIVE IMMUNIZATION

Infants are protected by transplacental transfer of maternal antibodies up to 6 months of age, but in some cases the immunity may persist for 9 months. Measles immunoglobulin (Human) can be administered to prevent measles but it is only effective when administered in early incubation period (within 6 days of exposure). The recommended dose is 0.25 mL/kg (0.5 mL/kg in immunocompromised subjects). Maximum dose is 15 mL. It can be used for prevention of disease in infants and immunodeficient contacts of acute cases.

## GLOBAL MEASLES AND RUBELLA INITIATIVE

Measles vaccination coverage has been selected as an indicator of progress towards achieving Millennium Development Goal 4 (MDG-4 goal). It is a joint effort of WHO, United Nations Children's Fund (UNICEF), the American Red Cross, the United States Centers for Disease Control and Prevention, and the United Nations Foundation to support countries to achieve measles and rubella control goals. Since the year 2000, with support from this effort over 1 billion children all over the world have been reached through mass vaccination campaigns. The goals of this initiative are that by the end of 2015, global measles death to be reduced by 95% as compared to 2000 levels. Further, by 2020, the goal is to achieve measles and rubella elimination in at least five WHO regions.

WHO recommends that every child receive two doses of measles vaccine. The World Health Assembly in the year 2010 established three milestones towards the future eradication of measles, to be achieved by the year 2015:

- Increase routine coverage with the first dose of measles-containing vaccine (MCV1) for children aged 1 year to more than or equal to 90% nationally and more than or equal to 80% in every district or equivalent administrative unit;
- Reduce and maintain annual measles incidence to less than 5 cases per million; and
- Reduce estimated measles mortality by more than 95% from the 2000 estimate.

## MORE ON THIS TOPIC

American Academy of Pediatrics. Measles. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS (Eds). Red Book 2012 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2012. pp. 489-99.

Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet*. 2010;375:1969-87.

Gupta SK, Sosler S, Haldar P, et al. Introduction strategy of a second dose measles containing vaccine in India. *Indian Pediatr*. 2011;48:379-82.

John TJ, Choudhury P. Accelerating measles control in India: opportunity and obligation to act now. *Indian Pediatr*. 2009;46:1-5.

Strebel PM, Papania MJ, Dayan GH, Halsey NA. Measles vaccine. In: Plotkin S, Orenstein W, Offit P (Eds). *Vaccines*. 5<sup>th</sup> ed. Philadelphia: Saunders; 2008.

Sudfeld CR, Halsey NA. Measles case fatality ratio in India: a review of community based studies. *Indian Pediatr*. 2009;46:983-9.

United Nations. Millennium Development Goals, Goal 4. Reduce Child Mortality. [online] From <http://www.un.org/millenniumgoals/childhealth.html>. Accessed November 3, 2014.

Vashishtha VM, Choudhury P, Bansal CP, et al. IAP Guidebook on Immunization 2013-2014. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.

Vashishtha VM, Choudhury P, Bansal CP, Gupta SG. Measles control strategies in India: Position paper of Indian Academy of Pediatrics. *Indian Pediatr*. 2013;50:561-4.

Vashishtha VM, Kalra A, Bose A, et al. Indian Academy of Pediatrics (IAP) recommended immunization schedule for children aged 0 through 18 years- India 2013 and updates on immunization. *Indian Pediatr*. 2013;50:1095-108.

World Health Organization. (2012). Global Measles and Rubella. Strategic Plan 2012–2020. [online] From: [http://www.who.int/immunization/newsroom/Measles\\_Rubella\\_StrategicPlan\\_2012\\_2020.pdf](http://www.who.int/immunization/newsroom/Measles_Rubella_StrategicPlan_2012_2020.pdf). Accessed November 3, 2014.

WHO. Measles vaccines: WHO Position paper. *WER*. 2009;84:349-60.

### IN A NUTSHELL

1. Measles contributes to about 4% of under-5 child mortality in India, and around 80,000 children die every year.
2. Routine measles vaccinations along with mass immunization campaigns are key public health strategies to reduce global measles deaths.
3. Measles vaccination resulted in a 78% drop in measles deaths between 2000 and 2012 worldwide.
4. Safe and effective measles vaccines are available as *stand-alone* and *combination vaccine* formulations.
5. Two doses of measles or measles containing vaccine are needed for effective control.
6. Measles can be eliminated globally with judicious use of vaccine.
7. The key objectives of Global Measles and Rubella Initiative are to achieve measles and rubella elimination in at least five WHO regions by year 2020.

## Chapter 23.12

# Rubella and Mumps Vaccines

Aashima Dabas, Piyush Gupta

### RUBELLA VACCINES

Rubella was first identified as a distinct exanthematous illness in 1964–65. The burden and impact of this illness was better understood after recognition of congenital rubella syndrome (CRS) which is characterized by congenital heart defects, hearing loss, cataracts/glaucoma, microcephaly, jaundice and hepatosplenomegaly. Countries from the developed world have recorded significant decline in incidence of CRS from 4 to 8 per 10,000 pregnancies to less than 0.01 per 10,000 pregnancies following rubella vaccine use. The developing countries account for most of burden of CRS with incidence of CRS in India varying from 1% to 15% as per hospital based data; hence the need for vaccination.

### Immunization against Rubella

#### Passive Immunization

The hyperimmune rubella immunoglobulin (Ig) was prepared in the past but is currently not available for use. Pooled Ig may be used instead in pregnant women exposed to rubella. It may modify the disease severity but does not reduce the risk of CRS and is thus no longer advocated.

#### Active Immunization

The rubella vaccine was first developed for use in 1969. The rubella vaccine was initially manufactured using the animal tissue culture cell lines. The current vaccine (RA 27/3) is a live attenuated vaccine derived from human diploid fibroblasts which was licensed for human use since 1979. It is to be reconstituted with distilled water and administered subcutaneously. The vaccine is available as monovalent form (Rubella only) or as a combination like measles-rubella (MR), measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV).

#### Immunogenicity

A single dose of vaccine results in good seroconversion reported as high as 95–100% after 4–8 weeks of vaccine administration.

#### Mucosal and Cellular Immune Response

The vaccine induces mucosal and cellular protective responses. Both IgM and IgG protective antibodies are demonstrable after 21–28 days post-vaccination. In addition, specific secretory IgA is also expressed in the nasopharynx which is implicated in providing protection from reinfection. The cellular responses like induction of lymphoblast proliferation also have some plausible role to play.

#### Age Specifications/Schedule

There are two age and host choices for vaccine administration—adolescent girls (to reduce CRS burden) or early childhood. India alone has a large pool (10–35%) of adolescent girls who are seronegative and susceptible to rubella. This susceptibility increases in a rural setting. The National Technical Advisory group on Immunization (NTAGI) thus recommended rubella vaccine to all adolescent girls 10–19 years in their report in 2010. However, by immunizing only adolescent girls, the chain of transmission remains undisrupted, thus the need for administering the vaccine in early childhood also. In 2014, a subcommittee of NTAGI

recommended introduction of rubella vaccine as bivalent MR vaccine into the Universal Immunization Program (UIP). The MR vaccine will replace measles at 9 months and second dose of the same combination will be given along with second booster of diphtheria, pertussis (whooping cough), and tetanus (DPT) vaccine at 16–24 months of age.

The seroconversion was reported to be as high as 96–99% after vaccine administration in 9–18 months age. The epidemiological studies later showed persistence of protective antibodies in 99% of recipients by 4–5 years age which dropped to 65–74% by adolescence. Therefore a single dose of rubella vaccine in early childhood failed to suffice protection during adolescence against CRS.

#### Duration of Immunity

A single dose administered after infancy provides adequate protection till 5 years age. Around 10% vaccinees are prone for reinfection after 5 years and thus a second dose is required at that age. The immunity after two doses is presumed lifelong.

#### Safety

The vaccine is a relatively safe vaccine with minimal local side-effects. It is contraindicated in those with history of anaphylaxis to vaccine component. The rare systemic side-effects include arthropathy and thrombocytopenia. Vaccine induced arthropathy is a rare occurrence in children. It was reported among adult recipients but lacked virological proof for causation or association. Thrombocytopenia may occur in 1:22,300 doses but is less severe than that resulting from natural infection. The second dose of vaccine should be administered with caution in any child who reported thrombocytopenia with an earlier dose. The earlier associations of rubella vaccine with Guillain-Barré syndrome, autism, ulcerative colitis and aseptic meningitis have been refuted. The US Centers for Disease Control and Prevention (CDC) now declares rubella as a safe vaccine. The vaccine should not be administered during pregnancy. Pregnancy should be delayed by 1 month after vaccination. Inadvertent vaccine administration during pregnancy does not warrant abortion. It should be avoided in immunocompromised children but may be given to an asymptomatic HIV positive child.

### Public Health Perspectives

A standing technical subcommittee (STSC) of NTAGI reviewed the overall burden of rubella and CRS in India and offered new recommendations which include:

- Introduction of rubella vaccine as MR vaccine in place of measles vaccine at 9 months of age and second dose at the time of first DPT booster at 16–24 months of age in states having achieved more than 80% coverage of first dose of measles vaccine;
- A onetime catch-up campaign of adolescent girls with rubella vaccine to offset potential increase in susceptible women in reproductive age group if children alone are vaccinated; and
- Sentinel surveillance for CRS to be included in MR surveillance program.

The rubella vaccine is part of the state health programs currently in Delhi, Goa, Puducherry and Sikkim whereas Kerala introduced rubella vaccine in 2014 as MMR. The vaccine is offered during second year of life and has reported low coverage rates as 42%, 30% and 5% from Delhi, Chandigarh and Goa, respectively. Globally, the launch of *Measles and Rubella Initiative* and new strategic plan to eliminate both the diseases by 2020 has shifted global focus on rubella and CRS. However, Southeast Asia including India was one of the last regions and countries to commit these goals. By 2012, 132 out of 194 World Health Organization (WHO) member states have introduced *rubella containing vaccine (RCV)* in their National

immunization programs, either as MR or MMR. Of these, 117 have RCV included in both routinely administered doses of measles-containing vaccine.

In addition to routine immunization services, there exists a need to maintain a surveillance system to track CRS incidence. A worldwide system LabNet has been established under WHO to monitor for both measles and rubella. India is also making efforts to setup a similar home surveillance network.

### Recommendations for Use

The Indian Academy of Pediatrics (IAP) recommendations state two doses of MMR as RCV at 9 and 15 months. There are many studies documenting efficacy of MMR vaccine when given before 12 months of age even in India. The Government of India has recently introduced rubella vaccination as MR vaccine substituting measles at 9 months and second dose along with second DPT booster at 16–24 months of age in areas with more than 80% vaccination coverage.

### MUMPS VACCINE

Mumps is a viral illness which frequently results in school and work absenteeism. In symptomatic individuals, it is characterized by parotitis (in 60–70%), epididymo-orchitis, meningitis, or rarely as other organ involvement. The burden of mumps is largely under-reported due to subclinical nature of the disease. The secondary attack rate among household contacts is high (31%). In Maharashtra, India around 60% of children less than 2 years of age were susceptible to illness as per 2007 data. Moreover, incidence rates have dropped by 98% and outbreaks have decreased in countries like United States since routine implementation of mumps vaccine. Considering the cost:benefit ratio of routine immunization to losses incurred by the economy due to disease morbidity, mumps vaccine seems a reasonable choice for all children.

### Immunization against Mumps

#### Passive Immunization

Immunoglobulins are not indicated in mumps as the defense is primarily by cellular immunity. Specific mumps Ig are no longer available.

#### Active Immunization

The vaccine is a live attenuated vaccine manufactured by either of the following strains—Leningrad-Zagreb (L-Zagreb), Leningrad 3, Urabe, Rubini and Jeryl-Lynn. All of them have shown comparable immunogenicity profile with varying safety concerns (discussed later). The current vaccine available for use in India uses the L-Zagreb and Jeryl-Lynn strain and is available as trivalent (measles-mumps-rubella). An earlier produced monovalent mumps vaccine has been withdrawn from US and UK and the quadrivalent (measles-mumps-rubella-varicella) is not yet available in India. The vaccine is to be reconstituted with distilled water and administered subcutaneously at dose of 0.5 mL.

#### Immunogenicity

The immunogenicity of various strains varies from 63% to 96% for Jeryl-Lynn and 84% to 95% for Urabe or L-Zagreb strains. The failure rate among vaccinees varies from 5.4% to 8.8% irrespective of the strain on vaccine.

#### Mucosal and Immune Responses

The vaccine induces a robust cellular response among recipients. The vaccine also results in herd immunity (approximately 90%) if used with high vaccine coverage (85–90%).

### Age Specifications/Schedule

Though the minimum age of offering the vaccine is after infancy to minimize the interaction of maternal antibodies, there are studies where mumps vaccine was successfully administered with good seroconversion at 9 months of age. High seroconversion rates (95–100%) were achieved at 10–15 months age in Indian children as per different studies; similar to western data. The seroconversion rates decline with increasing age to 93% in 5–6 years and 86% in 9–10 years age.

### Duration of Immunity

Since introduction of mumps vaccine in 1977, the prevalence of mumps had decreased by more than 98% by 1985 indicating robust primary response of the vaccine. The effectiveness of single dose vaccine is approximately 80%. A resurgence of cases was reported in 1989 among vaccinated school going children in the US. This suggested for recommending a second dose of mumps at 5–6 years age. The effectiveness of two dose vaccine ranges from 88% to 95% as per different studies. However, in 2006, an outbreak was reported among young adults (18–24 years age) in US who had received second dose of mumps almost 10 years earlier. People who were exposed to wild virus infections demonstrated natural boosting and higher protective antibodies. It was suggested that the asymptomatic transmission had chiefly accounted for the outbreak. Also a different serotype was causative for the outbreak than the mumps-vaccine-derived serotype, inferring lesser heterologous cross-protection with mumps vaccine.

### Safety

The most frequent side effects associated with the vaccine are mild fever, transient rash like illness and local site pain or redness. Allergic reactions in few susceptible individuals allergic to egg protein can occur. Parotitis or aseptic meningitis has been reported rarely after vaccination using the L-Zagreb or Urabe strain. Recently, there are reports on increased risk of febrile seizures with MMRV vaccine. The vaccine is best avoided in pregnancy and in symptomatic immune-compromised individuals but can be given in asymptomatic HIV children.

### Public Health Perspectives

The prevalence of mumps related encephalitis has decreased dramatically in post-vaccine era. The vaccine is in routine use in developed countries. In India, both limited routine immunization coverage and additional costs for mumps vaccine dissuaded the implementation of mumps vaccine in routine immunization. However, considering the economic benefits after reduction in work absenteeism in post-mumps vaccination phase, mumps vaccination seems a feasible and cost-effective measure in areas which have more than 80% vaccination coverage.

### Recommendations for Use

The vaccine is still not a part of National immunization schedule in India. The CDCs advisory committee on immunization practices (ACIP) and IAP advisory committee on vaccines and immunization practices (IAP-ACVIP) recommends two doses of mumps vaccine (given as combination MMR). The vaccine is a part of adult vaccination in few countries (like Scotland) and can be given in certain high-risk adults like international travelers, health-care workers, those visiting international universities or during outbreaks.

### IN A NUTSHELL

1. A highly effective live attenuated vaccine (RA 27/3) against rubella is available having close to 100% efficacy.
2. Government of India has decided to launch rubella vaccine as a bivalent measles-rubella (MR) vaccine into UIP. The MR vaccine will replace measles at 9 months and second dose of the same combination will be given along with second booster of DPT vaccine at 16–24 months of age.
3. Safe and reasonably effective live attenuated mumps vaccine is also available.
4. At least two doses of mumps vaccine are needed to have good protection.
5. Different strains of mumps virus are utilized in the production of mumps vaccine which is available as trivalent MMR vaccine.
6. The mumps vaccine has not yet been included in UIP of India though few states are offering this vaccine in their mass immunization programs.
7. The Indian Academy of Pediatrics has argued strongly in favor of inclusion of mumps into UIP in place of MR vaccine.

### MORE ON THIS TOPIC

- Dayan G, Rubin S, Plotkin S. Mumps outbreaks in vaccinated populations: are available mumps vaccines effective enough to prevent outbreaks. *Clin Infect Dis*. 2008;47:1458-67.
- Dewan P, Gupta P. Burden of congenital rubella syndrome in India: a systematic review. *Indian Pediatr*. 2012;49:378-99.
- Galazka A, Robertson S, Kraigher A. Mumps and mumps vaccine: global review. *Bull WHO*. 1999;77:3-14.
- Marin M, Broder KR, Temte JL, et al. Centers for Disease Control and Prevention (CDC). Use of combination measles, mumps, rubella and varicella vaccine: recommendations by the advisory committee on immunization practices (ACIP). *MMWR Recomm*. 2010;59(RR-3):1-12.
- Minutes of meeting- meeting of the National Technical Advisory Group on Immunization (NTAGI), 18<sup>th</sup> May, 2012, Ministry of Health and Family Welfare, Government of India. Available from <http://mohfw.nic.in/>. Accessed on November 07, 2014.
- Plotkin SA, Reef SE. Rubella vaccine. In: Plotkin SA, Ornestein WA (Eds). *Vaccines*. 5<sup>th</sup> ed. Philadelphia: Saunders; 2008. pp. 737-72.
- World Health Organization. Mumps virus vaccines. WHO position paper. *Wkly Epidemiol Rec*. 2007;82:51-60.



## Chapter 23.13

# Typhoid Fever Vaccines

Sushant Sahastrabudde,  
Mohammad Imran Khan

Typhoid fever, an acute febrile illness that is often fatal, remains an important public health problem globally; especially in the developing countries in Asia and Africa (**Fig. 1**). It causes 220,000 to 600,000 deaths and 16 to 22 million illnesses per year, predominantly in children of school-age or younger in the developing world. Improvement in water supply, hygiene and sanitation infrastructure have resulted in reduction of typhoid fever incidence in most developed countries. Though the same path must be followed for the countries that still suffer from typhoid, it may take a few decades for these countries to provide safe and hygienic environment. Given this fact, it is essential to consider a comprehensive approach that combines targeted vaccination of high-risk populations as a short- to medium-term measure, combined with the longer term solutions of water and sanitation improvements and elevated living standards.

## INACTIVATED WHOLE-CELL VACCINES

Heat-inactivated phenol-preserved whole-cell typhoid vaccines have been available since the 1890s. The vaccine was moderately efficacious (51–88%) in children and young adults in preventing typhoid fever, and the protection persisted for up to 7 years. However, their high levels of reactogenicity; fever (up to 30% of the vaccines), headache (up to 10%), and severe local pain (up to 35%), led to their removal from public health programs in most countries.

## NEW-GENERATION VACCINES

Two new-generation vaccines have been available in the market since late 1980s to early 1990s: the oral live attenuated Ty21a and injectable Vi polysaccharide vaccine (**Table 1**).

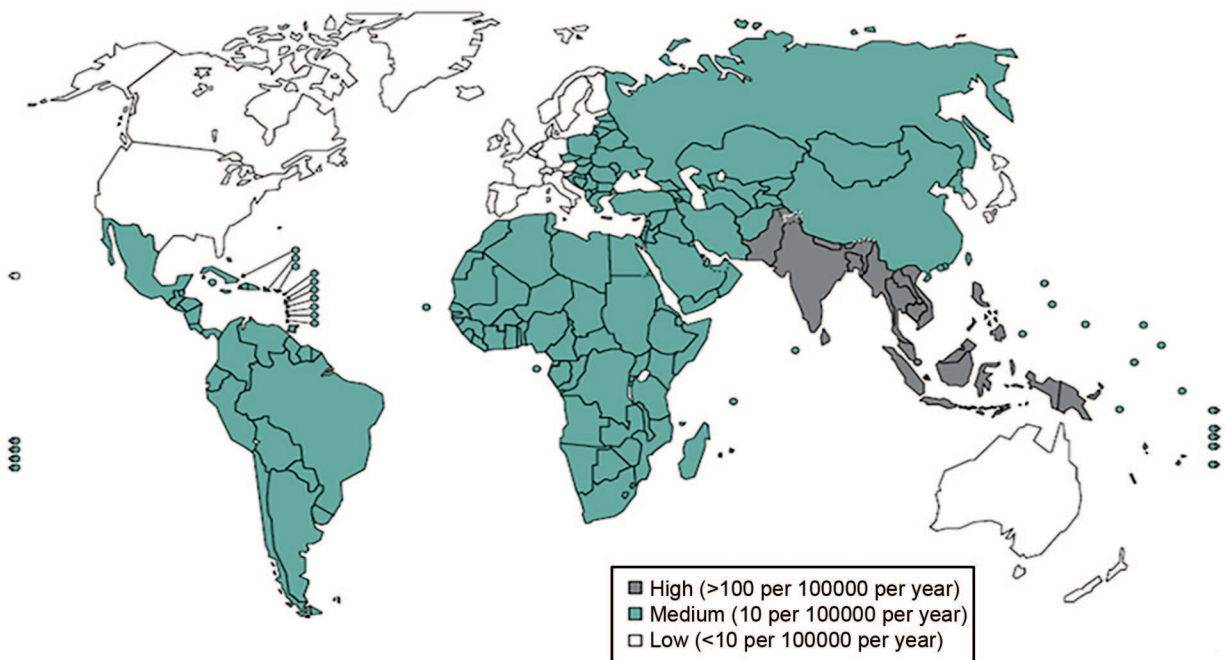
### Live, Oral Ty21a Vaccine

The Ty21a vaccine consists of a mutant strain of *Salmonella typhi* Ty2 which was isolated after chemical mutagenesis and has a galE- and Vi-negative phenotype. Immune response to the vaccine starts 14 days after vaccination, which is mediated by mucosal (IgA), serum (IgG), and cell-mediated antibodies. The overall protective efficacy for a three-dose regimen ranged between 67% and 80% in large-scale efficacy trials, conducted in 1980s in Chile. It is reported that the vaccine also protects against infection from *S. paratyphi B*. A recent study reported that the vaccine induces humoral response against *S. paratyphi A*, though no clinical protection has been studied. The most common adverse events reported with Ty21a were mild and transient gastrointestinal disturbances, followed by general symptoms such as fever. This vaccine is licensed for use in persons 2 years and above for the liquid formulation and 5 years and older for the capsule formulation, although the liquid formulation is currently unavailable. This vaccine is not available in Indian market now.

### Parenteral Vi Polysaccharide Vaccine

This subunit vaccine was developed from wild type *S. typhi* strain Ty2 on the basis of non-denatured purification of the Vi polysaccharide. The injectable Vi polysaccharide vaccine is given in a single dose and was found to confer, overall, 64–72% protection for 17–21 months and 55% over 3 years. Vi polysaccharide vaccine is well tolerated and safe. In a recent cluster-randomized effectiveness trial, the vaccine has also shown an evidence of herd protection. The most common side effects are pain, redness and

Geographical distribution of typhoid fever



**Figure 1** Country-specific incidence rates of typhoid fever

(Figure source: Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull WHO 2004;82:346-53. The map showing country-specific incidence rates for the year 2000)

**Table 1** Characteristics of the two new-generation typhoid fever vaccines; Ty21a and Vi polysaccharide

Characteristic	Live attenuated Ty21a	Vi capsular polysaccharide
Vaccine type	Live attenuated	Subunit
Composition	Chemically-mutated Ty2 strain of <i>S. typhi</i>	Purified Vi capsular polysaccharide of the Ty2 <i>S. typhi</i> strain
Immunogenic properties	<ul style="list-style-type: none"> <li>Elicits mucosal IgA and serum IgG antibodies against O, H and other antigens, as well as cell-mediated responses</li> <li>No booster effect has been shown</li> </ul>	<ul style="list-style-type: none"> <li>Elicits serum IgG Vi antibodies</li> <li>T-cell independent (no booster response)</li> </ul>
Route of administration	Oral	Parenteral (subcutaneous or intramuscular)
Minimum age vaccine is licensed for use	2 years old for liquid formulation and 5 years old for capsule formulation	2 years old
Formulation	<ul style="list-style-type: none"> <li>Enteric-coated capsules, or</li> <li>Liquid suspension (lyophilized vaccine + buffer mixed with water upon use)</li> </ul>	<ul style="list-style-type: none"> <li>Solution of 25 µg combined with buffer</li> </ul>
Number of doses required for complete vaccine regimen	Three to four	One
Storage requirements	Requires storage at 2–8°C	Requires storage at 2–8°C
Shelf life in higher temperature	14 days at 25°C	6 months at 37°C 2 years at 22°C
Safety/tolerability	High	High
Efficacy at 3 years (95% CI)	51% (36%, 62%)	55% (30%, 70%)
Length of protection	At least 5–7 years	At least 3 years

induration at injection site, and fever. In very rare cases, allergic reactions and rashes have been observed. Vi is not immunogenic in children less than 2 years of age. The vaccine is used in the private market in India, but not yet included in Universal Immunization Program for mass vaccination.

### Limitations of Current Vaccines and Newer Vaccine Candidates in Development

The currently available typhoid vaccines, although effective, have many limitations which have contributed to their limited uptake by the public sector globally. Both the available vaccines are modestly immunogenic, cannot be given to children less than 2 years of age, and are costly. Additionally, Ty21a is currently only available in capsule format that can be administered in children 5 years and above, requires multiple doses, and has to be maintained in strict cold chain. Vi polysaccharide requires repeated dosing every 3 years and because it is polysaccharide capsule-based, is T-cell independent. In view of these inadequacies, there have been many efforts in the recent past to improve upon the existing licensed vaccines.

#### Improvements in the Live Oral Vaccines

Several live oral typhoid vaccine candidates are currently under development. By utilizing recombinant DNA technology future live attenuated typhoid vaccines can become increasingly immunogenic, perhaps to the point of inducing protective immunity with only a single dose of vaccine. Some of the candidates in the pipeline are: Strain Ty800 with a mutation in *phoP/phoQ*, CVD 908-htrA, CVD 909, and M01ZH09.

#### Improvements in the Vi Polysaccharide Vaccine

Several aspects of Vi typhoid polysaccharide vaccines are similar to those of other polysaccharide bacterial vaccines such as Hib, pneumococcal and meningococcal C vaccines. The most important common feature is that all polysaccharide vaccines cannot produce immunological memory so they fail to induce anamnestic response

(*T-cell independent immunity*). These polysaccharide-based bacterial vaccines have shown that they cannot elicit sufficient immune responses in young children or infants. As shown in the precedents of other bacterial polysaccharide conjugate vaccines, typhoid vaccines can potentially overcome these issues associated with polysaccharide alone by a conjugation technology. Methods have been devised, therefore, to synthesize Vi protein conjugates in order to both enhance the antibody response and confer T-dependent properties to the Vi and theoretically increase its protective action in populations at high-risk for typhoid fever.

#### Vi-rEPA Prototype Typhoid Conjugate Vaccine

The scientists at the US National Institute of Child Health and Disease (NICHD) have developed a technique to bind Vi to a nontoxic recombinant carrier protein that is antigenically identical to *Pseudomonas aeruginosa* exotoxin A. The resultant conjugates (Vi-rEPA) were more immunogenic in mice and juvenile rhesus monkeys than the Vi alone. Conjugates of this polysaccharide with several medically relevant proteins induced booster responses also. The safety and immunogenicity of this vaccine candidate was evaluated in 2–5-year-old children in Vietnam. None of the recipients experienced fever or significant local reactions. The over-all efficacy after 27 months of active surveillance followed by 19 months of passive surveillance was 89%. In a randomized, vaccine controlled study of infants in Vietnam, Vi-rEPA was safe, elicited protective levels of IgG anti-Vi and was compatible with Expanded Programme on Immunization (EPI) vaccines.

### Typhoid Conjugate Vaccines in Development

#### Vi-polysaccharide-TT Conjugate Typhoid Vaccine (PedaTyph® by Biomed Pvt Ltd., India)

Biomed Pvt Ltd. in India developed a conjugate vaccine using tetanus toxoid as the carrier protein with 5 µg of Vi-polysaccharide. This product was tested in a clinical trial in 169 subjects more than 12 weeks with a comparison group (Vi) of 37 children more than

2 years. A fourfold or greater rise in antibody titer of each group was reported which was statistically equivalent to Vi-rEPA. The vaccine was licensed for use in children older than more than 3 months of age in 2008 in India as two doses injections of 0.5 mL each at interval of 4–8 weeks in 3 months to 2 years old children; followed by booster at 2 years and 2.5 years of age; and as two injections at interval of 4–8 weeks in children older than 2 years of age. Booster vaccination is recommended every 10 years thereafter.

### *Vi-Polysaccharide-TT Conjugate Typhoid Vaccine (Typbar-TCV<sup>®</sup> by Bharat Biotech)*

Bharat Biotech in Hyderabad, India also developed a typhoid conjugate vaccine using tetanus toxoid as the carrier protein with Vi-polysaccharide. This vaccine was tested in children (2–17 years) for safety, immunogenicity and dose ranging (15 µg versus 25 µg/0.5 mL). There was no significant difference in immune response between two doses of 25 µg/0.5 mL and two doses of 15 µg/0.5 mL. In the second clinical trial, comparative assessment of the immunogenicity of Vi-TT versus the polysaccharide vaccine was done in 981 participants (6 months to 45 years old). There was a 4-fold rise in the seroconversion in each treatment arm of Vi-TT at 6 weeks postvaccination. This vaccine is now licensed in India for a single dose indication above 9 months of age and is available as Typbar-TCV<sup>TM</sup>.

### *Vi-Polysaccharide-CRM197 Conjugate Typhoid Vaccine by Novartis Vaccines*

The Novartis Vaccines Institute for Global Health (NVIGH), Siena, Italy, has developed a typhoid conjugate vaccine (Vi-CRM197) using Vi from *Citrobacter freundii* WR7011 conjugated to the, CRM197, a nontoxic mutant of diphtheria toxin. Phase II studies have also been completed in India, Pakistan, and Philippines in four different age-groups: 18–45 years; 24–59 months; 9–12 months; and infants aged 6 weeks with each group having 40 subjects. The vaccine was found to be safe and immunogenic, but the lack of booster response and reduction in antibody titers after 6 months has thrown many questions about this candidate.

### *Vi-Polysaccharide-Diphtheria Toxoid (DT) Conjugate Typhoid Vaccine by IVI, Korea*

The International Vaccine Institute (IVI) based in Seoul, Korea also started the work on Vi-DT typhoid conjugate vaccine: Vi from *S. typhi* strain from India (C6524) conjugated to diphtheria toxoid as the carrier protein. The technology was then transferred to Shantha Biotechnics in India in 2009; PT Bio farma in Indonesia and SK Chemicals in Korea in 2013. Shantha Biotechnics since then has completed the preclinical studies and have produced the clinical trial batches.

### *Other Candidates*

Finlay Institute in Cuba is also developing a typhoid conjugate vaccine and has plans to replace the Vi-polysaccharide vaccine in their immunization programs with a typhoid conjugate vaccine.

## IAP RECOMMENDATIONS FOR TYPHOID VACCINES

**Primary schedule** According to new recommendations, typhoid conjugate vaccine is to be administered for primary immunization at 9–12 months of age. There are currently two typhoid conjugate vaccines, Typbar-TCV<sup>®</sup> and PedaTyph<sup>®</sup> available and licensed in the country. However, as of now this recommendation is applicable to the former only. Only a single dose of the vaccine is recommended for primary series, however, an interval of at least 4 weeks with the measles vaccine is recommended.

**Boosters** Those who received a dose of Typbar-TCV<sup>®</sup> at 9–12 months they can be prescribed booster of either Vi-polysaccharide (Vi-PS) or the Typbar-TCV<sup>®</sup> vaccine at 2 years of age. However, Vi-PS vaccine recipients would need revaccination every 3 years till the intended duration of protection.

## PUBLIC HEALTH PERSPECTIVES

Despite the slow progress, some countries and local governments have begun to consider typhoid vaccine for their public health programs. In the South Asian region, following publication of the updated WHO position paper, countries participating in a 2009 WHO South East Asia Regional Office (SEARO) prioritization workshop classified typhoid vaccination as an *immediate* priority. The Sri Lankan Ministry of Health has recently planned for the use of typhoid vaccines in high burden populations. The National Committee on Immunization Practices (NCIP) of Nepal has recommended the use of typhoid vaccines for disease control in the Kathmandu valley. The Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices (IAP ACVIP) has recommended the immediate inclusion of typhoid ViPS vaccines in the national immunization schedule. Typhoid vaccines are also recommended by the Indonesian Pediatric Association. Considering the heterogeneity of disease burden and antibiotics resistance at inter- and intra-country level, the WHO 2007 position paper on typhoid vaccine suggests the use of typhoid vaccines in high-risk population and in high endemic areas. Typhoid endemic countries are urged to review their disease burden data to identify the high-risk age groups and to introduce the vaccination program in conjunction with other measures, such as improvement in water and sanitation, provision of health education, and training of health-care workers for proper treatment and diagnosis.

### IN A NUTSHELL

1. Inactivated whole-cell vaccines though moderately effective against typhoid fever are no longer in use owing to high incidence of reactogenicity.
2. Two new-generation vaccines, the oral live attenuated Ty21a and injectable Vi-polysaccharide (Vi-PS) vaccine are currently available globally.
3. Vi-PS vaccine despite modest efficacy is the most commonly used vaccine in private sector in India whereas oral Ty21a is no longer available in Indian market.
4. Limitations of current Vi-PS vaccines like ineffectiveness below 2 years, need of repeated boosters and modest protection led to development of several Vi-PS-protein conjugate vaccines.
5. Two Vi-PS-protein conjugate vaccines are already licensed in India and few are in the pipeline.
6. Typhoid vaccination is not a part of Universal Immunization Program (UIP) in India despite high endemicity.
7. WHO has suggested the use of typhoid vaccines in high-risk population and in high endemic areas.

## MORE ON THIS TOPIC

- Acharya IL, Lowe CU, Thapa R, et al. Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of *Salmonella typhi*. A preliminary report. *N Engl J Med*.1987;317:1101-04.
- Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ*. 2004;82:346-53.
- Klugman KP, Gilbertson IT, Koornhof HJ, et al. Protective activity of Vi capsular polysaccharide vaccine against typhoid fever. *Lancet*.1987;2:1165-9.

- Kossaczka Z, Lin FY, Ho VA, et al. Safety and immunogenicity of Vi conjugate vaccines for typhoid fever in adults, teenagers, and 2- to 4-year-old children in Vietnam. *Infect Immun*. 1999;67:5806-10.
- Ochiai RL, Acosta CJ, Danovaro-Holliday MC, et al. A study of typhoid fever in five Asian countries: disease burden and implications for controls. *Bull World Health Organ*. 2008;86:260-8.
- Parry CM, Wijedoru L, Arjyal A, Baker S. The utility of diagnostic tests for enteric fever in endemic locations. *Expert Rev Anti Infect Ther*. 2011;9:711-25.
- Sur D, Ochiai RL, Bhattacharya SK, et al. A cluster-randomized effectiveness trial of Vi typhoid vaccine in India. *N Engl J Med*. 2009;361:335-44.
- Thiem VD, Lin FY, Canh do G, et al. The Vi conjugate typhoid vaccine is safe, elicits protective levels of IgG anti-Vi, and is compatible with routine infant vaccines. *Clin Vaccine Immunol*. 2011;18:730-5.
- Typhoid vaccines: WHO position paper. *Wkly Epidemiol Rec*. 2008;83:49-59.
- Vashishtha VM, Kalra A, Bose A, et al. Indian Academy of Pediatrics (IAP) recommended immunization schedule for children aged 0 through 18 years, India, 2013 and updates on immunization. *Indian Pediatr*. 2013;50:1095-108.
- World Health Organization. Background document: The diagnosis, treatment and prevention of typhoid fever. Geneva: WHO; 2003.



## Chapter 23.14

# Japanese Encephalitis Vaccine

VG Ramachandran

Japanese encephalitis (JE) vaccines first became available in the 1950s. Inactivated mouse brain derived vaccine using Nakayama strain of the virus and/or Beijing-1 strain was the first to be used. Its production stopped in 2005. Inactivated vaccine after cultivation in primary hamster kidney cells of the Beijing-3 strain was the second JE vaccine. Beijing 3 is the main variant of the vaccine strain used in China from 1968 to 2005. Central Research Institute, Kasauli, Himachal Pradesh used to produce the mouse brain vaccine but not any longer. Similarly, primary hamster kidney cell grown inactivated vaccine has also ceased production. Following new, second generation JE vaccines are available now:

- Live attenuated, cell culture-derived SA14-14-2 JE vaccine
- Inactivated SA14-14-2 vaccine (IC51) (IXIARO by Intercell and JEEV® by Biological Evans India Ltd.
- Inactivated vero cell culture-derived Kolar strain, 821564XY, JE vaccine (JENVAC® by Bharat Biotech)
- Chimeric vaccine (IMOJEV by Sanofi Pasteur)
- Inactivated vero-cell derived JE vaccine (Beijing-1 JE strain by Biken and Kaketsuken, Japan).

### LIVE ATTENUATED, CELL CULTURE-DERIVED SA14-14-2 JAPANESE ENCEPHALITIS VACCINE

This vaccine is based on the genetically stable, neuro-attenuated SA14-14-2 strain of the JE virus, which elicits broad immunity against heterologous JE viruses. Reversion to neurovirulence is highly unlikely. The live attenuated vaccine was licensed in China in 1989. Since then, more than 300 million doses have been produced and more than 200 million children have been vaccinated. Extensive use of this and other vaccines has significantly contributed to reducing the burden of JE in China from 2.5/100,000 in 1990 to less than 0.5/100,000 in 2004. This vaccine is also licensed for use in Nepal (since 1999); South Korea (since 2001); India (since 2006); Thailand (since 2007) and Sri Lanka.

**Dosage and route of administration** In China, the vaccine is licensed for 0.5 mL dose to be administered subcutaneously to children at 8 months of age and a second opportunity again at 2 years. In some areas, a booster dose is given at 7 years. It should not be used as an outbreak response vaccine. It can also be offered to all susceptible children up to 15 years as catch-up vaccination.

**Immunogenicity** After a single dose, antibody responses are produced in 85–100% of nonimmune 1–12-year-old children. A neutralization antibody titer of more than 1:10 is generally accepted as evidence of protection and post-vaccination seroconversion.

**Safety** The vaccine has an excellent safety profile.

**Efficacy** Case control studies and numerous large-scale field trials in China have consistently shown an efficacy of at least 95% following two doses administered at an interval of 1 year. In a field trial in Nepal in 1999, involving more than 160,000 subjects 1–15 years of age, reported efficacy of a single dose of 99.3% in the same year and 98.5% 1 year later. At 5 years the protective efficacy was 96.2%. Vaccine in this study contained  $10^{5.8}$  PFU/0.5 mL. However, data from postmarketing surveillance (PMS) in India showed that protective efficacy of the vaccine in India is not as high as that seen in Nepal. Achievement of a sustained reduction in JE in areas where many children received only a single dose of SA14-14-2 vaccine, suggests that the efficacy of this vaccine exceeds the ability to detect a circulating neutralizing antibody response to a single administered dose.

**Recommendations for use** Both Government of India and Indian Academy of Pediatrics have now recommended a second dose of the vaccine to provide more complete and sustained protection. First dose of the vaccine can be administered at 9 months along with measles vaccine and second at 16–18 months at the time of first booster of DTP vaccine.

### INACTIVATED SA14-14-2 VACCINE (IC51) (IXIARO BY INTERCELL AND JEEV® BY BIOLOGICAL E. INDIA LTD

IC51 is a purified formalin inactivated whole virus vaccine licensed in US, Australia and Europe during 2009 derived from the attenuated SA14-14-2 Japanese encephalitis virus (JEV) strain propagated in Vero cells. It has been evaluated in several clinical studies in adults and children in India and in several other countries. This vaccine has now been approved by US FDA and EU for use in children from the age of 2 months onwards. Each 0.5 mL liquid formulation in a ready-to use prefilled syringe contains approximately 6 µg of purified, inactivated JEV proteins and 0.1% aluminum hydroxide as an adjuvant.

**Dosage and schedule** 0.25 mL dose for children 2 months through 2 years of age, and 0.5 mL dose for children more than or equal to 3 years of age and adults. Primary series involves two doses administered 28 days apart.

**Immunogenicity** There is no efficacy data for JE-VC (IXIARO®), and the vaccine has been licensed in pediatric age group especially for travelers to Asian countries on the basis of a phase III randomized controlled trial (RCT) conducted amongst 1,867 subjects in the Philippines, and favorable interim data from a second phase III trial in EU, US and Australia. In both studies, the JE vaccine was shown to be highly immunogenic in children or adolescents aged 2 months to less than 18 years with a safety profile comparable to pediatric vaccines licensed for other diseases. A phase II trial from India investigated the safety and immunogenicity of JE-VC in healthy children aged 1 and 2 years in India, using a standard (6 µg) or half (3 µg) dose. Seroconversion was achieved in more than 90% of recipients. Exact duration of protective neutralizing antibodies in the serum is not known; however a boosting effect is demonstrated by repeat dose.

**Safety** The safety profile of JE-VC vaccine is similar to the JE-MB vaccines. However, it is less reactogenic, showed a higher potency, a higher persistency, and patient convenience (two instead of three doses: at 0 and 28 days) than mouse brain vaccines.

**JEEV-the Indian variant of IC51, IXIARO** A vaccine for endemic markets based on Intercell's technology was launched in 2012 under the trade name JEEV® in India. In 2011, BE Ltd. India conducted a multicentric open label randomized controlled phase II/study to evaluate safety and immunogenicity of JEEV® vaccine in almost 450 children ( $\geq 1$  to  $< 3$ -year-old) and compared to control Korean Green Cross Mouse Brain Inactivated (KGCC) vaccine. This study demonstrated seroconversion (SCR) of 56.28% on day 28 and 92.42% on day 56 in BE-JE (JEEV®) vaccinated group. JEEV® has been licensed by drug authorities in India for use in prevention of JE virus infection in children and adult.

**Recommendations for use** According to IAP, the vaccination against JE is not recommended for routine use, but only for individuals living in endemic areas. The Academy recommends a primary schedule of 2 doses of 0.25 mL for children aged between  $\geq 1$  and  $\leq 3$  years and 2 doses of 0.5 mL for children more than 3 years, adolescents and adults administered intramuscularly on days 0 and 28. However, the long-term persistence of protective efficacy and need of boosters are still undetermined.

## INACTIVATED VERO CELL CULTURE-DERIVED KOLAR STRAIN, 821564XY, JE VACCINE (JENVAC® BY BHARAT BIOTECH)

In the year 2013, Bharat Biotech International, a Hyderabad based firm obtained marketing and authorization rights from Drugs Controller General of India (DCGI), India for a JE vaccine after phase II or phase III trials, which showed good safety and seroprotection even after single dose administration. The vaccine is marketed as JENVAC® in Indian market is a Vero cell-derived purified, inactivated product that is said to be applicable to all age groups and also during epidemics. The seed strain is an indigenous JE isolate from Kolar, Karnataka, by NIV, Pune.

**Immunogenicity** A single dose of the test vaccine was sufficient to elicit good immune response. At 28th day, the subjects who had received a single dose were 98.67% seroprotected and 93.14% seroconverted (fourfold) for  $\leq 50\text{--}\geq 1$  years, whereas the corresponding figures for the reference vaccine were 77.56% and 57.69%, respectively. The seroconversion (93.14% and 96.90%) and seroprotection (98.67% and 99.78%) percentages on the 28th and 56th day were not significantly different and similarly, no statistically significant difference in these rates was noted amongst different age groups.

**Safety** The vaccine showed excellent safety during Indian trial. There was no serious adverse event (AE) or AE of any special interest noted in the study. None of the enrolled subjects were withdrawn from the study for vaccine related adverse reaction. AES were reported significantly lower after second dose, when compared to after first dose of test vaccination. The AES reported after second dose in test group were not significantly different than the AES reported after placebo administration as second dose in reference group.

**Recommendations for use** According to IAP recommendations, two doses of the vaccine (0.5 mL each) administered intramuscularly at 4 weeks interval for the primary immunization series starting from 1 year of age. A booster is needed at later stage; however the exact timing of the booster along with feasibility of single dose for primary series can be determined only after obtaining the long-term follow-up data.

## CHIMERIC VACCINE (IMOJEV BY SANOFI PASTEUR)

YF-JE is live attenuated and commercially available as IMOJEV. Licensed in Australia in August, 2010 and in Thailand in December, 2012, it is given in two intramuscular doses on day 0 and day 28. The vaccine strain is derived by insertion of nucleic acid sequences encoding envelope proteins for prM and E of the SA14-14-2 strain of JE into the yellow fever 17D backbone, lacking in neurotropic properties. Immunogenicity of IMOJEV is not affected by concomitant measles-mumps-rubella (MMR) administration. This vaccine is contraindicated in pregnancy. Also, a vaccinee should avoid pregnancy until 28 days post-vaccination. The trial of this vaccine is yet to be completed in India.

## INACTIVATED VERO-CELL DERIVED JE VACCINE (BEIJING-1 JE STRAIN)

The Osaka University, Biken, has produced Biken BK-VJE a vero-based vaccine formulated in alum and using the Beijing-1 JE strain. Kaketsuken, one of the Japanese producers of mouse brain-derived JE vaccines has produced a purified non-adjuvanted vero cell-derived vaccine formulated without gelatin or thimerosal. Phase III trials have demonstrated production of neutralizing antibody in 100% of subjects. These vaccines are not available in India.

## JAPANESE ENCEPHALITIS VACCINATION FOR TRAVELERS

Japan, South Korea, North Korea, Taiwan, Vietnam, Thailand and China practice routine childhood immunization against JE. Travel associated JE can occur in people of any age but risk is based on destination, duration, season and activities of the traveler. Risk of disease among travelers in Asia is 1 in 10,00,000. Susceptibility does not decrease with mass immunization. Vaccination in travelers will depend on the prevalence of disease in the area and type of exposure during travel. In area of no risk vaccination is not required. Increasing incidence of disease has been reported from Asia. Usually endemic disease is not noted and epidemics are detected late hence vaccination should be recommended for selected travelers to Asia who are at high-risk (outdoor activity and during epidemics), those who are to stay for more than 30 days. Travel high-risk areas include, India, Nepal, Myanmar, Sri Lanka, China, Cambodia, Korea, Laos, Malaysia, Philippines, Thailand, Vietnam. JE vaccine is not suitable for children below 1 year.

### IN A NUTSHELL

1. Japanese encephalitis (JE), mainly affects children aged 1–15 years. About 50,000 cases occur annually with 15,000 deaths and a case fatality rate ranging from 5% to 35%.
2. Most infections are asymptomatic with a population dependent variable symptote: asymptote ratio of 1:25 to 1:1000.
3. The survivors of JE are left with crippling neurological sequelae in as much as 50% of patients.
4. JE is widely prevalent in many parts of India with states like eastern UP, West Bengal, Assam, Bihar and some North-East states are badly affected.
5. Mass immunization, control of mosquito vectors, prevention of mosquito from biting humans, control or protection of reservoirs, changes in pig husbandry, and reduction in land utilized for rice cultivation are some key interventions needed to control JE.
6. Conventionally available *inactivated mouse brain derived JE vaccine* using Nakayama strain of the virus is no longer available in use.
7. Cost, efficacy and safety concerns led to the development of a number of new JE vaccines, many of which are licensed and available for use in the country.

### MORE ON THIS TOPIC

- Eder S, Dubischar-Kastner K, Firas C, et al. Long term immunity following a booster dose of the inactivated Japanese encephalitis vaccine IXIARO®, IC51. Vaccine. 2011;29:2607-12.
- Japanese encephalitis vaccines. In: Vashishtha VM, Choudhury P, Bansal CP, et al. IAP Guidebook on Immunization 2013-2014. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.
- Monath TP, Guirakhoo F, Nichols R, et al. Chimeric live, attenuated vaccine against Japanese encephalitis (ChimeriVax-JE): phase 2 clinical trials for safety and immunogenicity, effect of vaccine dose and schedule, and memory response to challenge with inactivated Japanese encephalitis antigen. J Infect Dis. 2003;188:1213-30.
- Monath TP, McCarthy K, Bedford P, et al. Clinical proof of principle for ChimeriVax: recombinant live, attenuated vaccines against flavivirus infections. Vaccine. 2002;20:1004-18.
- Vashishtha VM, Kalra A, Bose A, et al. Indian Academy of Pediatrics (IAP) recommended immunization schedule for children aged 0 through 18 years, India, 2013 and updates on immunization. Indian Pediatr. 2013;50:1095-108.
- World Health Organization. Japanese encephalitis vaccines. Wkly Epidemiol Rec. 2006;81:331-40.

## Chapter 23.15

# Rabies Vaccines

Anuradha Bose

The currently available vaccines in India are the modern cell culture vaccines (CCV) and include purified chick embryo cell vaccine (PCECV), human diploid cell vaccine (HDCV), purified vero cell vaccine (PVRV), purified duck embryo vaccine (PDEV) (**Table 1**). The production of nerve tissue vaccine (NTV) was stopped in India in 2004. These vaccines are available in lyophilized form with sterile water as diluent, are stable for 3 years at 2–8°C and should be used within 8 hours of reconstitution. Rabies vaccines contain more than 2.5 IU of antigen per intramuscular dose, with a diluent of 1.0 mL, or 0.5 mL depending on the product. The entire dose should be given intramuscularly regardless of the age or weight of the patient.

**Table 1** Rabies vaccines available in India

1.	Abhayrab	Purified vero cell rabies vaccines (PVRV)	Human biological
2.	Indirab	Chromatographically purified (PVRV)	Bharat Biotech International Ltd., Hyderabad
3.	Rabipur	Purified chick embryo cell vaccine (PCECV)	Novartis
4.	Rabivax	Human diploid cell vaccine	Serum Institute of India
5.	Verorab	Vero cell	Ranbaxy
6.	Verovax-R	Vero cell (monkey kidney cells)	Sanofi Aventis
7.	Vaxirab	Purified duck embryo cell vaccine	Zydus Healthcare Ltd., Ahmedabad
8.	Vaxirab N	Purified chick embryo cell vaccine (PCECV)	Zydus Healthcare Ltd., Ahmedabad

**Table 2** Rabies immunoglobulins available in India

Serial No	Type of Immunoglobulin	Name	Company	Strength
1.	Equine	Anti-rabies serum (ARS)	Central Research Institute, Kasauli	5 mL vial (300 IU/mL)
2.	Equine	Equirab	Bharat Serums and Vaccines, Mumbai	5 mL vial (300 IU/mL)
3.	Equine	Vinrig	VINS Biopharma, Hyderabad	5 mL vial (300 IU/mL)
4.	Equine	AbhayRig	Human Biologicals Institute, Hyderabad	5 mL vial (300 IU/mL)
5.	Human	Berirab-P	Bharat Serums and Vaccines, Mumbai	150 IU/mL; 2 mL (300 IU) 5 mL (750 IU) ampoules
6.	Human	ImogenRab	Sanofi Pasteur	150 IU/mL; 2 mL (300 IU) 5 mL (750 IU) ampoules
7.	Human	KamRab	Kamada Ltd. Israel/Synergy Diagnostics	150 IU/mL; 2 mL (300 IU) 5 mL (750 IU) ampoule

**Site of injection** The deltoid is the preferred site for the intramuscular injections, and the anterolateral aspect of the thigh in infants and young children. The gluteal region should not be used as it is believed that the fat in this region retards the absorption of the antigen.

**Antibody levels** These vaccines induce protective antibodies in more than 99% of vaccinees following pre exposure prophylaxis or postexposure prophylaxis (PEP). An antibody titer of 0.5 IU is considered protective.

**Adverse effects** The main adverse effects are local pain, swelling and redness and less commonly fever, headache, dizziness and gastrointestinal side effects. Systemic hypersensitivity reactions in vaccinees have been reported with HDCV particularly following booster injections. Intradermal vaccination may cause more local irritation than intramuscular.

### RABIES IMMUNOGLOBULIN

Rabies immunoglobulin (RIG) contains specific anti-rabies antibodies that neutralize the rabies virus. There are two types of RIG:

1. Human rabies immunoglobulin (HRIG)—dose is 20 U/kg body weight, maximum dose 1,500 IU.
2. Equine rabies immunoglobulin (ERIG)—dose is 40 U/kg body weight, maximum dose 3,000 IU.

Human rabies immunoglobulin is preferred, but is expensive. The currently available ERIG preparations (**Table 2**) are potent, safe, highly purified and less expensive as compared to HRIG and can be used if the HRIG is not accessible. There is a small risk of anaphylaxis and any administration of RIG should be done only with the full resuscitation kit available nearby. The World Health Organization (WHO) does not recommend skin testing prior to ERIG administration as they do not accurately predict anaphylaxis risk.

Rabies immunoglobulin is indicated in all cases of category III wounds (**Box 1**), and category II exposure in the immunocompromised. RIG is not indicated in individuals who have received pre-exposure prophylaxis or PEP in the past. RIG should be infiltrated thoroughly into and around the wound, diluting the RIG with saline if the area to be infiltrated is large. The remaining part if any is to be injected IM. Adverse reactions include tenderness

or stiffness at the injection site, low grade fever. The RIG should be administered as early as possible but no later than the seventh day after the first dose of vaccine was given, as the antibody response to the vaccine is presumed to occur from day 8 onwards.

## GENERAL PRINCIPLES

In a rabies endemic country like India, every bite should be considered as potentially infective. The factors to be considered while deciding treatment are:

- The *category of exposure* (**Box 1**).
- The *vaccination status of the animal* A history of vaccination of the animal is not evidence that the animal is protected. In case of bites by pet animals, PEP may be deferred only if the pet responsible for exposure is more than a year old, has a vaccination certificate indicating that it has received at least two doses of a potent vaccine, the first not earlier than 3 months of age and the second within 6–12 months of the first dose and in the past 1 year. Bites by puppies are potentially dangerous as they are too young to have been immunized and even very young pups have been known to transmit rabies.
- *Observation of the animal involved* The animal should ideally be kept under observation. The conventional observation period of 10 days is valid only for dogs and cats. If the animal cannot be observed, as in the case of a stray, or if the animal has been killed the animal is best considered as potentially rabid. If the animal remains well through the 10-day period,

the PEP can be converted to a pre-exposure prophylaxis, by omitting the day 14 dose and giving the day 28 dose of the Essen schedule. Full PEP should be started urgently if there are signs of illness in the pet.

- *The animal* PEP is indicated following exposure to the saliva of any warm blooded animal. These include dogs, cats, cows, buffaloes, sheep, goats, pigs, donkeys, horses, camels, foxes, jackals, monkeys, mongoose, bears and others. Rabies due to bats, and rodent bites has not been reported in India. Wild animal bites are considered as category III.
- *Special circumstances* Extremes of age, (infancy and old age), pregnancy, lactation, concurrent illness are not contraindications for rabies PEP. Patients who may be immunocompromised for any reason should be offered immunoglobulin even for category II exposure.
- *Timing of treatment* Prophylaxis should be given as soon as possible. It should not be denied or deemed unnecessary however late after exposure the patient presents. Even wound cleansing should be done at first contact, however late the patient presents, if there is a wound with a break in the skin.

## POSTEXPOSURE PROPHYLAXIS

All categories II and III bites merit rabies vaccine. PEP when administered strictly according to protocol (**Table 3**) protects against development of rabies.

### The Wound

The first step is thorough cleansing of the wound with soap and flushing under running water for 10 min. This should be followed by irrigation with a virucidal agent such as 70% alcohol or povidone iodine. Antimicrobials and tetanus toxoid should be given if indicated. Where indicated, RIG should be infiltrated into the wound. Any suturing of wound should be avoided. When suturing is unavoidable for purpose of hemostasis, it must be ensured that RIG has been infiltrated in the wound prior to suturing.

### Schedule

The standard schedule (Essen protocol) is five doses on days 0, 3, 7, 14 and 28, with day '0' being the day of commencement of vaccination. Dose is 1 mL intramuscular. (Some vaccines have 0.5 mL diluent only; dose is then 0.5 mL). The same product should be used for the course. Interchange of vaccines should be avoided. For

### BOX 1 Categories of rabies exposure

Rabies exposure is categorized into three and use of antirabies biological products depends on the category of exposure. All categories need to be washed and wound management done.

*Category I:* Touching, feeding of animals or licks on intact skin—*no exposure and if history is reliable: no treatment.*

*Category II:* Minor scratches or abrasions without bleeding or licks on broken skin and nibbling of uncovered skin: *use vaccine alone.*  
*Use immunoglobulin + vaccine if patient is immunocompromised.*

*\*Category III:* Single or multiple transdermal bites, abrasions that bleed, scratches or contamination of mucous membrane with saliva (i.e., licks) *Use immunoglobulin + vaccine.*

*Any bite from a wild animal is considered a category III bite.*

**Table 3** Rabies postexposure prophylaxis (PEP) schedule

Vaccination status	Intervention	Regimen*
Not previously vaccinated	Wound cleansing	All PEP should begin with immediate thorough cleansing of all wounds as described earlier
	Human rabies immunoglobulin (HRIG)	Administer 20 IU/kg body weight. Infiltration into the wound and remainder at an anatomical site (intramuscular [IM]) distant from vaccine administration. HRIG should not be administered in the same syringe as vaccine
	Vaccine	Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1.0 mL, IM (deltoid area†) or purified vero cell vaccine (PVRV), 1 each on days 0, 3, 7, 14 and 28 (5 doses)
Previously vaccinated**	Wound cleansing	Immediate thorough cleansing of all wounds
	HRIG	HRIG should not be administered
	Vaccine	HDCV or PCECV 1.0 mL, IM (deltoid area†), 1 each on days 0 and 3

\*These regimens are applicable for persons in all age groups, including children.

†The deltoid area or for younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.

\*\*The PEP recommendation of 2 doses, one each on days 0 and 3, is applicable regardless of time elapsed between the previous vaccination and the current exposure.



minor deviations from the schedule, vaccination can be resumed with the same intervals between doses as though the patient were on schedule. For example, if day 7 is missed and patient reappears on day 10, then the days are: 10, 17, and 31. The dose is the same at all ages and weights.

### Other Schedules

- **Zagreb schedule** is a reduced multisite intramuscular regimen (2-1-1): four doses distributed in three visits on days 0, 7 and 21. This is an alternative 4 day schedule, if an accelerated response is considered necessary: Two doses are given on day 0 in the deltoid muscle, right and left arm. Subsequent doses, one each on day 7 and day 21. This schedule is not recommended in India.
- **Reduced 4-dose schedule** (Not recommended by IAP). Dose 1 mL intramuscular on days 0, 3, 7, 14. The day 28 dose is omitted. The rationale for this is based on reviews of series of fatal cases, where most deaths occurred before day 28, and none of them could be attributed to a failure to receive the fifth (day 28) vaccine dose.
- **Intradermal schedules** Intradermal vaccination helps reduce costs. The dose required is only 0.1 mL. This volume should contain 0.25 IU of antigen.
  - **Thai Red Cross Regimen:** 2-2-2-0-1-1, two intradermal (ID) doses on the deltoid on days 0, 3, 7 and 1 dose on day 30 and 90.
  - **Updated Thai Red Cross Regimen:** 2-2-2-0-2-0, (ID) two doses on days 0, 3, 7 and 30.
  - **Eight Site Regimen: (Not approved in India):** 8-0-4-0-1-1, 8 intradermal doses on each upper arm, each lateral lower abdominal quadrant, each thigh and each suprascapular regions on day 0. Four doses are given on day 7 on each thigh and upper arm and one dose on day 30 and 90 on upper arm.
- **Re-exposure schedule** There are studies to show that good antibody levels persist up to 10 years. However, on account of the nature of the disease, for re-exposure at any point of time after completed (and documented) preexposure prophylaxis or PEP, two doses are given, one each on days 0 and 3.

### PRE-EXPOSURE PROPHYLAXIS

Where the exposure may be unrecognized (laboratory personnel) or unreported (children), preexposure prophylaxis may be considered. It has the advantage of eliminating the need for RIG. It also reduces the PEP to two doses only. Pre-exposure prophylaxis is recommended for certain high-risk groups (**Box 2**).

#### BOX 2 Indications for rabies pre-exposure prophylaxis

1. **Continuous exposure:** Laboratory personnel in research and industry.
2. **Frequent exposure:** Veterinarians, laboratory personnel involved with rabies diagnosis, doctors and allied staff treating rabies patients, dog catchers, zoo keepers, forest staff. Children who may be exposed to stray dog menace and pet owners.
3. **Infrequent exposure:** Postmen, courier boys, travelers (backpackers) to rabies endemic countries.

### Dosage

Three doses are given intramuscular on days 0, 7 and 28 (day 21 may be used if time is limited, e.g., as with imminent travel) but day 28 is the better option. The intradermal schedule has been shown to be effective for pre-exposure prophylaxis, but is not approved in India for this purpose.

### Assessment of Antirabies Antibodies Titers

Routine assessment of antibody titers is not recommended unless the person is immunocompromised. The highly exposed persons should check antibody titers every 6–12 months and have a booster dose of the vaccine if antibody levels fall below 0.5 IU/mL. When serologic testing is not available booster vaccination every 5 years is an acceptable alternative.

### MORE ON THIS TOPIC

- Chutivongse S, Wilde H, Supich C, et al. Postexposure prophylaxis for rabies with antiserum and intradermal vaccination. *Lancet*. 1990;335:896-8.
- Ichhpujani RL, Mala C, Veena M, et al. Epidemiology of animal bites and rabies cases in India. A multicentric study. *J Commun Dis*. 2008;40:27-36.
- Rupprecht CE, Briggs D, Brown CM, et al. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the advisory committee on immunization practices. *MMWR Recomm Rep*. 2010;59(RR-2):1-9.
- Strady A, Lang J, Lienard M, et al. Antibody persistence following pre-exposure regimens of cell-culture rabies vaccines: 10-year follow-up and proposal for a new booster policy. *J Infect Dis*. 1998;177:1290-5.
- Sudarshan MK, Mahendra BJ, Madhusudana SN, et al. An epidemiological study of animal bites in India: results of a WHO sponsored national multicentric rabies survey. *J Commun Dis*. 2006;38:32-9.
- Warrell MJ, Nicholson KG, Warrell DA, et al. Economical multiple-site intradermal immunisation with human diploid-cell-strain vaccine is effective for post-exposure rabies prophylaxis. *Lancet*. 1985;1:1059-62.

### IN A NUTSHELL

1. In a rabies endemic country like India, every bite should be considered as potentially infective. A history of vaccination of the animal is not evidence that the animal is protected.
2. Bites by puppies are potentially dangerous as they are too young to have been immunized.
3. The use of older *nerve tissue vaccine* (NTV) was stopped in India in 2004.
4. The new generation, currently available vaccines in India are the modern cell culture vaccines (CCV) and include purified chick embryo cell vaccine (PCECV), human diploid cell vaccine (HDCV), purified vero cell vaccine (PVRV), purified duck embryo vaccine (PDEV).
5. The deltoid and anterolateral aspect of the thigh (in infants and young children) are the preferred site for the intramuscular injections. The gluteal region should not be used.
6. The available rabies vaccines are highly efficacious and induce protective antibodies in more than 99% of vaccines following pre-exposure prophylaxis or postexposure prophylaxis.
7. Rabies immunoglobulin (RIG) is indicated in all cases of category III wounds, and category II exposure in the immunocompromised.
8. The currently available equine rabies immunoglobulin (ERIG) preparations are potent, safe, highly purified and less expensive than human RIG. There is no need of skin testing prior to ERIG administration.
9. For *postexposure prophylaxis* five doses are recommended on days 0, 3, 7, 14 and 30, with day '0' being the day of commencement of vaccination.
10. For re-exposure at any point of time after completed (and documented) pre-exposure prophylaxis or PEP, two doses are given, one each on days 0 and 3.
11. Pre-exposure prophylaxis involves three doses given IM on days 0, 7 and 28.

## Chapter 23.16

# Pneumococcal Vaccines

Puneet Kumar, Vipin M Vashishtha

Two types of vaccines are currently licensed against pneumococcus (*Streptococcus pneumoniae*): Pneumococcal polysaccharide vaccine (PPSV) and pneumococcal conjugate vaccines (PCVs). While PPSV offers *broad-based, add-on* protection, despite its limitations, to children who are at high-risk to contract pneumococcal disease (PD), PCVs have much greater public health importance as they *effectively* prevent *pneumococcal pneumonia*, one of the leading killers of under-5 children. This chapter would briefly discuss both of these vaccines, with special emphasis on current Indian scenario.

### PNEUMOCOCCAL POLYSACCHARIDE VACCINE

The first pneumococcal vaccine was developed as early as 1945. It was a tetravalent vaccine containing 30–60 µg each of capsular polysaccharide antigens of four serotypes (1, 2, 5 and 7), but was not widely distributed since its deployment coincided with the discovery of penicillin. In 1970s, Robert Austrian succeeded in developing 14-valent PPSV that was licensed in 1977. This finally evolved into 23-valent vaccine that was first licensed in 1983.

Currently available PPSV is a 23-valent vaccine containing purified capsular polysaccharide antigens (25 µg each) of the 23 serotypes of pneumococcus that were responsible for over 95% of cases of invasive disease in US and other developed countries *before* the introduction of PCV in routine vaccination. These serotypes are: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F. The vaccine does not contain any adjuvant. Being a polysaccharide vaccine, it is T-cell independent vaccine and thus is poorly immunogenic below the age of 2 years, has low immune memory, and lacks *booster effect* with repeated doses. It also does not reduce nasopharyngeal carriage and does not provide herd immunity.

#### Immunogenicity

A single dose of PPSV23 results in the induction of serotype-specific antibody response. Although being a polysaccharide vaccine, it is expected to mount only IgM response in absence of *class switching* to IgG typically associated with protein antigens, PPSV is unique as it induces IgM, IgA and IgG antibodies; the IgG antibodies predominantly belong to the IgG2 subclass. However, just like other polysaccharide vaccines, repeated doses are not associated with a booster response. On the contrary, there is evidence to suggest hyporesponsiveness with repeated doses. Thus, not more than two life time doses are recommended for this vaccine.

#### Efficacy and Effectiveness

Most of the data on its efficacy and effectiveness is based on studies conducted in adults with hardly any study in children. Despite the fact that PPSV is much older than PCV, the evidence on efficacy and effectiveness of PPSV23 continues to be conflicting. Possible causes of conflicting results in various studies are poor methodological quality of clinical trials, low rates of laboratory confirmed invasive pneumococcal disease (IPD) and the nonspecificity and varying definitions used for pneumococcal pneumonia. Moreover, the likelihood and biologic plausibility that efficacy and effectiveness vary with age and presence and severity of underlying high-risk condition that increases the risk of contracting pneumococcal pneumonia further complicates the issue of measuring the efficacy and effectiveness of this vaccine. A systematic review

commissioned by WHO concluded that the evidence was consistent with a protective effect against IPD and pneumonia in healthy adults and against IPD in the elderly. However, there was no evidence of efficacy against invasive disease or pneumonia in other high risk populations with underlying disease. In fact, one Ugandan study in HIV-infected adults showed an unexpected *increased* risk of pneumonia among those vaccinated with PPSV23.

#### Safety

PPSV23 is a safe vaccine, both in terms of immediate serious adverse events and potential long-term adverse consequences. Local adverse effects like pain and redness is reported in 30–50% of vaccines, occurring more commonly in those administered the vaccine subcutaneously as compared to intramuscularly and more in second dose as compared to first dose of the vaccine.

#### Recommendations for Use

PPSV23 is not effective in children below 2 years of age and thus is not recommended in this age group. It is also not recommended for routine use for healthy children of any age. Indian Academy of Pediatrics (IAP) recommends that this vaccine should only be used in certain high-risk groups of children and that too in conjunction with PCV. *PPSV should never be used alone for prevention of PDs amongst high-risk individuals.* The first dose of the vaccine should be given at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions (*vide infra*). The second dose of this vaccine should be given at the age of 5 years in these children. The dose is 0.5 mL to be given intramuscularly in deltoid muscle or subcutaneously.

When elective splenectomy, immunocompromising therapy, or cochlear implant placement is being planned; PPSV23 vaccination (along with PCV) should be completed at least 2 weeks before surgery or initiation of therapy. Following are the medical conditions for which PPSV23 (along with PCV) is indicated in the age group 24 through 71 months:

- *Immunocompetent children with chronic disease* like chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leaks; or cochlear implant.
- *Children with anatomic or functional asplenia* (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, or splenic dysfunction).
- *Children with immunocompromising conditions* HIV infection, chronic renal failure and nephrotic syndrome, diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemia, lymphomas and Hodgkin disease; or solid organ transplantation, congenital immunodeficiency.

### PNEUMOCOCCAL CONJUGATE VACCINES

In this type of pneumococcal vaccines, the *Streptococcus pneumoniae* capsular polysaccharides are chemically coupled with an immunogenic carrier. These were developed to overcome the immunological limitations of PPSV. PCVs have good immunogenicity even in infants, induce immunological memory and offer long-lasting protection.

#### Older PCVs

The first PCV was 7-valent vaccine (PCV7) containing capsular polysaccharides of 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) conjugated individually to a nontoxic diphtheria cross-reactive material carrier protein (CRM197). It was first licensed in February, 2000 in USA. It was subsequently replaced by 13-valent PCV (PCV13) in February 2010. A second 7-valent vaccine with the outer

membrane protein (OMP) complex of *Neisseria meningitidis* as the protein carrier was also developed but not licensed. Similarly, one 9-valent and two 11-valent PCVs were also developed but never licensed.

### Currently Available PCVs

The two PCVs that have been licensed and currently available are 10-valent (PCV10) and 13-valent (PCV13). PCV10 covers three additional serotypes besides those in PCV7: 1, 5, and 7F. It contains 3 µg each of the capsular polysaccharides of serotypes 18C and 19F conjugated to tetanus and diphtheria toxoid respectively, 3 µg of serotype 4 and 1 µg of rest of the serotypes each individually conjugated to an OMP of nontypeable *Haemophilus influenzae* (NTHi) (Protein D). It contains aluminum phosphate as an adjuvant, but no preservative. It is marketed as a pre-filled syringe in India. Latex is contained in syringe component.

PCV13 covers serotypes 3, 6A and 19A in addition to those contained in PCV10. It contains 4 µg of the capsular polysaccharide of serotype 6B and 2 µg of rest of the serotypes each individually conjugated to a nontoxic variant of diphtheria toxin, CRM197 (CRM, cross reactive material). The vaccine also contains aluminum phosphate as an adjuvant but no preservative. It is also available in India as prefilled syringes that do not contain latex.

### PCVs in Pipeline

An Indian company with active support of Department of Biotechnology (DBT), Government of India is developing 15-valent vaccine containing two additional serotypes, 2 and 12F to existing PCV13. Merck is also developing 15-valent vaccine with two additional serotypes, 22F and 33F to existing PCV13. Both these formulations are using CRM197 as a carrier protein. **Figure 1** shows serotype composition of the PCV formulations that have been evaluated in phase III clinical efficacy trials or under clinical development.

### Immunogenicity

PCVs induce serotype-specific antibody response. There is evidence in favor of cross-protection for the serotypes within the same serogroup (e.g., 6A and 6B serotypes of the serogroup 6), but the same is not seen in some other serogroups (e.g., between 19A and 19F). However, there is absolutely no protection against the serogroups not included in the particular formulation. Both the currently available vaccines have good immunogenicity in

the dosage schedules indicated by the respective manufacturers. Both of these meet the serological correlates of protection, clearly defined by the WHO. These criteria include:

- IgG (for all common serotypes collectively and not individually) of equal to or more than 0.35 mcg/mL measured by the WHO reference assay (or an equivalent alternative).
- The serotype-specific IgG geometric concentration ratios.

### Efficacy

The efficacy of PCV has been evaluated in different populations in both developed and developing countries in different regions of the world and against a number of different clinical outcomes.

**Invasive pneumococcal disease** The vaccine has been shown to be very efficacious in preventing IPD due to the serotypes contained in the vaccine. In a systematic review and meta-analysis from seven studies, a pooled vaccine efficacy of 80% [95% confidence interval (CI) 58% to 90%,  $P < 0.0001$ ] was observed against vaccine type invasive disease and 58% (95% CI 29% to 75%,  $P = 0.001$ ) against total invasive disease (irrespective of serotype).

**Pneumonia** Testing the vaccine efficacy against pneumococcal pneumonia is challenging, since its microbiological diagnosis is extremely difficult (unless it is associated with bacteremia). Thus, most of the studies have been conducted to test efficacy of these vaccines against radiologically defined pneumonia, using a standardized WHO definition and process for interpreting radiographs. The pooled estimate of vaccine efficacy against radiologically defined pneumonia has been found to be 27% (95% CI 15% to 36%,  $P < 0.0001$ ). Further, studies in South Africa have also shown reductions in hospitalization with virus-associated lower respiratory infection, suggesting that co-infection with pneumococcus contributes to severity of disease, resulting in hospitalization; receipt of PCV reduces the risk of severe disease associated with respiratory viruses that requires hospitalization. Thus, the full impact of PCV on pneumonia extends beyond the impact on radiologically defined pneumonia.

**Otitis media** Efficacy data for acute otitis media (AOM) is available for two formulations of PCV7, PCV9 and PCV11. Efficacy of around 56% has been found for AOM due to the serotypes contained in the respective vaccine formulations. However, with PCV7 and PCV9, increases in AOM due to other serotypes of pneumococcus and other organisms increased, such that the overall impact on otitis media was not significant. Nevertheless, PCV7-CRM197

Formulation	Protein carrier	1	2	3	4	5	6A	6B	7F	9V	12F	14	18C	19A	19F	22F	23F	33F
PCV 7	CRM 197																	
PCV 7	OMP																	
PCV 9	CRM 197																	
PCV 10	Protein D, TT, DT																	
PCV 11	TT, DT																	
PCV 11	Protein D																	
PCV 13	CRM 197																	
PCV 15*	CRM 197																	
PCV 15**	CRM 197																	

**Figure 1** Serotype composition of the pneumococcal conjugate vaccine formulations that have been evaluated in phase III clinical efficacy trials or under clinical development

■ Serotypes in the vaccine □ Serotypes with cross protection \*Under production in India by the support of DBT \*\*Under production in US by Merck



was observed to protect against recurrent or more severe forms of AOM, including otitis requiring tympanostomy tube placement. With PCV11, the protection against vaccine-type pneumococcal otitis was not completely offset by increases in otitis by other serotypes of pneumococcus or other bacteria; vaccine efficacy against all otitis media of 33.6% (95% CL 21, 44%) was observed. In this trial, significant protection was also observed against AOM caused by NTHi with observed efficacy of 35% (95% CL 1.8, 57.4%); this protection was attributed to the immune response to Protein D of NTHi, which was the protein carrier in this formulation of the vaccine. This PCV11 was later re-formulated as PCV10 (serotype 3 was removed) and is now marketed as PCV10 only.

**Nasopharyngeal carriage** Efficacy studies have also been conducted with PCV7 for reduction in nasopharyngeal carriage of pneumococci. These studies have shown about 50% reduction in nasopharyngeal carriage of vaccine serotypes with 50% increase in nasopharyngeal carriage of non-vaccine serotypes, resulting in net zero effect on overall nasopharyngeal carriage of pneumococci.

### Vaccine Effectiveness

The countries which have included PCVs in their national immunization programs have shown reduction in vaccine type invasive disease, not only in the targeted children, but also in older populations as a result of the indirect effects of the vaccine through reduction in nasopharyngeal carriage and transmission of the organism. This has been shown not only in developed countries like the USA and UK, but also in developing countries like Kenya and Nicaragua in the recent years. Moreover, since the incidence and mortality from IPD is generally higher in developing countries, the overall reduction in morbidity and mortality is likely to be greater. The reduction in socioeconomic inequalities in morbidity from PD observed in the United States supports this assumption. However, at least one study in Australia failed to document any reduction in radiologically defined pneumonia. One trial using PCV9, conducted in a high mortality setting in Gambia, showed reduction in *overall mortality* by 16% (95% CL 3, 28). The evidence in favor of using PCVs in otherwise healthy children over 5 years of age and use in pregnant women to protect their newborns is currently not sufficient, although WHO continues to consider and monitor the upcoming data on these fronts.

The prevalence of serotypes in the community where the vaccine is being used obviously affects vaccine effectiveness significantly, since *Streptococcus pneumoniae* has over 90 serotypes and the serotypes that cause significant disease vary by age, disease syndrome, disease severity, geographic region, and over time. Further, each serotype has a distinct *personality*. While a wide variety of serotypes cause noninvasive diseases such as otitis media and sinusitis, serotypes 1, 5, 6A, 6B, 14, 19F, and 23F are common causes of IPD globally in children less than 5 years of age. Serotypes 1, 5, and 14 together account for 28–43% of IPD globally and for about 30% of IPD in 20 of the world's poorest countries; serotypes 23F and 19F are responsible for 9–18% of cases globally. Serotype 18C is common in regions with a large proportion of high-income countries (i.e., Europe, North America, and Oceania). Some serotypes such as 6B, 9V, 14, 19A, 19F, and 23F are more likely than others to be associated with drug resistance.

In the last two decades, another factor that has changed the serotype distribution is the introduction of PCVs themselves. Prior to introduction of PCVs, 6–11 serotypes accounted for more than or equal to 70% of all IPD occurring in children worldwide. The distribution has changed after introduction of PCVs. The countries which introduced PCV in national immunization schedule (i.e., routine vaccination) have demonstrated dramatic reduction in, and in some places virtual disappearance of IPD due to vaccine

serotypes. This has led to the serotypes not contained in the vaccine gaining importance. For example, introduction of PCV7 in the USA led to great reduction in the vaccine serotypes, especially serotypes 4, 6B and 9V, but has led to significant increase in other serotypes, especially 7F and 19A. Currently, 19A accounts for maximum cases of IPD in the USA. However, the increase in IPD due to nonvaccine serotypes has not been as much as the reduction in IPD due to vaccine serotypes in most of the regions or countries. Hence, significant net reduction in cases of pneumonia or IPD has been observed. Such surveillance data from developing countries is sparse. Thus, WHO strongly recommends continued surveillance for replacement serotypes, especially in developing countries where the potential for replacement may be different from that in industrialized countries.

### Vaccine Effectiveness of Partial or Incomplete Vaccination

Clinical trials have demonstrated the vaccine effectiveness of one dose of PCV13 of about 48%, two doses 87% and 2+1 doses 100%. One dose catch up for toddlers showed 83% effectiveness.

### Duration of Protection

Both the immunogenicity and the post marketing surveillance data has shown protective efficacy of the PCV vaccines lasting for over 6 years.

### Safety

Various formulations of PCVs have been shown to have an excellent safety profile. The most common (~ 10% of vaccines) adverse events observed are injection-site reactions, fever, irritability, decreased appetite, and increased and/or decreased sleep. Fever with temperature more than 39°C occurs in 1/100 to less than 1/10 vaccines, vomiting and diarrhea in 1/1,000 to less than 1/100, and hypersensitivity reactions and nervous system disorders (including convulsions and hypotonic-hyporesponsive episodes) are rare (in 1/10,000 to less than 1/1,000 of the vaccines).

## Recommendations for Healthy Children

### Indication

In India, both PCV10 and PCV13 are licensed for active immunization for the prevention of PDs caused by the respective vaccine serotypes in children from 6 weeks to 5 years of age. US (FDA) licensed PCV13 for use in the age group of 6–17 years also. Licensing for the latter age-group is under process in India (personal communication).

### Administration Schedule

For both PCV10 and PCV13, IAP recommends three primary doses at 6, 10, and 14 weeks, followed by a booster at 12–15 months of the age (3p+1 schedule). The booster can be given as early as 6 months after the third dose. In most developed countries, the primary doses are recommended at 2, 4 and 6 months rather than 6, 10 and 14 weeks of age. Further, based on data from immunogenicity studies and on effectiveness data in children who received incomplete courses of PCV, several countries adopted shortened schedules for use in their national immunization programs so as to cut down the cost of mass vaccination. The most common of these schedules are three primary doses with no booster (3p+0) and two primary doses with one booster dose (2p+1). The major limitation of the 3p+0 schedule is the likelihood of less efficacy against serotype 1, which is very invasive serotype and is a common cause of IPD in second year of life, when the antibody levels may be less in that age with this schedule. The



**Table 1** Recommended schedule for use of PCV13/PCV10 among previously unvaccinated infants and children by age at time of first vaccination

Age at first dose	Primary series		Booster dose	
	PCV13	PCV10	PCV13	PCV10
6 weeks–6 months	3 doses	3 doses	1 dose at 12–15 months*	1 dose at 12–15 months*
7–11 months	2 doses	2 doses	1 dose during second year	1 dose during second year
12–23 months	2 doses#	2 doses#	NA	NA
24–59 months	1 dose	2 doses#	NA	NA

NA = not applicable \*At least 6 months after the third dose; # At least 8 weeks apart  
Abbreviation: PCV, pneumococcal conjugate vaccine.

major limitation of 2p+1 schedule is that the antibody levels in the interval between the two primary doses and the booster dose may be lower for some serotypes like 6B and 23F. The 3p+0 and 2p–1 schedules are to be considered only for mass vaccination; they are not recommended for *individual protection* or office practice.

### Catch-up Vaccination

**Table 1** gives the schedule for catch-up vaccination.

### Route of Administration

The vaccines are given by injection into the anterolateral aspect of the thigh in infants and into the deltoid muscle in older age groups.

### Recommendations for High-risk Group of Children

Children less than 2 years of age in high-risk category (*vide supra*, section on PPSV) should receive all the doses of PCV10/PCV13 as recommended for healthy children. In addition, they should also receive PPSV23 after the age of 2 years, and at least 8 weeks after the last dose of PCV.

Children who have received PPSV23 previously also should receive recommended PCV13/PCV10 doses. For children aged 24 through 71 months with certain underlying medical conditions, administer one dose of PCV13/10 if three doses of PCV were received previously or administer two doses of PCV13/10 at least 8 weeks apart if fewer than three doses of PCV were received previously. A single dose of PCV13/10 is sufficient for previously unvaccinated children in the 6–18 years age group in the high-risk category.

As per the latest (November 2013) guidelines of IAP, preterm babies and very low birthweight (VLBW) infants are also considered in high-risk category for pneumococcal vaccination. These infants have up to 9-fold higher incidence of IPD in VLBW babies as compared to full size babies. PCV13/10 is strongly recommended in these babies on a priority basis.

### MORE ON THIS TOPIC

23-valent pneumococcal polysaccharide vaccine. WHO position paper. Wkly Epidemiol Rec. 2008;83:373–84.

Cherian T. Pneumococcal vaccines. In: Vashishtha VM. IAP textbook of Vaccines. 1<sup>st</sup> ed. New Delhi: Jaypee Brothers Medical Publishers; 2014.

Pneumococcal vaccines. In: Vashishtha VM, Choudhury P, Bansal CP, et al. IAP Guidebook on Immunization 2013–2014. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.

Pneumococcal diseases. In: Vashishtha VM. FAQs on Vaccine and Immunization Practices. 1<sup>st</sup> ed. New Delhi: Jaypee Brothers Medical Publishers; 2011.pp. 206–22.

World Health Organization. Pneumococcal vaccines: WHO position paper—2012. Wkly Epidemiol Rec. 2012;87:129–44.

### IN A NUTSHELL

- Two types of vaccines are currently available and licensed against pneumococcus (*Streptococcus pneumoniae*): Pneumococcal polysaccharide vaccine (PPSV) and pneumococcal conjugate vaccines (PCVs).
- PPSV being a polysaccharide vaccine, it is T-cell independent vaccine, poorly immunogenic below the age of 2 years, has low immune memory, lacks *booster effect* with repeated doses, and does not provide herd immunity.
- PPSV is mainly indicated for certain high-risk individuals along with PCVs. It should never be used alone for prevention of pneumococcal diseases amongst high-risk individuals.
- A wide variety of serotypes cause noninvasive diseases such as otitis media and sinusitis, serotypes 1, 5, 6A, 6B, 14, 19F, and 23F are common causes of IPD globally in children less than 5 years of age.
- Currently, two PCVs are licensed and available, PCV10 and PCV13. PCV10 includes three additional serotypes besides those in PCV7: 1, 5, and 7F. PCV13 includes serotypes 3, 6A and 19A in addition to those contained in PCV10.
- Both PCVs have been shown to be very efficacious in preventing IPD due to the serotypes contained in the vaccine, however, they have modest impact on overall pneumonia.
- The countries which have included PCVs in their national immunization programs have shown reduction in vaccine type invasive disease, not only in the targeted children, but also in older populations as a result of the indirect effects of the vaccines.
- Emergence of *replacement disease* caused by nonvaccine serotypes owing to vaccine pressure and other trends has caused serious concerns.
- The increase in IPD due to *nonvaccine serotypes* has not been as much as the reduction in IPD due to vaccine serotypes in most of the regions or countries.
- WHO strongly recommends continued surveillance for replacement serotypes, especially in developing countries where the potential for replacement may be different from that in industrialized countries.

## Chapter 23.17

# Rotavirus Vaccines

Gagandeep Kang

Rotaviruses, discovered in humans in 1973, are now known to be the primary etiological agents of severe gastroenteritis in children less than 5 years of age, estimated to be the cause of nearly 40% of hospitalizations for acute gastroenteritis. Nearly 500,000 children die every year from rotavirus, mainly in developing countries, and this figure represents about 5% of all deaths in children younger than 5 years. Mortality is greatest in South Asia and sub-Saharan Africa—approximately 100,000 or more children die of rotavirus disease in India alone.

### VIRAL STRUCTURE AND DIVERSITY

Rotaviruses are triple layered particles, with the middle coat protein VP6 determining the group, and the outer coat proteins VP7 (G-) and VP4 (P-) responsible for the further classification into genotypes or serotypes. Human rotaviruses are mainly group A and VP7 genotypes G14, G9 and G12 and VP4 P genotypes P[4], P[6] and P[8] are the common strains seen worldwide. G9 strains emerged during the 1990s, and in the past decade, G12 strains have been identified in many parts of the world. Data from a surveillance network run by the Indian Council for Medical Research from 2005 to 2008, showed that the proportion of gastroenteritis hospitalizations associated with rotavirus was 39% and that the most common strains were G2P [4] (25.7%), G1P [8] (22.1%), and G9P [8] (8.5%). G12 strains were seen in combination with P[4], P[6] and P[8] and together made up 6.5% of strains.

### CLINICAL DISEASE AND EPIDEMIOLOGY

Virtually all children worldwide have been infected by the time they reach 2–3 years of age. Most symptomatic episodes occur between 3 months and 2 years of age with a peak incidence between 7 months and 15 months. Rotavirus infection is transmitted mainly by the fecal-oral route and contact and has a short incubation period of between 1 day and 3 days. Rotavirus disease is characterized by the sudden onset of acute watery diarrhea, often accompanied by fever and vomiting. Treatment of rotavirus illness is limited to supportive measures, such as oral or intravenous rehydration, and the only specific method to combat rotavirus disease is vaccination. In the absence of vaccines, the incidence of rotavirus disease was similar in both industrialized and developing countries, suggesting that although improvements in hygiene did delay the age of infection, viral gastroenteritis continued to occur in settings with good water supply, hygiene, and sanitation.

### ROTAVIRUS VACCINES

#### Early Vaccines

All currently licensed rotavirus vaccines are live, orally administered vaccines that aim to mimic the protection given by naturally occurring rotavirus infection. Research to develop a safe, effective rotavirus vaccine began in the mid-1970s. The early studies with monovalent animal rotavirus based vaccines gave inconsistent results, so further vaccine development efforts began to use either naturally attenuated human rotavirus strains or reassortant rotavirus strains bearing a human rotavirus gene for the VP7 protein together with the other genes from an animal rotavirus strain. The first multivalent live oral reassortant vaccine developed, RRV-TV (RotaShield made by Wyeth Ltd.), contained a mixture

of four virus strains, and was evaluated in field trials and proved highly effective (80–100%) in preventing severe diarrhea due to rotavirus. After this vaccine was included in the immunization schedule in USA and over 600,000 infants immunized, cases of vaccine-associated intussusception were reported. The period of greatest risk of intussusception was shown to be 3–10 days after the first of three oral doses.

#### Currently Licensed Vaccines

In 2014, there were four licensed vaccines of the world, of which two have been used by multiple countries in public immunization programs. One pentavalent human-bovine (WC3) reassortant (G1, G2, G3, G4 and P[8]) live-attenuated, oral vaccine, RotaTaq, was developed as a three dose series by Merck Research Laboratories. A live-attenuated human rotavirus G1P[8] vaccine (strain 89-12) was originally developed by tissue culture passage of a rotavirus isolate from an infant, and developed as Rotarix, given as a two dose series at 1–2 month intervals, by GlaxoSmithKline Biologicals. Both were tested in 60,000–70,000 children in northern and Latin America and northern Europe and showed excellent efficacy against severe rotavirus gastroenteritis and no evidence of an intussusception risk.

These two rotavirus vaccines were licensed and introduced into national programs in some parts of the world in 2006, and data have emerged on the impact of vaccination on morbidity and mortality. A study from Mexico published in 2010 suggests that the introduction of rotavirus vaccine resulted in substantial reduction in rotavirus deaths. Nationally representative data on morbidity in several high income countries showed a reduction of 28–50% in hospitalization rates for acute gastroenteritis for children under-5 years of age. Both the vaccine showed efficacy against viruses of all serotypes. Because the changes in rotavirus activity appeared more pronounced than might be attributed to direct protective effects of vaccination alone, the surveillance suggests that vaccination of a proportion of the population might offer indirect benefits to unvaccinated children (i.e., herd immunity) by reducing transmission of rotavirus in the community.

Postmarketing surveillance in several countries also identified a low-risk of intussusception with either vaccine (approximately 1–5 cases per 100,000 infants and is mainly in the first week after the first or second dose of vaccine). The vaccines were also evaluated in developing countries, and showed much lower efficacy (**Table 1**) than the approximately 90% efficacy that had been reported in industrialized countries. Effectiveness studies in Bolivia and Nicaragua reported approximately 50–70% effectiveness in prevention of hospitalized rotavirus gastroenteritis, while effectiveness was less than 40% in Bangladesh. Both vaccines demonstrated reduced vaccine efficacy or effectiveness, but had a high public health impact because of the high burden of disease in these regions. Little is known about the reasons why oral vaccines are less efficacious in developing countries, but several factors such as nutritional status, maternal antibodies, competing enteric infections, altered composition of intestinal microbiota and age at infections have been proposed.

Given the low risk of intussusception and the major impact that the vaccines have had on disease, resulting in decreased diarrheal hospitalizations and mortality wherever the vaccines have been used for several years, the World Health Organization (WHO) has recommended that rotavirus vaccine be used in the national immunization programs of all countries.

In India, 116E, a human neonatal, naturally reassorted G9P[11] strain of Indian origin has been evaluated in phase I–III studies, and shown to have 56% protection in the first year of life (**Table 1**) and 49% in the second year. It was also effective against gastroenteritis caused by multiple serotypes. This vaccine, called

Rotavac, is anticipated to be priced at 1US\$ a dose and hence may be affordable for resourced-limited countries.

In Vietnam, Rotavin-M1, a human attenuated G1P[8] strain, has been developed for local use and was licensed based on immunogenicity studies in adults and children. Efficacy results are awaited.

**Table 1** Efficacy of rotavirus vaccines in the Asian and sub-Saharan Africa region

	Vaccine	No. of children enrolled	Percent efficacy (CI)
<i>Asia</i>			
Bangladesh	RotaTeq	1136	42.7 (10.4–63.9)
Vietnam		900	63.9 (7.6–90.9)
Taiwan	Rotarix	1141	96.1 (85.1–99.5)
Singapore		6542	85.1–99.5
Hong Kong		3025	96.1 (85.1–99.5)
India	Rotavac	3799	53.6 (35.0–66.9)
<i>Africa</i>			
South Africa	Rotarix	1944	76.9 (56.0–88.4)
Malawi		1030	49.4 (19.2–68.3)
Ghana	RotaTeq	2162	55.5 (28.0–73.1)
Kenya		1221	63.9 (–5.9–89.8)
Mali		1842	17.6 (–22.9–45.0)

### Vaccines in Development

Other vaccines are in development in India, Australia, Indonesia, Brazil and China. These candidates belong to two categories: human neonatal strains, and human-bovine reassortant strains. A neonatal strain vaccine candidate based on RV3 is in development in a partnership between Australia and Indonesia. Other manufacturers in India, Brazil and China are developing vaccines based on the UK bovine strain, which has been licensed from the National Institutes of Health, and is a bovine-human reassortant. These candidates are currently in phase II or III trials.

In order to improve the performance of rotavirus vaccine, non-replicating vaccines are being developed for parenteral use and have just entered early phase trials. Although we do not completely understand the mechanism of protection in rotavirus immunization, it is possible that a systemic response may be sufficient to protect the individual child. It is not known whether viral replication in humans is an absolute prerequisite for mounting a protective immune response, but it is likely that delivery of nonreplicating antigens parenterally could induce a stronger and sustained immune response.

### RECOMMENDATIONS FOR VACCINATION

For children, Rotarix is given as a two doses schedule 1–2 months intervals beginning at 6–12 weeks of age along with routine childhood vaccines, while RotaTeq is administered as three doses at 1–2 months intervals beginning at 6–12 weeks of age. One study evaluating the immunogenicity of Rotarix vaccine at multiple sites in India found 27% of the 8-week-old infants initially seropositive. The 1 month post-dose two seroconversion rates observed in the vaccinated group was 58.3%. For RotaTeq, 20% of 6–12 week old

Indian infants were initially seropositive. Overall, 83% infants demonstrated seroconversion, the percentage with 3-fold increase in neutralizing antibody titer was 38.2%, 14.7%, 30.4%, 37.2% and 30.4% for G1, G2, G3, G4 and P8 respectively.

Fever, diarrhea and vomiting are the most common adverse events with both vaccines and occur in less than or equal to 10% of children and are generally self-limiting. Contraindications for vaccination include hypersensitivity to vaccine or to any ingredient, severe combined immunodeficiency disease, infants with uncorrected congenital gastrointestinal malformation (such as Meckel diverticulum) that would predispose for intussusception or a history of intussusception.

Although, recommendations and package inserts state that the vaccines should not be given after 32 weeks of age, the WHO has stated that for countries introducing rotavirus vaccination, the benefit of preventing rotavirus gastroenteritis morbidity and mortality should be considered when decided whether or not to broaden the age window for administration.

It has been estimated that with 70% coverage in the 72 countries eligible for funding by the GAVI alliance, vaccinating one single birth cohort would prevent about 55% of rotavirus associated deaths. Using the WHO's cost-effectiveness threshold of per-capita GDP, the vaccines would be cost-effective in 94% of GAVI eligible countries at a cost of 25 international dollars for each immunized child. However, in countries with large birth cohorts as in India, there are many factors which determine the ability of a national health-care system to deploy a new vaccine.

#### IN A NUTSHELL

1. Rotavirus is the leading cause of severe childhood gastroenteritis in both in developed and developing countries.
2. Two rotavirus vaccines Rotarix (GSK Biologicals) and RotaTeq (Merck Research Laboratories), are licensed in many countries in the world.
3. Rotavac is an Indian vaccine developed from 116E isolated at AIIMS, and has 53.6% efficacy against severe rotavirus vaccines caused by any serotype.
4. Rotavirus vaccine efficacy is lower in developing nations but still has a substantial public health impact.
5. Intussusception is a rare adverse event which appears to occur after the first or second dose of vaccine at a rate of 1 in 20,000 to 1 in 100,000 vaccines.
6. The World Health Organization has recommended that all national immunization programs should adopt these vaccines.

#### MORE ON THIS TOPIC

- Bhandari N, Rongsen-Chandola T, Bavdekar A, et al. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2014;383:2136–43.
- Glass RI, Parashar UD. Rotavirus vaccines—balancing intussusception risks and health benefits. *N Engl J Med*. 2014;370:568–70.
- Kang G, Desai R, Arora R, et al. Diversity of circulating rotavirus strains in children hospitalized with diarrhea in India, 2005–2009. *Vaccine*. 2013;31:2879–83.
- Rotavirus vaccines. WHO position paper. *Wkly Epidemiol Rec*. 2013;88:49–64.
- Tate JE, Burton AH, Boschi-Pinto C, et al. WHO-coordinated Global Rotavirus Surveillance Network. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programs: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12:136–41.



## Chapter 23.18

# Cholera Vaccines

Monjori Mitra

The annual global burden of cholera is estimated to be 3–5 million cases with 100,000–130,000 deaths (WHO estimates). Of the 32 countries that reported deaths from cholera, 20 were on the African continent which accounted for nearly 45% of the global total. In May 2011, the World Health Assembly recognized the re-emergence of cholera as a significant global public health problem and adopted resolution WHA 64.15, calling for implementation of an integrated and comprehensive global approach to cholera control.

**Disease burden in India** Cholera is endemic in India where only 25% of the population has access to piped water supply and sanitation. More than 95% strains are serotyped as Ogawa. Cholera is reported to be more common in children above 5 years of age. A recent study from Kolkata showed the highest incidence in children below the age of 2 years, highlighting a need for protection in early age.

### VACCINES

Vaccination against cholera was first tested in the 19th century and played a role in controlling epidemics. Injectable (parenteral) whole cell vaccines were used in the 1960s and 1970s, but were withdrawn as their efficacy was thought to be low and short-lived, and had high rate of adverse effects. Subsequently two types of oral cholera vaccines were developed. Oral vaccine is always preferable as it has been seen that the efficacy of injectable vaccine is around 50% only and moreover, it does not prevent introduction of cholera into a country or interrupt transmission (no herd immunity). Also it cannot prevent development of carrier state. For all these reasons, parenteral vaccine is not recommended by WHO for controlling epidemics.

### Oral Cholera Vaccines

#### *Killed Whole Cell Oral Cholera Vaccine*

Inactivated whole cell bivalent cholera vaccines against *Vibrio cholerae* O1 and O139 were developed for public health purposes in Vietnam in the 1990s. This bivalent vaccine has been found to be safe and to confer significant protection against El Tor cholera in both children and adults and has over the last decade being used in Vietnam to protect against cholera.

**Dukoral-TM (Crucell, Netherlands)** This vaccine contains a mixture of killed *V. cholerae* O1 bacteria and the non-toxic B subunit of cholera toxin (CTB). It showed 85% protection for the first 4–6 months and 60% protection for 2 years after a primary regimen of two or three doses. The protection declined substantially in the third year and was evident against *V. cholerae* O1 El Tor only in the first year for individuals younger than 5 years. Because heat labile toxin of enterotoxigenic *Escherichia coli* (ETEC) cross reacts with CT, this vaccine also provides short-term protection against ETEC. The limitation of the vaccine is that the vaccine is supplied with a buffer (as CTB is sensitive to stomach acid), which is to be dissolved in a glass of water. This needs safe drinking water and it also needs to be stored at 2–8°C. Further, as this vaccine does not have O139 strain, it is not recommended in India.

**Shanchol-TM (Shantha Biotechnics, India)** This vaccine developed and licensed in India in 2009 contains the same *V. cholerae* O1 whole-cell strains as Dukoral, at different doses, and killed *V. cholerae* O139 bacteria but not the B subunit component. It contains both Ogawa and Inaba serotypes of classical and El Tor biotypes with a recombinant B subunit of oral cholera toxin. A

large Phase III study in Kolkata (12,000 + participants age 1 year and above) showed over 60% protection against cholera. The vibriocidal antibody response rate was 80% in children and 53% in adults. Shanchol-TM is recommended for children 1–5 years. Two doses are given 14 days apart. Cumulative protective efficacy of the vaccine at 5 years was 65% and point estimates by year of follow-up suggested no evidence of decline in protective efficacy.

#### *Live Attenuated (CVD 103-HgR) Oral Cholera Vaccine*

CVD 103-HgR (Orochol-TM or Mutachol-TM) is a single dose live attenuated vaccine consisting of genetically manipulated classical *V. cholerae* O1 strain—available since 1994. Safety profile is good due to poor colonization in the human intestine. As the vaccine strain is live, maintenance of cold chain is needed to preserve the bacteria. The bacteria must also be protected from stomach acid, which is achieved by formulating and packaging of the vaccine with a buffer. The vaccine efficacy is near 60% for 6 months but does not any protection against O139 strain; long-term protection is also doubtful. This vaccine may be useful in prevention of cholera before or during epidemic.

#### *Herd Immunity Conferred by Killed Oral Cholera Vaccines*

Killed oral cholera vaccines confer significant herd protection to neighboring non-vaccinated individuals. This effect was attributed to vaccine induced reduction of fecal excretion of vibrios in vaccinated individuals giving rise to less environmental contamination and thus reducing fecal-oral transmission. Use of these vaccines could have a major effect on the burden of cholera in endemic settings.

### Cholera Vaccine in Epidemic Situation

In a case of cholera outbreak, a reactive vaccination campaign with a two-dose vaccine is almost impossible. Ideally a single dose-vaccine requiring no buffer and no cold chain, easy to administer, and providing long-term protection should be preferred. Dukoral-TM thus is not suitable for mass vaccination in epidemic situation. However, Shanchol-TM was recently found effective in response to a cholera outbreak in Guinea. In view of limited evidence, vaccination with the current internationally available prequalified vaccine is not recommended once a cholera outbreak has started.

### Future Vaccines

A number of other live oral vaccines are under development in the USA (Peru 15, CVD 110, 111, 112) and in Cuba (Cuban 638 strain). Results are promising and phase II and III trials are planned. Safety and immunogenicity study has also been conducted among Bangladeshi adults. Live oral vaccine against O139 is also undergoing safety and efficacy trials. A research on polysaccharide conjugate vaccine for cholera is currently being conducted in France and USA for parenteral use and evaluations are planned in countries with endemic cholera.

### IN A NUTSHELL

1. Parenteral whole cell vaccines, used initially during 1960s and 1970s, are no longer available. They were withdrawn due to poor efficacy and high reactogenicity.
2. Two types of oral cholera vaccines, killed and live attenuated are now currently in use globally.
3. A killed whole-cell oral cholera vaccine (Shanchol-TM) is currently available in India with reasonably good efficacy and long-term protection.
4. Shanchol-TM is recommended for children above 1 year of age in a schedule of two doses given 14 days apart.



## MORE ON THIS TOPIC

- Ali M, Emch M, von Seidlein L, et al. Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. *Lancet*. 2005;366:44-9.
- Bhadra RK, Dasgupta U, Das J. Cholera vaccine: developmental strategies and problems. *Indian J Biochem Biophysics*. 1994;31:441-8.
- Garg S, Saha PK, Ramamurthy T, et al. Nationwide prevalence of the new epidemic strain of *Vibrio Cholerae* O139 Bengal in India. *J Infect Dis*. 1993;27:108-9.
- Kanungo S, Sah BK, Lopez AL, et al. Cholera in India: an analysis of reports 1997-2006. *Bull World Health Organ*. 2010;88:185-91.
- Luquero FJ, Grout L, Ciglenecki I, et al. Use of *Vibrio cholerae* vaccine in an outbreak in Guinea. *N Engl J Med*. 2014;370:2111-20.
- Qadri F, Chowdhury MI, Faruque SM, et al. Randomised controlled study of the safety and immunogenicity of Peru-15, a live attenuated oral vaccine candidate for cholera, in adult Volunteers of Bangladesh. *J Infect Dis*. 2005;192:573-9.
- Sur D, Lopez AL, Kanungo S, et al. 5 year efficacy of a bivalent killed-whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis*. 2013;13:1050-6.
- Sur D, Lopez AL, Kanungo S, et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;374:1694-702.

## Chapter 23.19

# Varicella Vaccine

Rakesh Kumar

Available vaccine against varicella is quiet effective if vaccination is done as per the recommendations. However, varicella vaccination has not yet found a place in our National Immunization Schedule for its high cost and varicella not being a high priority health problem for India.

### LIVE VARICELLA VACCINE

In India only single antigen (monovalent) vaccine is available at present. Vaccine is made up of live-attenuated Oka strain of Varicella-zoster virus (VZV). An FDA approved quadrivalent vaccine (MMR-V), containing antigens for MMR and varicella, is available in USA. A higher concentration Oka strain vaccine is licensed by the FDA since 2006 which reduces the risk of herpes zoster and postherpetic neuralgia in people 60 years and older. However, it is not yet available in India. Monovalent varicella virus vaccine is lyophilized and should be stored at conditions prescribed by manufacturers. Reconstituted vaccine should contain a minimum of 1,000 plaque-forming units (PFU) in each 0.5 mL dose. Each 0.5 mL dose also contains 12.5 mg of gelatin, trace amounts of neomycin and fetal bovine serum along with sucrose.

### Vaccination Schedule, Dosage, Site and Route

Recommended schedule for primary active vaccination for children is first dose at 15–18 months and second dose anywhere between 4 years and 6 years. Second dose can be given earlier with at least a gap of 3 months in children less than 12 years. For older children and adults second doses given at an interval of 4–8 weeks completes active immunization. For postexposure prophylaxis vaccine dose is to be given within 3–5 days postexposure and second dose should be given as above.

### Vaccine Efficacy

Single dose vaccination (previously recommended) had lower efficacy of around 70–85% compared to more than 98% efficacy of second dose schedule as assessed over at least 10 years post-vaccination. Efficacy for preventing severe form of varicella is almost 100%. Also chances of breakthrough varicella after second dose schedule are almost 1/3rd as compared to single dose. The concentration of varicella antibody [ $> 5$  gp enzyme-linked immunosorbent assays (ELISA) units/mL] tested 6 weeks after immunization is known to confer vaccine efficacy rate of 95.5%.

### Adverse Reactions

Local reactions include pain, soreness, swelling and erythema, pruritus, hematoma, induration, stiffness, fever and rash. Around 5% of vaccines can develop vaccine virus related mild varicella like rash 2–3 weeks after vaccination. Anaphylaxis and Stevens-Johnson syndrome can be rare potentially serious complications. Ataxia, encephalitis, stroke, idiopathic thrombocytopenic purpura, and pneumonia, although reported after varicella vaccination, are very rare.

### Breakthrough Disease

Breakthrough varicella is defined as wild-type VZV infection occurring more than 42 days after vaccination. In cases of breakthrough disease, the median number of skin lesions is

commonly less than 50 (as against  $> 200$  in varicella in unimmunized cases). In addition, vaccine recipients have fewer vesicular lesions (have atypical lesions with papules not progressing to vesicles), shorter duration of illness, and lower incidence of fever. Secondary attack rate for breakthrough varicella is only 15% compared to 95% for varicella in unimmunized persons. Varicella occurring within 2 weeks after vaccination is due to wild VZV infection acquired before vaccine had its effect. Varicella occurring between 2 weeks and 42 days of vaccination can be either because of vaccine VZV or due to wild VZV and tends to be less severe compared to unimmunized persons.

### Catch-up Vaccination

If a person of any age has missed vaccination in early childhood, two doses of vaccine are administered at an interval of at least 4 weeks (3 months for  $< 12$  years) when there is no evidence of immunity against varicella. If only one dose is given previously and there is no evidence of immunity against varicella second dose is to be administered.

### Postexposure Prophylaxis

There are three options available for postexposure prophylaxis of varicella infection. First option being active vaccination as discussed above. Vaccination within 3 days of exposure to rash is more than or equal to 90% effective in preventing varicella whereas vaccination within 5 days of exposure to rash is approximately 70% effective in preventing varicella and 100% effective in modifying severe disease. Second option is of passive immunization with varicella-zoster immunoglobulin (VZIG). Third option of chemoprophylaxis with acyclovir also seems effective but there are no studies documenting its efficacy in preventing transmission after exposure. Indications for using VZIG as part of postexposure prophylaxis are: (1) Immunocompromised patients without evidence of immunity after direct exposure to varicella, including patients with primary and acquired immune-deficiency disorders, patients with neoplastic diseases, and those receiving immunosuppressive treatment. Patients receiving monthly high-dose intravenous immune globulin (IVIG) ( $\geq 400$  mg/kg) are likely to be protected and probably do not require VZIG if the last dose of IVIG was administered less than or equal to 3 weeks before exposure. (2) Healthy newborns where mother developed varicella between 5 days prior to delivery to 2 days after birth and premature newborns with exposure anytime during neonatal period. (3) Pregnant women without evidence of immunity against varicella. VZIG is supplied in 125-U vials. The recommended dose is 125 units/10 kg of body weight intramuscular, up to a maximum of 625 units (5 vials). The minimum dose is 125 U. Only preparation available in India is given at a dose of 0.2–1.0 mL/kg diluted in normal saline as intravenous infusion over 1 hour.

Any person receiving VZIG should subsequently receive varicella vaccine (if not contraindicated) but after an interval of 5 months. Administration of VZIG prolongs incubation period of varicella infection to up to 28 days (against usual average of 14 days), so patients receiving VZIG should be observed for appearance of signs or symptoms of varicella for at least 28 days.

### Contraindications

It is contraindicated in persons with history of severe anaphylactic reaction to vaccine or its components. It is also contraindicated in pregnancy. It should not be given to children who have congenital or acquired T-lymphocyte immunodeficiency, leukemia, lymphoma, malignant neoplasms affecting lymphoreticular system and children on long-term immunosuppressive therapy.

### Precautions

Varicella vaccine should not be administered to people who have moderate or severe illness, with or without associated fever. It should be administered with precaution in person who has recently received blood products or immune globulins or has a family history of immunodeficiency. A child who has thrombocytopenia or a history of thrombocytopenic purpura also needs close observation for deteriorating platelet counts.

### Vaccination of Immunocompromised Children

Children with humoral immune deficiencies can safely be immunized, but not those having T-cell defects. It can be given to HIV positive patients when CD4+ T-cell count is more than or equal to 15% of age related cut-off. Children on high dose systemic steroids (2 mg/kg/day of prednisone or its equivalent or 20 mg/day of prednisone or its equivalent) for more than 14 days should be vaccinated only after 1 month of discontinuation of high dose. Children on any other form of steroid therapy like inhaled, topical or nasal steroids can be safely administered varicella vaccine.

## INDIAN ACADEMY OF PEDIATRICS RECOMMENDATIONS

Indian Academy of Pediatrics (IAP) recommends that all healthy children should be offered varicella primary vaccination with first dose at 15–18 months and second dose anytime between 4 years and 6 years of age. High-risk populations (listed below) should also be actively vaccinated.

### High-risk Conditions Needing Varicella Vaccination

- Children with humoral immune deficiencies.
- Children with HIV infection but with CD4 counts 15% and above the age related cut-off.
- Leukemia but in remission and off chemotherapy for at least 3–6 months.
- Children on long-term salicylates. Salicylates should be avoided for at least 6 weeks after vaccination.
- Children likely to be on long-term steroid therapy. The vaccine may be given at any time if the children are on low dose steroids/alternate day steroids but only 4 weeks after stopping steroids if the patients have received high dose steroids (> 2 mg/kg) for 14 days or more.
- In household contacts of immunocompromised children.
- Adolescents who have not had varicella in past and are known to be varicella IgG negative, especially if they are leaving home for studies in a residential school or college.
- Children with chronic lung or heart disease.
- Seronegative adolescents and adults if they are inmates of or working in the institutional setup, e.g., school teachers, daycare center workers, military personnel and health-care professionals.

- For postexposure prophylaxis in susceptible healthy nonpregnant contacts.

### Criteria for Adequate Immunity Against Varicella

- Documentation of two appropriately timed doses of varicella vaccine.
- Laboratory evidence of immunity or laboratory confirmation of disease.
- Varicella diagnosed by a health-care professional or verification of history of varicella disease.
- History of herpes zoster diagnosed by a health-care professional.

### IN A NUTSHELL

1. An efficacious vaccine against varicella is available with almost 100% efficacy against moderate to severe disease after two doses.
2. Indian Academy of Pediatrics recommends that varicella vaccination should be offered to all children (> 1 year) with special consideration to high-risk groups.
3. Two doses are recommended for all ages with interval of at least 3 months for less than 12 years and 4–8 weeks for more than 12 years old.
4. Immunodeficiency, lymphoreticular malignancies, immunosuppressive drugs, previous severe reaction to vaccine and pregnancy are important contraindications.
5. Postexposure prophylaxis includes vaccination within 3–5 days with varicella-zoster immunoglobulin in some special situations with or without acyclovir.
6. The varicella vaccine is not yet included in the Universal Immunization Program (UIP) of India.

### MORE ON THIS TOPIC

- American Academy of Pediatrics Committee on Infectious Diseases. Prevention of varicella: recommendations for use of varicella vaccines in children, including a recommendation for a routine 2-dose varicella immunization schedule. *Pediatrics*. 2007;120:221–31.
- Bhave SY. Controversies in chicken-pox immunization. *Indian J Pediatr*. 2003;70:503–7.
- Indian Academy of Pediatrics Committee on Immunization (IAPCOI). Consensus recommendations on immunization and IAP immunization timetable 2012. *Indian Pediatr*. 2012;49:549–64.
- Marin M, Güris D, Chaves SS, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56:1–40.
- Varicella vaccine. In: Vashishtha VM, Choudhury P, Bansal CP, et al. *IAP Guidebook on Immunization 2013–2014*. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.
- Verma R, Bairwa M, Chawla S, et al. Should the chickenpox vaccine be included in the National Immunization Schedule in India? *Human Vaccin*. 2011;7:874–7.

## Chapter 23.20

# Hepatitis A Vaccine

Vikram Gagneja, AJ Chitkara

Hepatitis A is a vaccine-preventable, acute, self-limiting disease of the liver caused by the hepatitis A virus (HAV) which is transmitted primarily via the fecal/oral route either through ingestion of contaminated food and water or through direct contact with an infectious person.

The incidence of hepatitis A is strongly correlated with socioeconomic indicators; with increasing incomes and access to clean water and adequate sanitation, the incidence of HAV infection decreases. India has been hyperendemic for HAV infection. Studies conducted in the 2000s observed that nearly 90% of adolescents, adults, and most children acquire immunity to HAV infection in their preschool years. However, recent studies have indicated a shift in epidemiology of HAV infection and shown significant decrease in seropositivity over the years. The overall seroprevalence of HAV in the group aged 6–10 years (50.3%) was significantly higher than in the group aged 18 months to 6 years (30.3%). The seroprevalence of HAV is higher in community with poor access to education and potable drinking water.

## ACTIVE IMMUNIZATION

The best way of giving cost effective and long-term protection is by active immunization which can be achieved by giving formaldehyde *inactivated vaccines* produced in several countries and which are the most commonly used globally or *live-attenuated vaccines*, which are manufactured in China and available in several other countries. Children younger than 12 months should receive passive prophylaxis as HAV is not licensed for this age group.

## Inactivated Hepatitis A Vaccines

**Composition** HAV is propagated in human fibroblasts. Following purification from cell lysates, the HAV preparation is formaldehyde-inactivated. Most available vaccines are adjuvanted by adsorption to aluminum hydroxide. One available vaccine uses a virosome adjuvant. Inactivated hepatitis A vaccines are currently available in single-dose presentations and most are formulated without preservative. For children, several manufacturers provide a half-volume presentation of the vaccine with the same antigen concentration as the adult formulation. Inactivated hepatitis A vaccines should be refrigerated at 2–8°C; the vaccines should not be frozen. When stored at the recommended temperature, the shelf-life for inactivated hepatitis A vaccines ranges between 24 months and 36 months, as specified by the manufacturers.

**Dosage and schedule** Combined vaccines that include hepatitis A and B or hepatitis A and typhoid have been developed, mainly intended for use in adult travelers. Inactivated hepatitis A vaccines are licensed for use in persons older than or equal to 12 months of age and complete vaccination schedule consists of two doses with an interval of 6–12 months; however, the interval between the doses is flexible and can be extended to 18–36 months. Few studies have shown this interval to be as big as 54 months. Hepatitis A vaccines can be administered simultaneously with vaccines like diphtheria, pertussis, tetanus (DPT), polio, *Haemophilus influenzae* type B (Hib), measles, mumps, rubella, typhoid, hepatitis B, cholera, Japanese encephalitis, rabies and yellow fever, without biologically significant interference in the immunogenicity, reactogenicity or safety of the individual vaccines.

**Immunogenicity and efficacy** All inactivated hepatitis A vaccines are highly immunogenic and gives 95% protective efficacy following second booster. Antibody levels ranging from 10 IU/mL to 33 IU/mL, using different assays, have been proposed as the threshold for protection from HAV infection in humans. Within 2–4 weeks of the first dose of inactivated hepatitis A vaccine, up to 100% of immunocompetent children and young adults achieve anti-HAV immunoglobulin G (IgG) titers over 20 mIU/mL and this protection persisting 9–11 years after two doses has been reported in the studies. Using a cut-off of greater than or equal to 20 mIU/mL, the median predicted duration of protection was estimated at 45 years.

**Safety** The overall safety profile of all formaldehyde-inactivated hepatitis A vaccines has been excellent, irrespective of schedule and manufacturer. Except for some local reactions (soreness or tenderness at injection site), headaches (rarely), no vaccine-related, serious adverse events has been reported. The only precaution and contradiction of hepatitis vaccine is hypersensitivity to any of the vaccine components. Inactivated hepatitis A vaccines are well tolerated in patients with mild-to-moderate chronic liver disease, in liver and renal transplantation recipients and in dialysis patients. The safety of these vaccines during pregnancy has not been confirmed, but because they are prepared from inactivated virus the risk to the developing fetus is likely to be negligible.

## Live-attenuated Hepatitis A Vaccine

**Composition** Two live-attenuated hepatitis A vaccines, based on the viral H2 strain and on the L-A-1-strain, have been licensed in China since 2008 for subcutaneous administration in children aged older than or equal to 1 year. These live vaccines are attenuated through multiple cell culture passages and subsequently propagated in human diploid embryonic lung fibroblast cells.

**Dosage and schedule** The live-attenuated vaccine is administered as a single subcutaneous dose. Experience during clinical trials and through passive surveillance did not identify any substantial safety concerns related to the Chinese live-attenuated hepatitis A vaccines. However, as with most other live-attenuated vaccines, these vaccines are not recommended for use in pregnant women and in immunocompromised patients.

**Safety and immunogenicity** In a multicenter study conducted in India, single dose schedule of live-attenuated hepatitis A vaccine was found to be immunogenic and tolerable with minimal reactogenicity. Safety profile was also satisfactory in the study population. The persistence of protective antibodies has been documented for 5 years after a single dose and the follow-up continues.

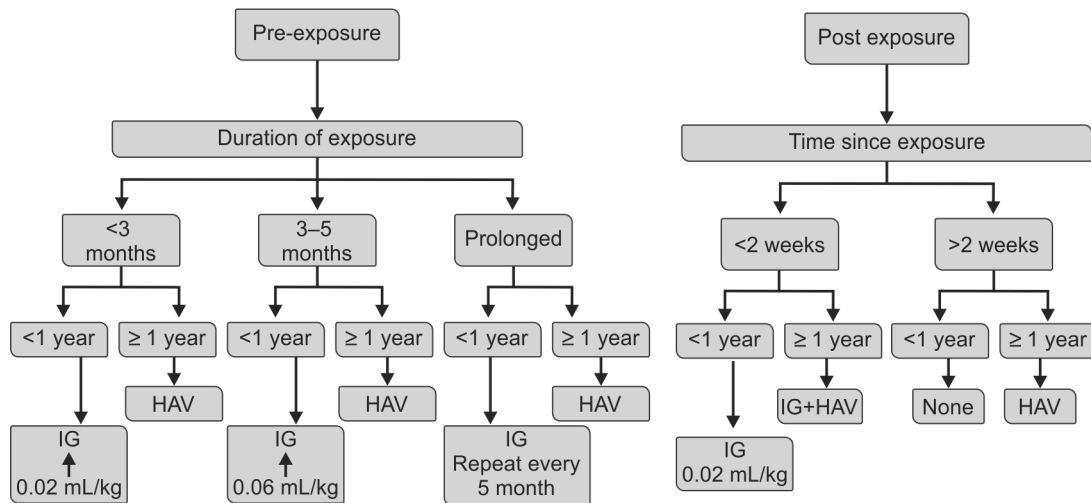
## Pre-exposure Prophylaxis

Pre-exposure prophylaxis for all children older than 12 months of age with either vaccine schedule and catch-up vaccination of unimmunized children from 2 years to 18 years of age in view of changing epidemiology should be considered. International travelers are at high-risk of getting hepatitis infection especially those travelling from low endemic area to high endemic area are candidates for routine prophylaxis with HAV. The Centers for Disease Control and Prevention (CDC) recommends combination of active and passive immunization for international travelers as per age and duration of likely exposure (**Flow chart 1**).

## Postexposure Prophylaxis

The use of hepatitis A vaccine rather than passive prophylaxis with Ig should be considered for travelers to areas of higher hepatitis.



**Flow chart 1** Recommendations for pre- and postexposure prophylaxis

Abbreviations: IG, immunoglobulin; HAV, hepatitis A vaccine.

An endemicity and postexposure prophylaxis for contacts of acute cases of hepatitis A in closed or institutional settings is cost-effective and as good as passive prophylaxis (**Flow chart 1**).

### Recommendations for Use

**Routine use** Hepatitis A vaccine is licensed for use in children above 12 months and older with two doses schedule when using inactivated vaccine and single dose with live-attenuated vaccine. The adult formulations are recommended for people 19 years of age and older. As per IAP recommendations the hepatitis A vaccine can be started any time after 12 months of age and second dose can be given between 6 months and 12 months after the first dose. The dose is 0.5 mL and 1 mL in pediatric and adult respectively by intramuscular route.

**Catch-up vaccination** It can be considered in children between 2 years and 18 years without the need for preimmunization serological testing. In cases where there has been missed or lapsed schedule the immunization should be completed at immediate contact with person. The vaccine is highly efficacious and this protective efficacy in preventing clinical HAV infection is 94–100%. Although the same vaccine is preferable for two dose schedule but vaccine interchangeability between different brands has no effect on immunogenicity.

### Recommendations in Special Circumstances

High-risk groups for hepatitis A infection include those who are at increased risk of HAV exposure as well as those at increased risk of a serious clinical outcome after acquiring the infection. These include those requiring life-long treatment with blood products, such as hemophiliacs, men who have sex with men, workers in contact with nonhuman primates and injection drug users. Vaccination of high-risk groups offers benefits to individual recipients but there is little evidence that such vaccination efforts are successful in reaching high coverage among targeted groups and effective in reducing reported rates of hepatitis A in the general population. Practical constraints, including staff turnover, may limit the effectiveness of vaccinating food handlers to prevent common-source food-borne hepatitis A. People with chronic liver diseases are at increased risk of fulminant hepatitis A, susceptible patients should receive routine immunization with hepatitis A vaccine.

The previously unimmunized household and sexual contacts after contact with confirmed case of HAV infection should immediately receive two dose schedule of hepatitis A vaccine. Newborn infants born to HAV-infected mother should receive Ig (0.02 mL/kg) if mother's symptoms started 2 weeks before and 1 week after delivery. School exposure does not warrant prophylaxis unless transmission within school is documented. However, unimmunized close contacts of an index case need prophylaxis.

Immunosuppressed patients show a reduced immune response and waning protective level to inactivated hepatitis A vaccines. Most individuals with compensated chronic liver disease who do not receive immunosuppressive therapy achieve similar seroprotection rates as those in healthy subjects. However, anti-HAV antibody levels following immunization are reduced, proportional to the degree of liver failure. Anti-HAV antibody seroconversion rates in HIV-infected individuals ranged from 52% to 94%.

**Outbreaks** During outbreaks in addition to general and contact precautions, exclusion of cases from childcare center, schools or workplaces especially those who work as food handlers for at least 1 week after onset of symptoms should be done. Prevention of further spread by isolation of source of infection and improving sanitation and personal hygiene should be contemplated. Prophylaxis for pre-exposure and postexposure with either vaccine or Ig has shown to be beneficial. Recommendations for hepatitis A vaccination in outbreak situations depend on the epidemiologic features of hepatitis A in the community and the feasibility of rapidly implementing a widespread vaccination program. The use of a single dose regimen of hepatitis A vaccine to control community-wide outbreaks has been most successful in small self-contained communities, when vaccination was started early in the course of the outbreak, and when high coverage of multiple age-cohorts was achieved. Vaccination efforts should be supplemented with health education and improved sanitation.

### PASSIVE PROPHYLAXIS

Passive prophylaxis with Ig against HAV infection is well documented and can be used for both pre- and postexposure prophylaxis. However the duration of protection is limited to approximately 1–2 months and 3–5 months following

administration of IgG at doses of 0.02 mL/kg and 0.06 mL/kg body weight, respectively. Prophylaxis is achieved within hours of injection and is 80–90% effective when administered before, or no later than 14 days after exposure. The use of Ig for protection against HAV has declined because of insufficient concentrations of anti-HAV IgG in nonspecific Ig preparations, the high cost of specific HAV IgG preparations, the limited duration of protection following passive IgG prophylaxis against HAV infection, and because controlled trial showed no significant difference in terms of protection against symptomatic and asymptomatic hepatitis A infection when either an IgG preparation or a hepatitis A vaccine was administered to contacts of confirmed hepatitis A.

### MORE ON THIS TOPIC

- Acharya SK, Madan K, Dattagupta S. Viral hepatitis in India. *Natl Med J India*. 2006;19:203-17.
- Arankalle V, Mitra M, Bhav S, et al. Changing epidemiology of hepatitis A virus in Indian children. *Dove Press Journal*. 2014;4:7-13.
- Bhave S, Bavdeker A, Madan Z, et al. Evaluation of immunogenicity and tolerability of a live attenuated hepatitis A vaccine in Indian children. *Indian Pediatr*. 2006;43:983-7.
- Bhave S, Bavdeker A, Sapru A, et al. Immunogenicity of single dose of live attenuated hepatitis A vaccine. *Indian Pediatr*. 2011;48:135-7.
- Bovier PA, Farnelli T, Loutan L. Predicted 30-year protection after vaccination with an aluminum-free virosomal hepatitis A vaccine. *J Med Virol*. 2010;82:1629-34.
- Faridi MM, Shah N, Ghosh TK, et al. Immunogenicity and safety of live attenuated hepatitis A vaccine: a multicentric study. *Indian Pediatr*. 2009;46:29-34.

- Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. *Vaccine*. 2010;28:6653-7.
- Vashishtha VM, Choudhury P, Bansal CP, et al. IAP Guidebook on Immunization 2013-2014. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.
- WHO position paper on hepatitis A vaccines—June 2012. *Wkly Epidemiol Rec*. 2012;87:261-76.

### IN A NUTSHELL

1. India has been hyperendemic for HAV infection with nearly 90% of adolescents, adults, and most children were found seropositive.
2. Epidemiology of HAV infection is changing in India.
3. Recent studies have indicated a shift in epidemiology with significant decrease in seropositivity of HAV infection over the past decade.
4. In India, HAV has shown to be associated with up to 50% of all cases of fulminant hepatic failure (FHF) in children with high case fatality rate.
5. Highly efficacious and safe inactivated and live-attenuated hepatitis A vaccines are available in India.
6. Immunization generates long-lasting, possibly life-long, protection against HAV infection in children as well as in adults.
7. Passive prophylaxis with Igs against HAV infection is well documented and can be used for both pre- and postexposure prophylaxis.

## Chapter 23.21

# Meningococcal Vaccine

Jaydeep Choudhury

Meningococcal disease is caused by *Neisseria meningitidis*, which is a gram-negative diplococcus bacterium. The bacteria appear as paired bean with flat surfaces facing each other and enclosed in a polysaccharide capsule. There are 13 serological variants of *Neisseria meningitidis* (A, B, C, 29E, H I, K L, W135, X, Y and Z). Serotypes A, B, C, W135 and Y are responsible for invasive disease. Humans are the sole natural reservoir. Meningococcal infections are though rare but often serious result in fatality if the treatment is not started early. It is an important cause of meningitis and sepsis, particularly in children below 5 years. *Neisseria meningitidis* spreads through infected droplets or through contact with respiratory secretions. The disease spectrum includes meningitis, pneumonia, septicemia, myocarditis and arthritis. Rarely does it present with shock, known as Waterhouse-Friderichsen syndrome.

There is low incidence of meningococcal disease in India, hence childhood vaccination with meningococcal vaccine is not routinely recommended. According to a recent Indian review, meningococcal meningitis constitutes 1.5–3.3% of all acute hospital admissions in children. It is indeed the third most common cause of bacterial meningitis amongst Indian children less than 5 years of age. Septicemia due to meningococcal infection is responsible for 2.8% of all hospital admissions. While there is low incidence of endemic disease, frequent outbreaks of meningococcal meningitis, particularly of type A, are noted mainly from the temperate northern than tropical southern regions of the country. These outbreaks occur mostly during the dry and cold season, usually during postmonsoon season. There are two peaks of the disease encountered globally that include young children around 2 years and adolescents.

## MENINGOCOCCAL VACCINES

### Meningococcal Polysaccharide Vaccine (MPSV)

Polysaccharide vaccine is available against serogroups A, C, W135 and Y. The vaccines are either bivalent (A and C) or quadrivalent (A, C, Y and W135). These vaccines can be given only in children above 2 years of age. These vaccines are safe. Most common side effects are local pain and redness at site of injection.

**Immunogenicity and efficacy** While the serogroup A polysaccharide is capable of inducing antibodies in some children as young as 3 months, the serogroup C is poorly immunogenic in children less than 2 years. Both these serogroups (A and C) have good immunogenicity and the good clinical efficacy among children 5 years of age or older and adults. Serogroup Y and W-135 polysaccharides are safe and immunogenic in older children and adults.

### Meningococcal Conjugate Vaccines

The polysaccharide vaccines elicit poor immunological response and they are not T-cell dependent, hence they do not produce good immunological memory. These shortcomings of polysaccharide vaccines led to development of polysaccharide-protein conjugate vaccines. Two types of meningococcal conjugate vaccines (MCVs) are licensed in India—a quadrivalent vaccine Menactra® from Sanofi Pasteur and another a monovalent serogroup A vaccine from

Serum Institute of India (SII). The latter is not available in private market in India. These vaccines are T-cell dependent and more immunogenic. They also exhibit herd effect through protection from nasopharyngeal carriage. They can also be given to children below 2 years of age. The conjugate meningococcal vaccines are heat labile and should be stored in cold chain at 2–8°C.

### Quadrivalent Meningococcal Conjugate Vaccine

It is a polysaccharide-protein conjugate vaccine covering serogroups A, C, W135 and Y. It uses diphtheria toxin as carrier protein. It is administered as a 0.5 mL dose intramuscular injection. It is licensed in India for use amongst individuals aging 2 years or above. A single dose is recommended in the age group of 2 years through 55 years whereas the vaccine is licensed in the United States to be used above 9 months of age. Two doses are recommended 3 months apart in children between ages of 9 months and 23 months.

It has got minor side effects like local pain, induration, redness and swelling. Guillain-Barré syndrome has been reported as possible, but unproven risk in some adolescents following vaccination with quadrivalent meningococcal conjugate vaccines. There is possibility of interference of immune response with 13 valent conjugate pneumococcal vaccine (PCV 13). In children where both the vaccines are recommended, PCV 13 should be administered first and meningococcal conjugate vaccines should be given after a gap of 4 weeks.

### Monovalent Meningococcal Conjugate Vaccine

Monovalent polysaccharide-protein conjugate vaccine covers serogroup A. Tetanus toxoid is used as carrier protein. The vaccine is recommended as single 0.5 mL IM to individuals 1–29 years of age. The vaccine has been found to be very effective in Africa where meningococcal A disease is prevalent. The vaccine is also very safe.

## INDIAN ACADEMY OF PEDIATRICS RECOMMENDATIONS

The Academy has not recommended routine use of meningococcal vaccine owing to very low incidence of the disease. It is recommended only for certain high-risk conditions and situations as detailed below in children aged 2 years or more (3 months or older if risk of meningococcal disease is high, e.g., outbreaks/close household contact). Conjugate vaccines should be preferred over polysaccharide vaccines due to superior immunogenicity and their potential for inducing herd effect, particularly in children less than 2 years of age.

Meningococcal vaccine should be offered to the following high-risk groups:

- Immunocompromised individuals like people suffering from human immunodeficiency virus (HIV), complement deficiency, individuals with B-cell defects, etc.
- Children with functional/anatomic asplenia/hyposplenia (vaccination should ideally be done 2 weeks prior to splenectomy)
- Students staying in boarding hostels or studying abroad
- Hajj pilgrims
- In outbreak situations
- Laboratory personnel and health-care workers
- Adjunct to chemoprophylaxis, in close contacts of patients with meningococcal disease
- Travellers to countries in the African meningitis belt.

**IN A NUTSHELL**

1. *Neisseria meningitides* has got 13 different serogroups, of which only A, B, C, W135 and Y serotypes are responsible for invasive disease (meningitis, pneumonia, septicemia, myocarditis and arthritis).
2. The overall burden of endemic meningococcal disease in India is very low, hence routine childhood vaccination is not recommended.
3. Outbreaks of group A meningococcal meningitis are regularly reported from many northern states of India.
4. Two types of meningococcal vaccines have been developed, polysaccharide and conjugate vaccine.
5. Polysaccharide vaccines cannot be given to children below 2 years of age be given only in children above 2 years of age.
6. The polysaccharide-protein conjugate vaccines are T-cell dependent and more immunogenic and can be given in children below 2 years of age.

**MORE ON THIS TOPIC**

Meningococcal vaccines. WHO Position Paper. Wkly Epidemiol Rec. 2011;86:521-39.

Sinclair D, Preziosi MP, Jacob John T, et al. The epidemiology of meningococcal disease in India. Trop Med Int Health. 2010;15:1421-35.

Vashishtha VM, Kalra A, Bose A, et al. Indian Academy of Pediatrics (IAP) recommended immunization schedule for children aged 0 through 18 years-India, 2013 and updates on immunization. Indian Pediatr. 2013;50:1095-108.



## Chapter 23.22

# Seasonal and Pandemic Influenza Vaccines

*Shobha Broor*

The influenza viruses types A and B are important global causative agents of flu, causing annual epidemics which are associated with excess hospitalizations and mortality, particularly among children and the elderly and those having comorbidities such as, cardiopulmonary and metabolic diseases and immunodeficiency. Prevention of infection by influenza virus by means of vaccination is recommended for all of these populations and their contacts. In the United States an estimated 25–50 million cases of influenza occur annually and resulting in approximately 225,000 hospitalization. Further this results in 30,000–70,000 excess deaths/year. In developed countries, influenza associated hospitalization rates per 100,000 have varied from 78 to 108 in the United States to 190 in the United Kingdom.

The exact disease burden for influenza for India is not known but approximately 0.6 million hospitalizations related to influenza are expected in India. Among children less than 5 years old, influenza-related hospitalization rates are highest in those, less than 1 year of age. Influenza disease burden in India is comparable to other parts of the world. In a recent study, among children aged less than 5 years, estimated influenza associated hospitalization rate was 93 per 100,000 children in Ballabgarh and 350 per 100,000 in Vadu.

## EPIDEMIOLOGY OF INFLUENZA

### Influenza Epidemics

Influenza outbreaks have a well-defined seasonality. Influenza A outbreaks typically begin abruptly, peak over a 2–3-week period, and last for 2–3 months. In most outbreaks, the earliest indication of influenza activity is an increase in febrile respiratory illnesses in children, followed by increases in influenza-like illnesses in adults. One factor that may influence which influenza strains will predominate during an influenza season is the seroprotection rate among children during the preceding season. In a study in which children and adults were tested for antibodies to locally circulating influenza strains during three consecutive influenza seasons (2006–2007, 2007–2008 and 2008–2009), the lowest rates of seroprotection in children (but not in adults) coincided with the dominant influenza subtype during the following winter epidemic. The protection rate in children is important for shaping future epidemics because children are prolific disseminators of respiratory virus infections. Most outbreaks have attack rates of 10–20% in the general population, but rates can exceed 50% in pandemics.

### Seasonality of Influenza Epidemics

In temperate regions of the Northern and Southern hemispheres, influenza peaks during winter season (which occur at different times of the year) and these annual winter epidemics are associated with excess deaths from influenza and pneumonia. Although they occur in distinct periods of the year, influenza strains circulating in the two hemispheres are not independent of each other, and strains circulating in one hemisphere will inevitably spread to the other hemisphere during the next season. The pattern of influenza is different in tropical and subtropical areas, with year-round

circulation in some areas and biannual peaks in others. It remains unclear whether tropical regions where influenza circulation is reported throughout the year serve as reservoir for the epidemics in both hemispheres. Recent studies from Bangladesh, Cambodia, India, Laos, Myanmar, Singapore, Thailand and Vietnam outlined an important role of regular influenza surveillance. Influenza activity peaked between June/July and October in 7 out of 10 countries, 3 of which showed a second peak in December to February. In Bangladesh, Cambodia, India, the Lao People's Democratic Republic, the Philippines, Thailand and Vietnam, more than 60% of cumulative proportion of specimens positive for influenza were from June to November from 2006 to 2011. Countries closer to the equator (Indonesia, Malaysia and Singapore) had year-round circulation without discrete peaks. Since the peak of influenza circulation coincides with rainfall during July to October for most countries in Southeast Asia, influenza vaccination prior to monsoon season in some countries in the tropical Asian region in the northern hemisphere may be more beneficial.

### Pandemics of Influenza

Pandemics of influenza occur unpredictably and relatively infrequently, but they are important as they result in the global circulation of a new influenza A virus subtype that can lead to substantially increased morbidity and mortality in all age groups. In June 2009, the World Health Organization (WHO) raised its pandemic alert level to the highest level, phase 6, indicating widespread community transmission in at least two continents. The pandemic was declared to be over in August 2010. The 2009 to 2010 H1N1 influenza A pandemic was caused by an A/H1N1 virus that had not been recognized previously in pigs or humans. This strain represented a genetic reassortment of swine, human and avian strains of influenza. Pandemic H1N1 influenza A infections were uncommon in persons older than 65 years, possibly as a result of pre-existing immunity against antigenically similar influenza viruses that circulated prior to 1957.

Recent H1N1 pandemic of 2009 has estimated 285,000 deaths globally. It is predicted that Southeast Asia and Africa had the highest mortality and 59% of all deaths may have occurred on these two continents, which are home to 38% of the world's population. Increased morbidity and mortality among children was observed with 2009 pandemic H1N1 influenza virus as compared to seasonal influenza. Although the majority of reported deaths occurred in individuals with underlying comorbidities, up to one-third of hospitalized patients had no underlying chronic illness. Higher mortality and severe illness was also seen with pandemic H1N1 infection in pregnant women. In pandemic influenza unlike seasonal influenza where elderly are more affected, a shift in the age distribution towards children is seen. Data from three recent influenza pandemics show that school-aged children had the highest disease rates and may serve as a key source of transmission to adults.

### Seasonal and Pandemic Influenza in India

A laboratory-based virological surveillance network of influenza viruses has been setup in geographically distinct regions in northern, central, southern and eastern India by Indian Council of Medical Research. Extensive surveillance carried out in India reveals a major peak of influenza which coincides with rainy season in tropical region of India in Pune, Delhi, Kolkata and Chennai and a minor peak in winter, though some level of circulation has been observed throughout the year. In contrast, influenza circulation peaks in winter in Srinagar, similar to what has been observed for temperate regions. The influenza surveillance network has identified varying seasonality, with cocirculation of all subtypes.

## INFLUENZA VACCINES

Influenza vaccines have two different formulations one for Northern hemisphere and second for Southern hemisphere. The vaccine strains may be similar for both formulations or different depending on the circulating strains. Influenza vaccines are modified annually, based on WHO recommendations. Annual update of vaccine strains is essential for vaccines to be effective due to constant antigenic changes in influenza viruses. Since 1973, WHO has provided recommendation for the composition of influenza vaccines based on the information provided by WHO Global Influenza Surveillance Network (GISN). Twice annually WHO specialist meet in February and September to consider the epidemiological data collected during the previous year and to recommend which influenza strains will be most likely to cause epidemics the following year and should therefore be part of the vaccine to be used for Northern hemisphere and Southern hemisphere formulations. High yield candidate vaccine strains are then developed by reassortment by WHO collaborating centers (CCs). These are then sent to CCs which carry out complete identification of the viruses, with detailed antigenic descriptions.

### Types of Influenza Vaccines

**Killed vaccines** Trivalent inactivated influenza vaccine (TIV), this terminology has now been replaced with inactivated influenza vaccine (IIV) which can be egg or cell-culture based. This included IIV3 (trivalent vaccine) and IIV4 (quadrivalent vaccine). Cell-culture-based vaccine is also referred as ccIIV/ccIIV3. In recent years a recombinant hemagglutinin (HA) vaccine has also been licensed which is called trivalent recombinant influenza vaccine (RIV3).

**Live vaccines** Live-attenuated influenza vaccine (LAIV) which can be trivalent LAIV3 or quadrivalent LAIV4.

### Inactivated Influenza Vaccines (IIV3/IIV4)

Inactivated vaccines are the primary means of preventing influenza infection, due to the vast experience of their use worldwide. Vaccines made with whole viruses induce good levels of immunogenicity, but have greater reactogenicity, and are known to cause fever in children and, therefore, are not indicated for this age group. Split vaccines are made either from fragmented or subunit viruses; these have a good safety profile with the first being more immunogenic than the second and both are recommended for children under 12 years. Virosome vaccines are inactivated vaccines in which the HA and neuraminidase (NA) influenza virus surface antigens are incorporated into virus-like particles that have an adjuvant role. This type of vaccine offers similar immunogenicity and safety to other vaccines.

Current formulations of these vaccines (IIV3) contain three influenza virus strains, i.e., (1) influenza A subtypes H1N1 and (2) H3N2 and (3) influenza B. The strains to be included in the vaccine are selected annually on the basis of the viruses anticipated to be circulating during the upcoming influenza season. Quadrivalent IIV (IIV4) vaccine has two influenza B strains, (1) Victoria and (2) Yamagata, lineage. Hemagglutinin is the main immunogen in IIVs. Virus strains to be included in IIV are grown in embryonated hen eggs, inactivated and then (in most instances) preserved with thimerosal (1:10,000).

### Efficacy and Immunogenicity

The results of clinical trials investigating the efficacy of the IIV vary greatly, depending upon age group, season, vaccine strain match with circulating strain and endpoint of analysis of efficacy. In

general, efficacy against confirmed influenza virus infection varies from 31% to 91% and is not uniform for the subtypes. Protective efficacy for acute otitis media (AMO) is more variable, being reported as absent by some authors and up to 36% by others. IIVs are less effective in children and elderly, the two populations at most risk of developing severe disease. Other limitations of IIVs include extended production times (which has led to vaccine shortages in the past) and decreased efficacy against influenza viral strains that are antigenically different from those contained in the vaccine.

### Safety and Adverse Events

Inactivated influenza vaccines are very safe in children as seen over last many years in many populations based studies. The most common side effects seen with IIV administration are soreness at the injection site and fever. Fever, is more common in children less than 2 years of age (10–35% of recipients), and usually occurs within 6–24 hours after immunization. Mild systemic symptoms such as nausea, lethargy, headache, muscle aches and chills are also reported in some cases.

During the *swine flu* vaccine program in 1976, an increase in the number of cases of Guillain-Barré syndrome (GBS) was reported in adults within 10 weeks after immunization. Additional investigations have revealed that there may be a slight increase in the risk of GBS (approximately 1 additional case of GBS per 1 million vaccine recipients) among adults after influenza immunization, at least in some years. The Institute of Medicine evaluated the association of demyelinating diseases and influenza vaccine and concluded that there is no evidence bearing on a causal relationship between influenza vaccines and demyelinating neurologic disorders in children 6–23 months of age.

Even in with human immunodeficiency virus (HIV)-affected individuals, most experts believe that the benefits of influenza immunization with IIV far outweigh the risks in children with HIV infection.

Because influenza vaccine is grown in embryonated hen eggs, children demonstrating anaphylactic reactions to chicken or egg proteins may rarely experience a similar reaction to influenza vaccine and therefore should not be given IIV unless they undergo desensitization. IIV containing thimerosal should not be given to individuals with hypersensitivity to thimerosal.

### Live-attenuated Influenza Vaccine

Live-attenuated, cold-adapted, trivalent influenza vaccine has been developed by repeated passages of influenza viruses at lower temperature. The cold adapted strains grow better at 25°C and their replication is restricted at 38°C–39°C. The LAIV strains for vaccine for each year are made by reassortment with these cold adapted master strains and grown in eggs to a high titer. LAIV is given by intranasal route 0.25 mL in each nostril using an accuspray device and is more effective than IIV in children. LAIV is thus a good and effective approach for prevention of influenza in children. In India Serum Institute of India (SII) is making trivalent LAIV using Russian virus master strains. In the United States of America Medimmune makes both trivalent and quadrivalent LAIV. Each 0.5 mL dose of trivalent vaccine contains approximately 10<sup>7</sup> tissue culture infectivity doses of influenza strains A subtype H1N1, A subtype H3N2, and B. Children younger than 9 years of age being immunized against influenza for the first time should receive two doses of LAIV given 4–6 weeks apart before the start of the influenza season.

**Efficacy** Efficacy of LAIV in various studies varies from 26% to 93%. Vaccine efficacy against influenza A (H3N2) and B outbreaks has

shown to be greater than 80% efficacious in preventing influenza illness in a multicenter trial of FluMist in pediatric population in the United States.

**Safety** Live-attenuated influenza vaccine has been found to be very safe and no reversion to virulent phenotype has been reported. Side effects in children can include runny nose, headache, wheezing, vomiting, muscle aches and fever. Studies of transmission of LAIV strains to nonimmunized contacts have failed to show transmission as vaccine virus is shed for shorter duration and smaller quantity.

### Choice of Influenza Vaccine

The choice of vaccine for an individual child depends upon age and risk factors for severe or complicated influenza. Persons at risk for severe complications of influenza are shown in **Table 1**. IIV is indicated for children older than or equal to 6 months, including those who cannot receive LAIV. The following groups should receive IIV rather than LAIV:

- Children older than or equal to 6 months through 23 months of age
- Children aged 2 years through 4 years who have asthma or who have had a wheezing episode noted in the medical record within the past 12 months, or for whom parents report that a health-care provider stated that they had wheezing or asthma within the last 12 months
- Children (of any age) with asthma
- Children aged 2 years through 17 years who are receiving aspirin or aspirin-containing products
- Children who have experienced allergic reaction to vaccine or any of its component to a previous dose of LAIV
- Children with medical conditions that increase the risk for severe or complicated influenza infection
- Children who are close contacts of severely immunocompromised individuals (e.g., hematopoietic stem cell transplant recipients).

Children older than 2 years who are not in one of the categories listed above may receive either IIV or LAIV. According to several studies in children, LAIV may be more efficacious than IIV, and provides better immunity against mismatched strains, may provide

immediate protection during an outbreak, may provide better T-cell responses and may provide longer-standing protection than IIV. Compared with IIV, LAIV also provided better protection in preventing culture-confirmed influenza in children. A randomized controlled trial conducted among 7,852 children aged 6–59 months demonstrated a 55% reduction in culture-confirmed influenza among children who received LAIV compared with those who received IIV. LAIV efficacy was higher than that of IIV against both antigenically drifted and well-matched influenza viruses. Side effects appear to be similar for LAIV and IIV. **Table 2** provides a comparative analysis of LAIV and IIV for seasonal influenza while **Table 3** lists the available and licensed influenza vaccines in India.

### INFLUENZA VACCINATION RECOMMENDATIONS

Both *Government of India* (GoI) and *Indian Academy of Pediatrics* (IAP) have not recommended universal immunization of healthy children against influenza. IAP has recommended seasonal influenza vaccine, IIV only for the category of *high-risk children*, which includes the following:

- Chronic cardiac, pulmonary (excluding asthma), hematologic and renal (including nephritic syndrome) condition, chronic liver diseases and diabetes mellitus
- Congenital or acquired immunodeficiency (including HIV infection)
- Children on long-term salicylates therapy
- Laboratory personnel and health-care workers.

*Advisory Committee on Immunization Practices* [ACIP; a branch of the United States Centers for Disease Control and Prevention (CDC)] recommends routine annual influenza vaccination for all persons aged older than or equal to 6 months who do not have contraindications.

### Best Time to Vaccinate

Vaccination optimally should occur before onset of influenza activity in the community. Since in India, Influenza peaks mainly are seen during rainy season, vaccination should be offered before onset of monsoon in the country. The best time for offering vaccine for individuals residing in southern states would be just before the onset of rainy season, i.e., before October while for rest of the country, it should be before June. According to WHO classification, the recommendations on vaccine formulation for India strongly favor the *Southern hemisphere vaccine* rather than *Northern hemisphere*. However, since there is a lag period of 6 months between issuance of recommendations on constitution of the vaccine for a particular hemisphere and production and availability of vaccine in the market, it is advisable to use the vaccine available with the newest strain rather than delaying the vaccination.

### Dosage and Schedule

Children aged 6 months through 8 years require two doses of influenza vaccine (administered greater than or equal to 4 weeks apart) during their first season of vaccination to optimize immune response. This is truer for influenza B as children who received one dose had a lower response as compared to children who had received two doses in the prior season. In determining the appropriate number of doses, previous receipt of vaccine containing 2009 influenza A (H1N1) pandemic antigen (included in monovalent pandemic vaccine during 2009–10 and in seasonal influenza vaccines since the 2010–11 season) also should be considered. In addition, because the strains contained in the 2014–15 seasonal influenza vaccines are identical to those contained in the 2013–14 vaccines, only one dose is required for any child aged 6 months through 8 years who previously received more than one dose of 2013–14 seasonal influenza vaccine (**Flow chart 1**).

**Table 1** Groups at high-risk for influenza complications

- Children 6–59 months of age
- All persons 50 years of age and older
- Anyone with chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurological, hematologic, or metabolic disorders (including diabetes mellitus)
- Persons who have immunosuppression, including immunosuppression caused by medications or HIV infection
- Women who are or will be pregnant during the influenza season
- Children (6 months through 18 years) receiving long-term aspirin therapy and who might be at risk for experiencing Reye's syndrome after influenza virus infection
- Residents of nursing homes and other long-term care facilities
- Persons who are morbidly obese (BMI  $\geq 40$ )

#### People who live with or care for those at highest risk

- Health-care personnel
- Household contacts (including children) and caregivers of children younger than 5 years (i.e., prior to the 5th birthday) and adults 50 years of age and older—particular emphasis on vaccinating contacts of children younger than 6 months
- Household contacts (including children) and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza

**Abbreviations:** HIV, human immunodeficiency virus; BMI, body mass index.

**Table 2** Comparison of live-attenuated influenza vaccine (LAIV) with inactivated influenza vaccine (IIV) for seasonal influenza

	LAIV	IIV
Route of administration	Intranasal spray	Intramuscular injection**
Type of vaccine	Live attenuated	Killed virus
Number of included virus strains	Three/four (two influenza A, one/two influenza B)	Three/four (two influenza A, one/two influenza B)
Vaccine virus strains updated	Annually*	Annually*
Frequency of administration	Annually	Annually
Approved age	Persons aged > 2 years to 49 years	Persons aged ≥ 6 months
Interval between two doses recommended for children aged ≥ 6 months to 8 years who require two doses	≥ 4 weeks	≥ 4 weeks
Can be administered simultaneously with other vaccines	Yes	Yes
If not administered simultaneously, can be administered within 4 weeks of another live vaccine	Prudent to space ≥ 4 weeks apart	Yes
If not administered simultaneously, can be administered within 4 weeks of an inactivated vaccine	Yes	Yes

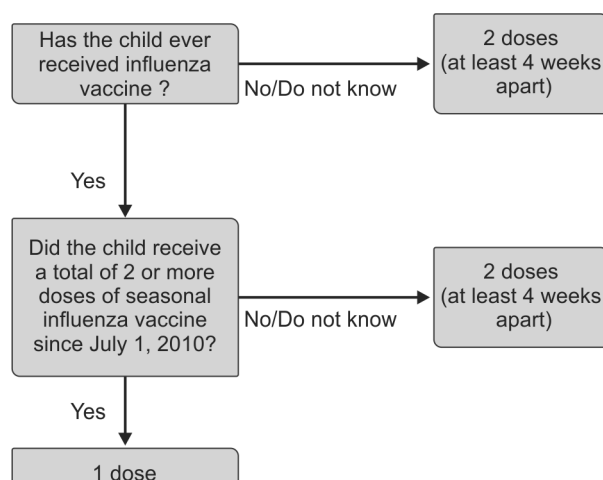
\* Every year World Health Organization (WHO) decides regarding which virus strains will be included in the vaccine for the upcoming influenza season. Even in years in which the vaccine composition is the same as the previous season, annual vaccination is necessary since immunity wanes.

\*\* For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.

**Table 3** Influenza vaccines licensed in India

Brand names	Composition	Manufacturer
Vaxigrip	TIV (both SH and NH)	Sanofi Pasteur India Private Limited
Aggripal	TIV (NH)	Chiron Panacea (Panacea Biotec Ltd)
Influgen	TIV (NH)	Lupin Laboratories Ltd
Influvac	TIV (NH)	Solvay Pharma India Pvt Ltd (Abott)
Fluarix	TIV (NH)	Glaxo Smithkline Pharmaceuticals Ltd.
Nasovac-S	LAIV (Trivalent)	Serum Institute of India Ltd
Vaxiflu	TIV (NH)	Zydus Cadila

Abbreviations: TIV, trivalent influenza vaccine; LAIV, live-attenuated influenza vaccine; SH, Southern hemispheres; NH, Northern hemispheres.

**Flow chart 1** Algorithm for influenza dose in children from 6 months to 8 years of age

### Influenza Vaccination of Persons with a History of Egg Allergy

With the exceptions of RIV3 [(FluBlok), Protein Sciences] and cell-culture-based IIV [ccIIV3 (Flucelvax), Novartis], currently available influenza vaccines are prepared by propagation of virus in embryonated chicken eggs. However, a review of published data has shown that severe allergic reactions to egg-based influenza vaccines are unlikely. History of mild egg allergy is not an absolute contraindication for IIV/LAIV; however, they should be used with caution in these individuals. On the other hand, a previous severe allergic reaction to influenza vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine.

### Influenza Immunization of Pregnant Women

Influenza may cause more severe illness in pregnant women than in women who are not pregnant. Changes in the immune system, heart and lungs during pregnancy make pregnant women more



prone to severe illness. Even deaths due to influenza are more common in pregnant women; pregnant woman with influenza can also have adverse effect on pregnancy outcomes in terms of prematurity, low birth for term babies. Influenza vaccination of pregnant mothers with killed influenza vaccine has been shown to be safe and provides protection to both mother and newborn baby up to 6 months. Live influenza vaccine however should not be given to pregnant mothers.

### MORE ON THIS TOPIC

- Azziz Baumgartner E, Dao CN, Nasreen S, et al. Seasonality, timing, and climate drivers of influenza activity worldwide. *J Infect Dis.* 2012;206:838-46.
- Belshe RB, Gruber WC, Mendelman PM, et al. Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. *J Pediatr.* 2000;136:168-75.
- BraccoNeto H, Farhat CK, Tregnaghi MW, et al. Efficacy and safety of 1 and 2 doses of live attenuated influenza vaccine in vaccine-naïve children. *Pediatr Infect Dis J.* 2009;28:365-71.
- Broor S, Sullender WS, Fowler K, et al. Demographic Shift of Influenza A (H1N1)pdm09 during and after pandemic, rural India. *Emerg Infect Dis.* 2012;18:1472-5.
- Chadha MS, Broor S, Gunasekaran P, et al. Multisite virological influenza surveillance in India: 2004-2008. *Influenza Other Respir Viruses.* 2012;6:196-203.
- Chandra S, Kuljanin G, Wray J. Mortality from the influenza pandemic of 1918-1919: the case of India. *Demography.* 2012;49:857-65.
- Grohskopf LA, Olsen SJ, Sokolow LZ, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2014-15 influenza season. *Morb Mortal Wkly Rep.* 2014;63:691-7.
- Koul PA, Broor S, Saha S, et al. Differences in influenza seasonality by latitude, Northern India. *Emerg Infect Dis.* 2014;20:1746-9.
- Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis.* 2012;12:36-44.
- Saha S, Chadha M, Abdullah MA, et al. Influenza seasonality and vaccination timing in tropical and subtropical areas of southern and south-eastern Asia. *Bull WHO.* 2014;92:318-30.

Vashishtha VM, Choudhury P, Bansal CP, et al. Influenza. In: Vashishtha VM, Choudhury P, Bansal CP, Yewale VN, Agarwal R (Eds). *IAP Guidebook on Immunization 2013-2014*. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.

WHO. Vaccines against influenza WHO position paper—November 2012. *Wkly Epidemiol Rec.* 2012;87:461-76.

### IN A NUTSHELL

1. Influenza virus infection is associated with increased rates of hospitalization in children particularly in those younger than 2 years.
2. Immunization is the major means of influenza prevention.
3. Two types of influenza vaccines are available: (1) IIV, which is administered intramuscularly and (2) LAIV, which is administered intranasally.
4. Both the killed and live vaccines are safe and efficacious.
5. Routine vaccination against influenza to healthy children is not recommended in India by both Gol and IAP.
6. The choice of vaccine for an individual child depends upon age and risk factors for severe or complicated influenza. IIV is indicated for children older than or equal to 6 months, including those who cannot receive LAIV.
7. Individuals older than 2 years and younger than 50 years who are not among of the categories listed above may receive either TIV or LAIV. As LAIV has broader and more durable immunity if available should be used in these groups.
8. Annual immunization is necessary even if the previous season's vaccine contained one or more of the antigens to be administered in the current season because immunity declines during the year following vaccination.
9. Vaccine with the newest strain should be preferred at the time of vaccination. The best time to vaccinate is before onset of monsoon in India.
10. For individuals residing in southern states, the best time would be just before the onset of rainy season, i.e., before October while for rest of the country, it should be before June.

## Chapter 23.23

# Human Papillomavirus Vaccines

Srinivas G Kasi

Genital infection with human papillomavirus (HPV) is a necessary cause of cervical cancer and an important etiologic agent for other anogenital cancers (anus, vulva, vagina and penis) and head and neck cancers. HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases worldwide. It is estimated that cervical cancer affects approximately 527,624 women each year, of whom 444,546 (80%) live in developing countries.

Cervical cancer in India ranks as the second most frequent cancer among women. About 7.9% of women in the general population are estimated to harbor cervical HPV infection at a given time, and 84.1% of invasive cervical cancers are attributed to HPVs 16 or 18. Current estimates indicate that every year, in India, more than 100,000 women are diagnosed with cervical cancer with a crude incidence rate of 20.2 and more than half of them die from the disease, with a crude mortality rate of 11.1. This is the highest in the world.

## VIROLOGY

The HPVs are a family of nonenveloped viruses that belong to the family Papillomaviridae. They have an icosahedral capsid of approximately 60 nm in diameter. L1 is the major capsid protein while L2 is the other capsid protein. The early proteins (E1, E2, E4, E5, E6 and E7) regulate viral transcription and genome replication. There are over 100 HPV genotypes with distinct tissue tropism for squamous epithelia of either cutaneous or mucosal tissue regions. Mucosal infections of HPV fall in two groups: (1) low-risk type viruses (mainly HPV6 and 11), which induce genital warts and (2) high-risk types (HPV16, 18 and others), which lead to malignancies such as cervical carcinoma, anal cancer and oropharyngeal carcinoma.

While most HPV infections are transient, about 1% of individuals infected with HPV types 6 and 11, develop clinically significant genital warts. Approximately 70% of new infections resolve within 1 year and 91% within 2 years. About 25% of all women infected with high-risk HPV develop cervical intraepithelial neoplasia (CIN) and less than 1% develops invasive cervical cancer.

## PATHOGENESIS

Microabrasions that occur at the cervicovaginal junction during penetrative or nonpenetrative sexual encounter expose the basal undifferentiated keratinocyte cells. The virion gets attached to these cells by binding to its receptor, heparan sulfate proteoglycans (HSPGs) by a L1 dependent mechanism, gets internalized by endocytic mechanisms and delivers the genome to the host nucleus. In the basal cells the viral early genes are expressed and the genome is replicated at approximately 100 copies/cell. As the basal keratinocytes mature, they move up the epithelial layers, where the late proteins get expressed. In the superficial layers viral particles are assembled and released into the cervical lumen. Thus, in the initial stages of infection, the host immune system remains largely unaware of the ongoing infection.

Risk factors for development of cervical cancer include infection with certain oncogenic types of HPVs, sexual intercourse at an early age, multiple sexual partners, multiparity, long-term oral contraceptive use, tobacco smoking and low socioeconomic status.

## HUMAN PAPILLOMAVIRUS VACCINES

The two presently available HPV vaccines in India are produced by recombinant technology. The L1 gene of the HPV is inserted into a host (*baculovirus* or *Saccharomyces cerevisiae*), which results in the production of large quantities of L1 proteins which undergo self-assembly into virus-like particles (VLPs) that resemble the outer capsid of the whole virus. The HPV VLPs do not contain viral deoxyribonucleic acid (DNA) and are therefore noninfectious and nononcogenic, but elicit a strong immune response comparable to the intact virion.

Cervarix<sup>®</sup>, manufactured by GSK, is a bivalent vaccine containing the VLPs of types 16 and 18 and Gardasil<sup>®</sup>, manufactured by Merck and Co, United States of America, is a quadrivalent vaccine containing the VLPs of types 6, 11, 16 and 18. Both vaccines are preservative free (**Table 1**).

For vaccine licensure, the World Health Organization (WHO) has recommended the endpoints of CIN2/3 or adenocarcinoma in situ (AIS) as a proxy for cervical cancer as these endpoints can be studied feasibly considering the long incubation period of cervical cancer. In children or young adolescents, bridging studies are conducted by comparing antibody responses in younger persons with those in the women for whom data on the clinical endpoint of CIN2/3 or AIS are available.

## Vaccine Indications, Schedule and Dosage

Cervarix<sup>®</sup> is indicated for the prevention of premalignant lesions of the cervix, vagina and vulva and cervical cancer causally related to certain oncogenic HPV types. Gardasil<sup>®</sup> is indicated for the prevention of premalignant lesions of the cervix, vagina and vulva and cervical cancer causally related to certain oncogenic HPV types and genital warts causally linked to certain HPV types. In addition, Gardasil<sup>®</sup> is indicated in certain countries for the prevention of external genital warts and anal intraepithelial neoplasia in males 9–26 years of age.

The dose for both vaccines is 0.5 mL intramuscular in deltoid. Both vaccines are intended to be administered to females before the onset of sexual activity, that is, before first exposure to HPV infection. The recommended age for initiation of vaccination is 10–12 years. Presently, in India, the vaccines are permitted for usage up to the age of 45 years.

According to 2014 recommendations of IAP-ACVIP and the WHO, two doses of HPV vaccine are advised for 9–14 years old girls, the minimum interval between doses should be 6 months. The interval between the first and second dose may be extended up to 12 months, should this facilitate administration say in school settings. For girls, primed before the age of 15 years, even if older at the time of boosting (second dose), a two-dose schedule will be applicable. For girls 15 years and older, a 3 dose schedule for both vaccines is recommended. For the quadrivalent human papillomavirus (QHPV), the 3 dose schedule consists of three doses at 0, 2 and 6 months (minimum interval between first and second dose of 4 weeks and second and third dose, 12 weeks) and 0, 1 and 6 months for the bivalent vaccine. However, for immunocompromised individuals, including those known to be HIV-infected, the three dose schedule is recommended irrespective of age. HPV vaccines can be given simultaneously with other vaccines such as hepatitis B and Tdap. Since syncope following any vaccine is common in adolescents, the vaccine should be administered in a sitting/lying down position and post vaccination the patient should be observed for 15 minutes.

The new recommendations for a 2-dose schedule in 9–14 years old have been made on the basis of data generated from randomised and non-randomised comparison of 2 doses in the 9–14 years old versus 3 doses in 9–14 years old and young women. These studies

**Table 1** Comparison of available human papilloma virus (HPV) vaccines

	<i>Gardasil®</i>	<i>Cervarix®</i>
Manufacturer	Merck and Co, United States of America	GSK, Belgium
VLP types	6, 11, 16 and 18	16 and 18
Antigen content	HPV6: 20 mcg HPV11, 16, 18: 40 mcg each	HPV16, 18: 20 mcg each
Production system	<i>Saccharomyces cerevisiae</i>	<i>Baculovirus</i>
Adjuvant	Proprietary aluminum hydroxyphosphate sulfate (225 µg)	Proprietary aluminum hydroxide (500 µg) plus 50 µg 3-deacylated monophosphoryl lipid A (GSK AS04 adjuvant)
Route	Intramuscular	Intramuscular
Schedule	0–2–6 months	0–1–6 months
Target age group	9–45 years	10–45 years
Approved indications	<ul style="list-style-type: none"> <li>• Prevention of cervical cancers and precancers</li> <li>• Vulvar and vaginal cancers and precancers</li> <li>• Anal cancers and precancers</li> <li>• External genital warts</li> <li>• Approved in males 9–26 years for prevention of anal cancers and precancers</li> <li>• All caused by HPV16 and 18</li> </ul>	<ul style="list-style-type: none"> <li>• Prevention of cervical cancers and precancers</li> <li>• Vulvar and vaginal cancers and precancers (In European only)</li> <li>• All caused by HPV 16 and 18</li> </ul>

®Tradenames

have shown that seroconversion and seropositivity were non-inferior or inconclusive at all-time points in the 2-dose schedule. The 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all the age groups enrolled.

### Protective Mechanism

No immune correlate of protection has been established in the efficacy trials. Existing evidence suggest that neutralizing antibodies are the primary effectors of vaccine induced protection. It is suggested that direct exudation of serum antibodies at sites of trauma is the primary mechanism of protection. High levels of anti-VLP antibodies prevent binding of the virion to the basement membrane, while lower levels prevent transfer of the virion to the keratinocytes.

### Immunogenicity and Duration of Protection

Both vaccines are highly immunogenic with the highest immune responses being observed in young girls aged 9–15 years. The antibody titers against HPV16 and 18 antibodies produced were several folds higher than after natural infection. With the bivalent vaccine, anti-HPV16 and 18 titers remained at high levels for at least 8.4 years with 100% seropositivity maintained, with the quadrivalent vaccine anti-HPV16 titers remained high at least 5 years with 98.8% seropositivity maintained. However, 18 months after first vaccination, anti-HPV18 antibody titers return to the level of natural infection, with a further reduction in seropositivity over time. Since the efficacy has remained undiminished for the QHPV vaccine, the clinical significance of this observation is still to be established.

Immunobridging studies done for both vaccines, in young adolescents, have shown that the neutralizing antibody responses in boys and girls were statistically noninferior and observationally higher than those observed in young females. Noninferiority in boys was demonstrated in another study. In women aged 26–55 years, the immunogenicity of the BHPV was several times higher

than that induced after a natural infection, remained high for the 24 months of follow-up and followed the same kinetics as those observed in young women. For QHPV, in 24–45 years old women, at month 48, 91.5%, 92.0%, 97.4% and 47.9% of vaccinated women were seropositive to HPV 6/11/16/18, respectively. A rapid and strong anamnestic humoral immune response was elicited following a fourth dose of both vaccines.

**Prophylactic efficacy** The prophylactic efficacies of both vaccines have been studied in large phase II and III studies and followed up for 3–5 years. Vaccine efficacies against clinical endpoints of both the vaccines are provided in **Table 2**. Long-term efficacy for both vaccines has been demonstrated across all age groups.

**Cross protection** Immunity to HPV is type-specific. However, HPV16 is phylogenetically related to HPV types 31, 33, 52 and 58 (A9 species) and HPV18 is related to HPV45 (A7 species). For the bivalent vaccine, vaccine efficacy against CIN2+ associated with 12 nonvaccine oncogenic types was 54.0% (34.0–68.4; ATP-E). Individual cross-protection against CIN2+ associated with HPV-31, HPV-33, and HPV-45 was seen in the total vaccinated cohort (TVC). For the quadrivalent vaccine, efficacy against CIN2/3 or AIS during a 3-year follow-up was reported against combined HPV31/45 types (point efficacy: 62%), five combined HPV types, 31/33/45/52/58 (point efficacy: 43%) and 10 combined HPV types, 31/33/35/39/45/51/52/56/58/59 (point efficacy: 38%).

### Vaccine Safety

The safety of bivalent human papillomavirus (BHPV) and QHPV has proven to be excellent in various phase II and III trials both in females and males. With greater than 175 million doses distributed worldwide, the WHO-GAVACS has extensively studied all the potential signals associated with these vaccines and found no causative link with any of them including, GBS, VTE (Guillain-Barré syndrome, venous thromboembolism), seizures, stroke and other severe allergic reactions. Pregnancy outcomes in women

**Table 2** Vaccine efficacy against clinical endpoints in phase II/III studies of Cervarix® and Gardasil®

	Vaccine efficacy	
	Cervarix®	Gardasil®
<b>Cervical lesions</b>		
<i>CIN2+</i>		
ATP/PP	92.9 (79.9–98.3)	98.2 (93.3–99.8)
TVC/ITT	52.8 (37.5–64.7)	51.5 (40.6–60.6)
TVC-naïve	98.4 (90.4–100)	100 (91.9–100)
<i>CIN3</i>		
ATP/PP	80 (0.3–98.1)	96.8 (88.1–99.6)
TVC/ITT	33.6 (–1.1–56.9)	45.1 (29.8–57.3)
TVC-naïve	100 (64.7–100)	100 (90.5–100)
<b>External genital lesions and vulvar vaginal lesions</b>		
<i>ATP</i>		
Genital warts		96.4 (91.4–98.8)
VIN 1/VaIN 1		95.2 (70.0–99.9)
VIN 2+/VaIN 2+		95.4 (71.5–99.9)
<i>ITT</i>		
Genital warts		79.5 (73.0–84.6)
VIN 1/VaIN 1		76.0 (54.2–8.3)
VIN 2+/VaIN 2+		78.5 (55.2–90.8)
<b>Precursor anogenital lesions</b>		
<i>ATP</i>		
AIN 2/3		91.7% (44.6–99.8)
Persistent 16/18 lesions	83.6% (66.7–92.8%)	
<i>ITT</i>		
AIN 2/3		54.2% (18.0–75.3%)
Persistent 16/18 lesions	62.0% (47.1–73.1%)	
<b>Precursor penile lesions</b>		
PIN 2/3 (ATP)		100% (–431–100%)
PIN 2/3 (ITT)		–48.9% (–1,680–82.1%)

Abbreviations: ATP, according to protocol; PP, per protocol; TVC, total vaccinated cohort; ITT, intention to treat; CIN, cervical intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia; AIN, anal intraepithelial neoplasia; PIN, penile intraepithelial neoplasia.

inadvertently administered these vaccines during pregnancy, have not resulted in any adverse outcomes above expected rates. No adverse effects have been reported on vaccination during lactation.

## NEW HUMAN PAPILLOMAVIRUS VACCINES

The limited protection against cervical cancer, the high price of the current HPV vaccines which have limited their use in the developing countries having the highest burden of cervical cancer and lack of any therapeutic effect, have been the main drawbacks of the current vaccines. Thus, newer HPV vaccines must address the issues of cost, duration of protection and broader protection. The newer vaccines under study include:

- **Nanovalent vaccine:** A nanovalent vaccine, containing HPV31/33/45/52 and 58, in addition to 6, 11, 16 and 18, code named V503, is in phase III trials. The results of the trials are

still unpublished. It is estimated that this vaccine will raise the protection rate to 90% of squamous cell carcinoma (SCC) worldwide.

- **L2 vaccines:** L2 contains several broad cross-reacting epitopes which elicits antibodies which can neutralize a wide variety of HPV types. However, it is weakly immunogenic. Studies in mice using bacteriophage VLPs and orally administered *Lactobacillus casei* expressing L2 on their surface has given encouraging results.
- **L1 capsomer vaccines:** L1 capsomers can be produced in bacteria, which is cheaper than using the conventional virus and yeast-based systems.
- **Therapeutic vaccines:** The HPV early proteins, E6 and E7 are expressed in all HPV infected cells, and are upregulated in cancer cells. Thus, E6 and E7 have been the choice for therapeutic vaccines. Different strategies are being investigated including the use of live viral or bacterial vectors, peptides, proteins, DNA and dendritic cells. Recently a phase I trial using recombinant HPV16E7 and HPV18E7 established the safety of the product and has progressed to a phase II trial.

## POPULATION IMPACT OF HUMAN PAPILLOMAVIRUS VACCINES

Since its introduction, the HPV vaccines are being used on a large scale in many developed countries and more recently, with global alliance for vaccines and immunizations (GAVI) assistance, in some developing countries. Australia was the first country to introduce the QHPV vaccine in 2007. Between 2007 and 2011, there was 83.4% reduction in inpatient treatment for vulvar/vaginal warts in 15–24-year-old women. There was a significant reduction of high-grade cervical abnormalities in vaccinated women (4.8/1,000 PY in vaccinated vs 6.4/1,000 PY in unvaccinated) within 5 years of implementation, with the greatest vaccine effectiveness (VE) observed for the youngest women.

In Sweden, VE against genital warts was 76% (95% CI = 73–79%) among those who received three doses of the vaccine with their first dose before the age of 20 years, with the highest effectiveness in girls vaccinated before the age of 14 years (effectiveness = 93%, 95% CI = 73–98%). Similar reductions in atypia+ have been reported from Denmark, with the QHPV.

In the United States of America, by 2010, the coverage in 13–19-year group was 32%. With this coverage, a 56% decline in vaccine type HPV prevalence was observed. With GAVI assistance, by 2020, it is estimated that over 30 million girls in more than 40 countries will be vaccinated against HPV.

## THE INDIAN SCENARIO

India accounts for about 25% of all new cervical cancer cases and cervical cancer deaths occurring in the world. According to the 2013 Globocan data, in India, HPV16 and 18 account for 81.3% of all cervical cancer cases. Hence a vaccine containing HPV16 and 18 is bound to be greatly beneficial. However numerous barriers exist in the path towards its acceptance in the National Immunization Program (NIP). Most data on disease burden is obtained from regional cancer registries, while population based data is scanty. Also, due to high cost, HPV vaccines are far beyond the reach of most Indians. Sociocultural issues associated with the HPV vaccine because it targets a sexually transmitted infection and primarily targets female adolescents and young adults are a great barrier.

While routine screening with Pap smear at regular intervals and early treatment of precancerous conditions in the developed countries have been very effective in preventing squamous cervical cancer, these measures are difficult to implement in low-resource settings. Thus, prevention of HPV infections by vaccination has assumed great public health importance.



## MORE ON THIS TOPIC

- Castellsagué X, Muñoz N, Pitisuttithum P, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24–45 years of age. *Br J Cancer*. 2011;105:28-37.
- Dochez C, Bogers JJ, Verhelst R, et al. HPV vaccines to prevent cervical cancer and genital warts: an update. *Vaccine*. 2014;32:1595-601.
- FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*. 2007;356:1915-27.
- Herrero R, Wacholder S, Rodríguez AC, et al. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomized clinical trial in Guanacaste, Costa Rica. *Cancer Discov*. 2011;1:408-19.
- Indian Academy of Pediatrics (IAP) Recommended Immunization Schedule for Children Aged 0 through 18 Years—India, 2014 and updates on Immunization. Vipin M Vashishtha, Panna Choudhury, Ajay Kalra, Anuradha Bose, Naveen Thacker, Vijay N Yewale, CP Bansal and Pravin J Mehta. *Indian Pediatrics*. Volume 51, October 15, 2014, 785-800.
- Lehtinen M, Paavonen J, Wheeler CM, et al. Overall efficacy of AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol*. 2012;13:89-99.
- Ma B, Maraj B, Tran NP, et al. Emerging human papillomavirus vaccines. *Expert Opin Emerg Drugs*. 2012;17:469-92.
- Muñoz N, Manalastas R, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised double-blind trial. *Lancet*. 2009;373:1949-57.
- Paavonen J, Naud P, Salmerón J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet*. 2009;374:301-14.
- WHO. (2014). Immunization, vaccines and biologicals. Summary of the SAGE April 2014 meeting. [online] Available from [http://www.who.int/immunization/sage/meetings/2014/april/report\\_summary\\_april\\_2014/en/](http://www.who.int/immunization/sage/meetings/2014/april/report_summary_april_2014/en/). [Accessed November, 2014].
- Weekly epidemiological record. 24 October 2014, No. 43, 2014, 89, 465-92. <http://who.int/wer>.

## IN A NUTSHELL

1. India has the highest rate on cervical cancer cases and deaths in the world.
2. Human papillomavirus is responsible for greater than 99% of cervical cancers and an important etiologic agent for other anogenital cancers (anus, vulva, vagina and penis) and head and neck cancers.
3. Two vaccines against HPV infections are presently available. Cervarix®, manufactured by GSK, is a bivalent vaccine containing the VLPs of types 16 and 18 and Gardasil®, manufactured by Merck and Co, United States of America, is a quadrivalent vaccine containing the VLPs of types 6, 11, 16 and 18.
4. Both vaccines are highly immunogenic with the highest immune responses being observed in young girls aged 9–15 years. The antibody titers against HPV16 and 18 antibodies produced are several folds higher than after natural infection.
5. Both vaccines are highly efficacious in preventing infection with virus types 16 and 18. They are also highly efficacious in preventing precancerous cervical lesions caused by these types.
6. The QHPV vaccine is also highly efficacious in preventing anogenital warts, vulvar and vaginal cancers and precancers.
7. Long-term efficacy for both vaccines has been demonstrated across all age groups.
8. The primary target group in most of the countries recommending HPV vaccination is young adolescent girls between 9 years and 14 years.
9. Data from clinical trials and postmarketing surveillance conducted in several continents have shown both vaccines to be safe.

## Chapter 23.24

## Yellow Fever Vaccine

Parang N Mehta

Yellow fever is a serious disease caused by a virus of the family flaviviridae. It is transmitted to humans by mosquitoes and is maintained in nature in monkeys. Because of this sylvatic cycle, yellow fever cannot be eradicated and preventive measures are important. About 200,000 cases of yellow fever occur annually, mainly in Africa. Cases occur in South and Central America also. Currently, the disease does not occur in Europe and North America and the disease has never occurred in Asia. Yellow fever ranges from subclinical infection to severe hemorrhagic disease with multiple organ system failure. The mortality of yellow fever can be 20–50%.

## YELLOW FEVER VACCINES

The yellow fever virus was isolated in 1927. A killed vaccine could not be made at that time, and an attenuated live vaccine, the 17D vaccine, was developed soon after. This vaccine has been in use for almost 80 years now and has been found to be very effective and quite safe. Currently, two strains of the vaccine are in use: (1) the 17DD vaccine and (2) the 17D-204 vaccine. Both these vaccines protect against all known strains of the yellow fever virus.

**Dosage and administration** The vaccine is supplied freeze dried and must be stored at 2–8°C. It should be reconstituted just before use and given subcutaneously. It can be given together with other vaccines like Bacille Calmette-Guérin (BCG), polio, typhoid, hepatitis A and B and cholera. Live vaccines like measles and mumps and rubella (MMR) should be given on the same day, or separated by a month. Other flavivirus vaccines like *Japanese encephalitis* and *dengue* may interfere with the *yellow fever* vaccine, but there is insufficient data at present. World Health Organization (WHO) recommends this vaccine for all persons over 9 months of age who are living in or traveling to an endemic area. The contraindications and precautions to *yellow fever* vaccination are displayed in **Table 1**. The vaccine must be given at least 10 days before arrival in an endemic area.

**Efficacy** About 90% of vaccinees developed neutralizing antibodies in 10 days and almost 100% by day 21. Protective efficacy can be measured by the log neutralizing index or by plaque

reduction neutralization test (PRNT). Tests such as enzyme-linked immunosorbent assay (ELISA) and hyaluronic acid (HA) are nonspecific and not recommended.

**Duration of protection** Persistence of antibodies for 30–35 years has been shown. Protection is likely to be life long after one dose. However, international regulations require revaccination after a period of 10 years.

**Effectiveness** The vaccine is highly effective. After millions of doses administered, only five cases of yellow fever have been reported in vaccinated individuals. The vaccine has also been found to be effective in stopping epidemics.

**Vaccination during pregnancy and lactation** It is a live virus vaccine and therefore not recommended in pregnancy, although fetal anomalies have never been reported. Immune response to this vaccine is poor in pregnancy and revaccination is recommended after delivery if required for further travel. The vaccine is transmitted via breastmilk and neurological disease in babies has been reported. Nursing women should receive the vaccine after careful consideration.

**Vaccination of human immunodeficiency virus (HIV)-infected individuals** HIV-infected children can be given this vaccine if the CD4 counts are over 200/cmm and HIV ribonucleic acid (RNA) is less than 50 copies/mL. In these circumstances the vaccine is quite safe. However, the protection is poor and slow to develop and neutralizing antibodies should be measured 1 month after vaccination to detect nonresponders.

## ADVERSE EVENTS

Mild adverse events occur in 20–30% of recipients. These usually consist of low fever, headache, and myalgia and require only symptomatic treatment. Serious adverse events are of mainly three types: (1) hypersensitivity reactions, (2) neurotropic disease and (3) viscerotropic disease.

**Hypersensitivity reactions** The incidence is 8–18 people/million doses, and is most common in people with egg allergy, since the vaccine is prepared in embryonated eggs. Reactions can occur also to other components like gelatin, latex and chicken protein.

**Neurotropic disease** This was earlier called postvaccinal encephalitis. The current designation is yellow fever vaccine-associated neurotoxin disease (YEL-AND). Most of the reported cases were in babies under-9 months of age. The incidence of this adverse effect is estimated as 3–8/million vaccine doses. YEL-AND appears 4–24 days after the vaccine is given. It manifests as fever, headache and focal neurological signs. Other presentations are acute disseminated encephalomyelitis (ADEM) and the Guillain-Barré syndrome. On investigation, cerebrospinal fluid (CSF) pleocytosis, elevated CSF proteins, and elevated yellow fever virus specific immunoglobulin M (IgM) is found. The complication is often serious but rarely fatal. Although no specific treatment is available, most patients recover fully.

**Viscerotropic disease** This dangerous adverse effect, known as yellow fever vaccine-associated viscerotropic disease (YEL-AVD), was identified recently. The incidence is 3–4 persons/million vaccinated, and it is a serious, often fatal condition. YEL-AVD manifests with fever, jaundice, bleeding dyscrasias, and multiorgan failure. The manifestations start 2–5 days after the vaccine dose and can be moderate to severe. Hepatocellular enzymes are elevated and active viral replication and dissemination in multiple organs is seen. No specific treatment is available and only supportive treatment is recommended. Mortality is high. This complication is an important factor to consider when taking a decision about the yellow fever vaccine for a traveler.

**Table 1** Yellow fever vaccine—contraindications and precautions

Contraindications	Precautions
Allergy to the components	Age 6–9 months
Age less than 6 months	Pregnancy
Primary immunodeficiency	Lactation
HIV infection—symptomatic, or with CD4 counts less than 200/mm <sup>3</sup>	First time vaccination at age more than 60 years
Malignant neoplasm	Asymptomatic HIV infection and CD4 counts 200–499 mm <sup>3</sup>
Organ transplantation	Family history of yellow fever vaccine adverse effects
Immunosuppressive or immunomodulatory therapy	
Thymus disease	

Abbreviation: HIV, human immunodeficiency virus.

Source: Thomas RE, Lorenzetti DL, Spragins W, et al. The safety of yellow fever vaccine 17D or 17DD in children, pregnant women, HIV+ individuals, and older persons: systematic review. *Am J Trop Med Hyg*. 2012;86:359–72.

Severe complications of the yellow fever vaccine are most common at the extremes of age. Children below 6 months should not be vaccinated. Those between 6 months and 9 months should only be vaccinated if travel cannot be avoided and they have a high probability of infection.

### Vaccination for Travelers

Yellow fever is a serious and even fatal disease and no specific treatment is available. The vaccine is important for travelers to endemic areas, but it has serious adverse events. The risk of the disease should be balanced against the adverse effect profile of this vaccine for individual traveler and a decision to vaccinate (or not) should be taken after considering relevant factors (**Box 1**). Persons who cannot be given the vaccine should take other measures for avoiding this disease (**Box 2**).

#### BOX 1 Factors affecting decision to administer the yellow fever vaccine

- The specific destination. Risks for yellow fever are higher in Africa than in South America, and rural areas have a greater risk.
- The activities, recreational or work related, to be undertaken.
- The season of the year. Late monsoon and the period immediately after has high transmission.
- Local yellow fever transmission incidence and pattern.
- Likelihood of vector exposure.
- Risk factors for yellow fever vaccine-associated viscerotropic disease (YEL-AVD).

#### BOX 2 Other measures to avoid yellow fever

- Mosquito avoidance measures like full sleeved clothing and mosquito repellent cream in daytime.
- Sleeping under bed nets at night, though the yellow fever vectors are day biters.
- Spraying indoor spaces with insecticides.
- Staying in urban areas where disease transmission is low. Disease transmission is high in rural and forest areas.

### Legal Requirements

Many countries where yellow fever does not exist require travelers to produce a certificate of yellow fever vaccination. This is not for individual protection, but to prevent the import and establishment of the disease in the country.

### FUTURE VACCINES

For half a century the yellow fever vaccines were considered safe but the recent identification of YEL-AVD has caused concern.

This condition is rare but dangerous, and has led to a search for a safer vaccine. Also, the current live vaccines have a high incidence of neurological disease in infants and travelers of this age group cannot be protected.

An early effort to make a killed vaccine did not succeed but now a candidate vaccine named XRX-001 is under trial. It is a whole virus propionolactone preparation and has been found to induce neutralizing antibodies in recipients. This vaccine could be given to infants under-6 months of age, as well as during pregnancy and lactation.

Also under trial are vaccines in which the immunogenic component of the yellow fever virus has been inserted into other live vaccines that are safe. The yellow fever vaccine itself has been used as a base to make *Chimeric* vaccines against *dengue*, *West Nile fever* and *Japanese encephalitis*.

#### IN A NUTSHELL

1. Yellow fever is a serious and even fatal disease and no specific treatment is available.
2. It is caused by a virus of the family flaviviridae.
3. A safe and effective live-attenuated live vaccine, the 17D vaccine is available and in use for almost 80 years now.
4. Protection is likely to be life long after one dose. However, international regulations require revaccination after a period of 10 years.
5. Serious adverse events like hypersensitivity reactions, neurotropic disease and viscerotropic disease are rarely encountered.
6. It is recommended to use this vaccine for all persons over 9 months of age who are living in or traveling to an endemic area.

#### MORE ON THIS TOPIC

Lown BA, Chen LH, Wilson ME. Vaccine administration decision making: The case of yellow fever vaccine. *Clin Infect Dis*. 2012;55:837-43.

Silva ML, Espírito-Santo LR, Martins MA, et al. Clinical and immunological insights on severe, adverse neurotropic and viscerotropic disease following 17D yellow fever vaccination. *Clin Vaccine Immunol*. 2010;17:118-26.

Staples JE, Gershman M, Fischer M, et al. Centers for Disease Control and Prevention. Yellow Fever Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2010;59:1-27

Van Epps HL. Broadening the horizons for yellow fever: new uses for an old vaccine. *J Exp Med*. 2005;201:165-8.

## Chapter 23.25

# Combination Vaccines

Niranjan Shendurnikar, Sheila Aiyer

The term combination vaccine implies a physical combination of two or more than two separate antigens/immunogens into a single preparation. This combination can be done at the time of its manufacture [diphtheria and tetanus toxoids and acellular pertussis with inactivated poliovirus, diphtheria and tetanus toxoids and whole-cell pertussis with hepatitis B, *Haemophilus influenzae* type b, measles, mumps and rubella (DTaP/IPV, DTwP/Hep B/Hib, MMR)] or is mixed and reconstituted into a single injection just before the vaccine administration (DTwP/Hib). The administration of any combination vaccine thus protects the recipient against more than one infectious disease. However, when a particular vaccine contains more than one antigen or a strain or a serotype of a single infectious organism it is not labeled as a combination vaccine. The classical example of such vaccines are Bacillus Calmette–Guérin (BCG) vaccine which contains different antigens of *Mycobacterium tuberculosis* and pneumococcal vaccines which contains different serotypes but are not labeled as combination vaccines. When two or more different vaccines are given to the recipient on the same visit but at different sites or routes, then these are termed as simultaneous vaccines [DTwP + oral polio vaccine (OPV) or inactivated polio vaccine (IPV)]. Vaccination providers should not combine separate vaccines into the same syringe to administer together unless mixing is explicitly specified. The presently available different combination vaccines and their preparations are shown in **Table 1**.

## BENEFITS OF COMBINATION VACCINES

The advent of pediatric combination vaccines offers several practical and logistic benefits both to the administration and the vaccine recipient.

- Combination vaccines reduce the number of injections and that infants and children receive during an immunization session, thereby reducing the pain in the vaccinee and the anxiety in the parents.
- It also reduces the amount of cumulative exposure to the preservatives and the stabilizers that may contribute the adverse events.

**Table 1** Combination vaccines currently available in India\*

<i>DTwP combinations</i>
• DTwP, DTwP/HB, DTwP/Hib, DTwP/Hib/HB and DT
<i>DTaP combinations</i>
• DTaP//Hib, DTaP/Hib/IPV, Tdap
<i>MMR (Measles, mumps and rubella)</i>
<i>Hepatitis A/Hepatitis B</i>

\*The names of vaccine before and after virgule (/) indicate that these vaccines are combined and supplied in the same vial or container; if there are two virgule(//) then these two vaccines are mixed or reconstituted just before the vaccine administration. A plus (+) indicates a separate but simultaneous administration.

**Abbreviations:** DTwP, diphtheria and tetanus toxoids and whole-cell pertussis; HB, hepatitis B; Hib, *Haemophilus influenzae* type b; DT, diphtheria and tetanus toxoids; DTaP, diphtheria and tetanus toxoids and acellular pertussis; IPV, inactivated poliovirus; MMR, measles, mumps and rubella.

- The lesser number of clinic visits, less costs and logistic requirements can ultimately increase the parental compliance and vaccine coverage.
- The administration of combination vaccines benefits the health establishment by reducing the storage space and handling and improving the cost effectiveness and the documentation process.
- The facilitation of uptake of a new vaccine when combined with an older vaccine. The availability of pentavalent combination vaccine has facilitated the incorporation of additional vaccine (Hib) into the national immunization schedule and thereby a higher immunization coverage. Advisory Committee on Immunization Practices (ACIP) recommends that licensed combination vaccines can be used whenever any components of the combination are indicated and its other components are not contraindicated. The use of combination vaccines generally is preferred over separate injections of the equivalent component vaccines.

## COMBINATION VACCINES AND IMMUNE RESPONSES

Although some earlier studies showed an altered immune responses to different vaccines when they were administered concurrently with other vaccines but at separate sites, there is no evidence that the efficacy of any vaccine recommended for routine use in childhood was materially altered by concomitant administration with any other vaccine(s) recommended for use at the same age. However, the techniques used to produce an antigen and/or a conjugation of a carrier proteins to a polysaccharide antigen vaccine (such as Hib or pneumococcal) can have important implications for the immunogenicity and the efficacy of the vaccine. The phenomenon of carrier induced specific suppression occurs when the antibody responses to the haptens on a carrier protein are inhibited by the prior immunization with the specific carrier. Thus the prior exposure to the carrier proteins, dose, route, choice of carrier protein and the adjuvants are the determinants of such a suppression or enhancement. Concurrent administration of two conjugate vaccines using same carrier proteins may lead to interference and unpredictable response and therefore simultaneous use of such vaccines must be evaluated for each vaccine combination and given only when recommended.

Chemical and physical interactions between the vaccine components and the adjuvants such as aluminum hydroxide by altering the binding and affect the immune responses to one or more vaccine antigens. Similarly presence of stabilizers, buffers and excipients may interfere with vaccine components of another vaccine. The immune response in viral combination vaccines is improved either by increasing the number of administered doses (OPV) or by modifying the concentrations of the individual virus strains (e.g., MMR vaccine or MMR-V vaccine).

## COMBINATIONS OF DTwP

Diphtheria and tetanus toxoids and whole-cell pertussis was the first combination vaccine licensed in 1948 and whole cell pertussis vaccine by itself is a potent adjuvant and the combination of three antigens (D, wP and T) enhances the immunogenicity of the toxoids when compared with their separate administration. The adsorption of aluminum to DTwP further improved the immunogenicity and reduced the severity of adverse reactions associated with pertussis component. DTwP-based combinations with other vaccines are one of the most widely used combination vaccines. Though many earlier studies showed that the combination of DTwP with Hib resulted



in reduced mean polyribosylribitol phosphate polysaccharide (PRP) antibody titer to Hib, as compared to when the components were given separately, the antibody levels were still high and in protective range and thus the reduced immunogenicity of Hib in combination with DTwP appears to be of no clinical significance. In general currently available combinations of DTwP with Hib and or Hep B do not result in clinically important interference amongst the different components without any increase in adverse reactions in frequency or severity when the same DTwP vaccine is given alone.

Addition of Hep B to DTwP has been reported to result in a higher anti-HBs antibodies and an unchanged DTwP response. Addition of Hib to this combination leads to no consistent changes in the antibody responses. Liquid DTwP/Hep B/Hib vaccine(s) are easily available and are widely integrated by several states in India in National Immunization Program. Studies have shown that the use of such vaccines either as liquid DTP/Hep B combination or mixing of DTwP liquid to the lyophilized Hib vaccine, these combinations have shown similar efficacy and side effects as when given separately. A study from India with a fully liquid DTwP/Hep B/Hib vaccine reported seroconversion rates of 99.4%, 99.4%, 89.9%, 97.8% and 98.3% respectively for D, T, P, Hep B and Hib components, respectively. The same brand of DTP vaccine and Hib vaccine as recommended by the manufacturer in combination must be used and not any DTP with any Hib vaccine. In western world combinations like DTwP + Hep B + IPV or even DTwP + Hep B + Hib + IPV are available as pentavalent or hexavalent vaccines and have shown similar efficacy and adverse reactions as when given separately.

### COMBINATIONS WITH ACELLULAR PERTUSSIS VACCINES (DTaP)

Combinations of DTaP with Hib conjugate vaccines showed a significantly reduced antibody response to Hib antigen. This resulted in a slowed development of DTaP/Hib combinations and lead to a development of alternate combinations such as DTaP/IPV, DTaP/Hep B and DTaP/IPV/Hep B vaccines. However in spite of a reduced response to Hib, most European nations do not regard this as clinically significant as this is unlikely to be clinically relevant after a few months of primary Hib immunizations. Additionally when the Hib vaccine is used in combination for the booster dose in infants who have been primed with the same vaccine in primary doses, then the immune responses are comparable to those when the Hib vaccine is coadministered as a separate dose. Experience in Indian studies has shown that Hib vaccine combined with DTaP or IPV and coadministered with Hep B has resulted in excellent responses to all the antigens including Hib-PRP.

The addition of Hep B with DTaP or with DTaP/IPV generally produces a somewhat higher response against DTaP and polio viruses than what are achieved with the same vaccines given separately on the same schedule. However, the lower Hep B antibody response observed in combinations than with separate Hep B vaccine are not due to antigenic interference but due to more closely spaced schedules for Hep B vaccination and particularly due to reduced interval between the second and third doses of Hep B vaccine (i.e., 6, 10 and 14 weeks or 2, 4 and 6 months instead of 0, 1 and 6 months). Several other childhood vaccines such as conjugate pneumococcal, meningococcal and rotavirus vaccines can be safely coadministered with DTaP and Hib containing vaccines.

### COMBINATION OF HEPATITIS A AND B VACCINE

Combination of Hep A and B vaccines is available in several countries including India in an adult formulation that contains

720 EU of Hep A antigen and 20 mcg of Hep B antigen. The vaccine has been immunogenic in a schedule of 0, 1 and 6 months. An accelerated schedule of 0, 7 and 21 days has been found to evoke an excellent immunogenic response and can be administered to individuals for who are at risk for both Hep A and B (such as certain/unprotected international travelers) for rapid protection against both Hep A and B infections. A two-dose schedule (0 and 6 months or 0 and 12 months) with an adult formulation has been found to be effective both for children and adults.

### COMBINATIONS OF MMR AND VARICELLA VACCINE

Measles, mumps, rubella and varicella (MMRV) vaccine was approved and became available in the United States of America in 2005 and clinical studies involving the healthy children between the ages of 1 month and 23 months indicated that those children who received a single dose of MMRV vaccine developed similar levels of antibodies to measles, mumps, rubella and varicella, as children who received MMR and varicella vaccines at separate injections sites. MMRV vaccine is approved for its use in the United States of America for children between the ages of 1 year and 12 years. The vaccine is not yet available in India. Other vaccines and which are presently available elsewhere but not licensed in India are listed in **Box 1**.

#### BOX 1 Other combination vaccines not licensed in India

- DTwP/Hib/IPV, DTwP/IPV, DT/IPV, Td/IPV
- DTaP/Hib/IPV/Hep B
- DTaP/Hib
- Hep B/Hib
- Hep A/Typhoid
- MMRV
- MnC/Hib

*Abbreviations:* DTwP, diphtheria and tetanus toxoids and whole-cell pertussis; Hib, *Haemophilus influenzae* type B; IPV, inactivated poliovirus; DT, diphtheria and tetanus toxoids; Td, tetanus and diphtheria; DTaP, diphtheria and tetanus toxoids and acellular pertussis; Hep B, hepatitis B; MMRV, measles, mumps, rubella and varicella.

### COMPLEXITIES OF COMBINATION VACCINES

Combination vaccines are preferred when a child qualifies for the components contained in the combination vaccine without any contraindication. Presence of an extra and approved component (antigen) in the vaccine is acceptable but not necessarily preferred. The safety of a new combination product is rigorously evaluated and compared against the safety of single antigen products or existing combination vaccines prior to authorization for use. There may be differences in minor adverse events associated with combination compared to single component vaccines, but they are not considered to be clinically significant. In case of an adverse event following immunization, determining which component of a combination vaccine is responsible may be more challenging than in single component vaccines.

With the refinement of vaccine development and production, children today are exposed to far fewer vaccine antigens than in the past, even though they are immunized against more infections with more combination vaccines. Advisory Committee on Immunization Practices (ACIP) recommends that combination vaccines be used whenever possible and as new vaccines that target previously unaddressed diseases are added to the vaccination calendar, the use and improvement of currently available combination vaccines will be paramount if high vaccine coverage is to be maintained.

### IN A NUTSHELL

1. Combination vaccine implies a physical combination of two or more than two separate antigens/immunogens into a single preparation.
2. Combination vaccines offer multiple benefits such as less number of painful injections, reduced hospital visits and logistic benefits such as improved administration and storage issues.
3. There is no evidence that the efficacy of any vaccine recommended for routine use in childhood is materially altered by concomitant administration with any other vaccine(s) recommended for use at the same age.
4. Combination vaccines are preferred when a child qualifies for the components contained in the combination vaccine without any contraindication.
5. Indian Academy of Pediatrics recommends that combination vaccines be used whenever possible and as new vaccines that target previously unaddressed diseases are added to the vaccination calendar.

### MORE ON THIS TOPIC

- Bairwa M, Pilania M, Rajput M, et al. Pentavalent vaccine: a major breakthrough in India's Universal Immunization Program. *Hum Vaccin Immunother.* 2012;8:1314-6.
- Centers for Disease Control and Prevention. (2012). Epidemiology and Prevention of vaccine preventable diseases, 12<sup>th</sup> ed. [online] Available from <http://www.cdc.gov/vaccines/pubs/pinkbook/default.htm>. [Accessed November, 2014].
- Decker MD, Edwards KM, Bogaerts HH. Combination vaccines. In: Plotkin S, Orenstein W, Offit P (Eds). *Vaccines*, 6<sup>th</sup> ed. Philadelphia: Elsevier Saunders; 2013. pp. 981-1107.
- Dutta AK, Pemde H. Combination Vaccines. In: Vashishtha VM, Agrawal R, Sukumaran TU (Eds). *IAP Textbook of Vaccines*. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2014. pp. 392-98.
- Dutta AK, Verghese VP, Pemde HK, et al. Immunogenicity and safety of DTaP-IPV//PRP-T vaccine (Pentaxim) booster dose during the second year of life in Indian children primed with the same vaccine. *Indian Pediatr.* 2012;49:793-8.
- Karande S. Update on available vaccines in India: report of the APPA VU 2010: I. *Indian J Pediatr.* 2011;78:845-53.
- Skibinski DA, Baudner BC, Singh M, et al. Combination vaccines. *J Glob Infect Dis.* 2011;3:63-72.

## Chapter 23.26

# Immunization in Special Situations

Panna Choudhury

Every child has right to vaccination against vaccine preventable diseases. But, there are situations where immunizing some children become a challenging task due to various reasons which primarily include compromise in immunity status. Other situations like allergic disorders, bleeding diathesis, traveling to endemic areas also poses a problem and some of these will be discussed.

## IMMUNIZATION IN THE IMMUNOCOMPROMISED

While vaccinating an immunocompromised subject, the physician should judiciously weigh the expected benefits of immunization against the risk of adverse events. Generally, the vaccination in an immunocompromised is safer than often perceived. General principles for vaccination of the immunocompromised are:

- Inactivated vaccines are safer but immunogenicity and efficacy may be lower.
- All live vaccines are contraindicated in severe immunodeficiency (CD4+ count < 15%). In mild (CD4 count > 25%) and moderate (CD4 count 15–24%) immunodeficiency, live vaccines may be given if benefits outweigh the risks. Patients administered live vaccines inadvertently prior to diagnosis of immunodeficiency should be watched for vaccine related adverse effects.
- Antibody titers should preferably be checked postimmunization on regular basis and regular boosters may be administered if needed.
- More doses with higher potency should be given if indicated (e.g., Hepatitis B); antibody titers should be checked postimmunization/regular basis and regular boosters administered if needed. For major/contaminated wounds tetanus immunoglobulin (Ig) is required in addition to tetanus toxoid (TT) even if three or more doses of TT have been received in the past.
- Household contacts should not receive transmissible vaccines such as oral polio vaccine (OPV). Nontransmissible live vaccines such as measles, mumps and rubella (MMR) and varicella can be safely given. All household contacts should be fully immunized with varicella and influenza to reduce risk of transmission to the immunocompromised.
- If resources permits pneumococcal, varicella (depending on degree of immunocompromise and in two doses 4–12 weeks apart), hepatitis A, inactivated influenza vaccines should be given.
- At present data on safety and efficacy of the rotavirus and human papillomavirus (HPV) is insufficient.

## Congenital Immunodeficiency

In patients with severe B-cell immunodeficiency (X-linked agammaglobulinemia) live vaccines including OPV, Bacillus Calmette-Guérin (BCG), oral typhoid, and live-attenuated influenza are contraindicated. Measles and varicella vaccines may be given but may be ineffective due to concomitant Ig therapy. Inactivated vaccines may be given but are ineffective. In less severe B-cell deficiencies such as IgA and IgG subclass deficiency only OPV is contraindicated. In patients with severe T-cell immunodeficiency (SCID) all live vaccines are contraindicated and all vaccines are ineffective. Patients who have received live

vaccines especially BCG prior to diagnosis face an increased risk of complications including disseminated BCG disease. For patients with combined immunodeficiency such as DiGeorge syndrome, Wiskott Aldrich and ataxia telangiectasia, inactivated vaccines may be given but live vaccines are contraindicated. In complement deficiencies, all vaccines may be safely given; pneumococcal, *Haemophilus influenzae* type b (Hib) and meningococcal vaccines are particularly indicated. In patients with phagocyte defects such as chronic granulomatous disease, only live bacterial vaccines are contraindicated, other vaccines may be safely and effectively given.

## Human Immunodeficiency Virus Infection

Human immunodeficiency virus infection makes children prone to severe, recurrent or unusual infections by vaccine preventable pathogens. The efficacy and safety of vaccines depends on the degree of immunodeficiency. Generally, CD4+ counts less than 200 cells/cumm is known to elicit minimal or no host response. Antibody response also wanes at a faster rate in HIV-infected person. Antiretroviral therapy can improve immune responses to vaccine but not to the levels of an uninfected subject. Live viral and bacterial vaccines pose an enhanced risk for uncontrolled replication of the vaccine strains.

Vaccination is usually safe and effective early in infancy before HIV infection causes severe immune suppression. The duration of protection may be compromised as there is impairment of memory response with immunity wearing away. In older HIV1 infected children and adults, the immune response to primary immunization may be less but protective immunity to vaccines received prior to the infection is usually maintained. However immunity to measles, tetanus and hepatitis B wanes faster than other antigens.

World Health Organization (WHO) and Indian Academy of Pediatrics (IAP) recommend all the live vaccines in asymptomatic HIV1 infected children except BCG and OPV. However, in a symptomatic child live vaccines are not permissible, but at times measles/MMR/varicella vaccines may be considered on individual merit. Yellow fever vaccine is contraindicated in both symptomatic and asymptomatic. For killed vaccines in an HIV-infected child, ideally postvaccination regular monitoring of seroconversion are desirable. In an HIV-infected child, there is an enhanced risk of diseases like tuberculosis, hepatitis A, hepatitis B, measles, influenza, varicella, pneumococcal and meningococcal disease. In such situations physicians need to take a decision based on risk and benefit to the child. **Table 1** summarizes IAP recommendations for vaccination of HIV-infected children.

## Cancer Cases on Chemotherapy/Radiotherapy

Influence of cancer per se on immune function is minimal and does not contribute to a major extent in inducing immunocompromised state. However chemotherapy for cancer causes major secondary immunodeficiency. Radiotherapy does not affect the immune function to the extent of chemotherapy. Cancer cases need vaccination as they are prone to many vaccine preventable diseases as described here.

- Inactive influenza vaccine (IIV) should be given annually to all children aged older than or equal to 6 months with hematological malignancies or solid tumor malignancies except those receiving anti-B-cell antibodies or intensive chemotherapy, such as for induction or consolidation chemotherapy for acute leukemia.
- Pneumococcal conjugated vaccine (PCV) should be administered to newly diagnosed adults with hematological or solid malignancies and children with leukemia. Pneumococcal polysaccharide vaccine (23-valent) (PPSV23) should be administered to adults and children aged older than or equal to 2 years at least 8 weeks after PCV.

**Table 1** Immunization of HIV-infected children (IAP recommendations)

Vaccine	Asymptomatic	Symptomatic
BCG	Yes (at birth)	No
DTwP/DTaP/TT/Td/TdaP	Yes (as per routine schedule)	
Polio vaccines	<ul style="list-style-type: none"> <li>• IPV at 6, 10, 14 weeks, 15–18 months and 5 years</li> <li>• If indicated IPV to household contacts</li> <li>• If IPV is not affordable, OPV should be given</li> </ul>	
Measles	Yes, at 9 months	Yes, if CD4+ count > 15%
MMR	Yes, at 15 months and 5 years	Yes, if CD4+ count > 15%
Hepatitis B	Yes, at 0, 1 and 6 months	Yes, four doses, double dose, check for seroconversion, regular boosters
Hib	Yes (as per routine schedule)	
Pneumococcal vaccines (PCV and PPV23)	<ul style="list-style-type: none"> <li>• Yes (as per routine schedule)</li> <li>• What about PPV23 schedule?</li> <li>• One dose 2 months after PCV, second dose 5 years after first dose (not more than two doses)</li> </ul>	
Inactivated influenza vaccine	Yes (as per routine schedule)	
Rotavirus vaccine	Insufficient data to recommend	
Hepatitis A vaccine	Yes	Yes check for seroconversion, boosters if needed
Varicella vaccine	Yes, two doses at 4–12 weeks interval	<ul style="list-style-type: none"> <li>• Yes, if CD4 count ≥ 15%</li> <li>• Two doses at 4–12 weeks apart</li> </ul>
Vi typhoid vaccine	Yes (as per routine schedule)	
HPV vaccine	Yes (females only) as per routine schedule	

Abbreviations: BCG, Bacille Calmette-Guérin; DTwP, diphtheria and tetanus toxoids and whole-cell pertussis; DTaP, diphtheria and tetanus toxoids and acellular pertussis; TT, tetanus toxoid; Td, tetanus and diphtheria; TdaP, tetanus, diphtheria and acellular pertussis; IPV, inactivated poliovirus vaccine; OPV, oral polio vaccine; MMR, measles, mumps, rubella; Hib, *Haemophilus influenzae* type b; PCV, pneumococcal conjugated vaccine; PPV23, pneumococcal polysaccharide vaccine (23-valent); HPV, human papillomavirus.

- All inactivated vaccines can be considered for children who are receiving maintenance chemotherapy but these doses should not be considered valid unless there is documentation of a protective antibody level.
- Live viral vaccines should not be administered during chemotherapy.
- Three months after cancer chemotherapy, patients should be vaccinated with inactivated vaccines and the live vaccines for varicella, MMR as per schedule. In regimens that included anti-B-cell antibodies, vaccinations should be delayed at least 6 months.

### Corticosteroids/Other

#### Immunosuppressive Therapy

Children receiving high doses of oral corticosteroid (prednisolone > 2 mg/kg/day or for those weighing more than 10 kg, 20 mg/day or its equivalent for > 2 weeks) or immunosuppressive therapy should not receive live virus vaccines. Live vaccines can be given after the steroids have been discontinued for at least 1 month. Killed vaccines are safe but may be less efficacious. Children on inhaled, topical or low dose steroid therapy may be safely and effectively given their age appropriate vaccines. Physicians should always judge if immunization benefits outweigh risks.

#### Asplenia or Hyposplenia

Children with asplenia/hyposplenia are at high-risk of serious infections with encapsulated organisms. Asplenia or hyposplenia may result from sickle cell disease or radiation therapy involving spleen. Vaccination with pneumococcal (both conjugate and polysaccharide), Hib, meningococcal and typhoid vaccines is indicated in addition to all routine vaccines. All live vaccines may be safely given. In patients with planned splenectomy, vaccination should be initiated at least 2 weeks prior to splenectomy for

achieving a superior immunologic response. In those who have undergone emergency splenectomy, studies indicate that vaccination done 2 weeks after splenectomy is associated with a superior functional antibody response as compared to vaccination immediately following surgery.

### Chronic Diseases

Chronic neurologic, endocrinologic (diabetes), liver, renal, hematologic, cardiac, pulmonary and gastrointestinal disease cause increased risk of serious infections. These children should be offered pneumococcal, hepatitis A, varicella, influenza and rotavirus vaccines. The immunogenicity, efficacy and duration of protection of vaccines are lower than healthy children and hence if indicated higher antigen content/more doses (Hepatitis B), assessment for antibody response and frequent boosters (Hepatitis A and B) are recommended. It is important to stress the role of hepatitis A vaccine in patients with liver disease, pertussis boosting in those with stable neurologic disease. Children with severe cardiac and pulmonary diseases should receive pneumococcal and annual influenza vaccines. Live vaccines may be given safely in these children.

### IMMUNIZATION IN CHILDREN WITH HISTORY OF ALLERGY

Children should not receive a vaccine, if allergic to any of its components. The package label should be checked for vaccine constituents which in addition to antigen include stabilizers/buffers, preservatives, antibiotics and residue from the manufacturing process. Children with history of serious egg allergy should not receive *influenza* and *yellow fever* vaccines but can safely receive other vaccines including *measles* and MMR vaccines. Children with history of any hypersensitivity are at increased



risk for allergic reactions with inactivated *Japanese encephalitis* vaccines and thus should be monitored carefully. Children who had a serious hypersensitivity reaction to a particular vaccine must never receive it again. A mild reaction is not a contraindication to vaccination. In any case all children should be watched for at least 15 minutes after vaccination for allergy and resuscitation equipment should be kept standby.

## IMMUNIZATION IN RELATION TO ANTIBODY CONTAINING PRODUCTS

*(Whole blood, packed red cells, plasma and immunoglobulin)*

Inactivated vaccines can be safely administered simultaneously though at different site [exception administration of rabies immune globulin (RIG) 7 days after rabies vaccine]. Live vaccines including MMR and *varicella* should be avoided for at least 3 months after antibody containing products and antibody containing products should be avoided for 2 weeks after receipt of these vaccines. If immunization outside this prescribed period has occurred, serologic response should be checked and revaccination done if indicated. OPV and *yellow fever* may be given at any time in relation to antibody containing products. Rotavirus vaccine should be avoided for 6 weeks after giving antibody containing products but if this deferral results in vaccination being postponed beyond 15 weeks, the vaccine may be given.

## IMMUNIZATION DURING ILLNESS

Vaccination opportunity should not be missed during minor illnesses like upper respiratory tract infections, mild diarrhea and otitis media. However, in a moderate or severe acute illness vaccination may be postponed as immunogenicity may be lowered. Vaccination is also postponed as vaccine reaction may be mistakenly attributed to underlying illness.

## IMMUNIZATION OF CHILDREN WITH BLEEDING DISORDERS OR THOSE RECEIVING ANTICOAGULANTS

Hemophiliacs and children receiving anticoagulant therapy are at increased risk for bleeding after intramuscular injection. Vaccination can be scheduled shortly after administration of clotting factor replacement. A 23-gauge or smaller needle should be used for the vaccination and firm pressure without rubbing should be applied to the site for at least 5–10 min. Vaccines recommended for intramuscular injection could also be administered subcutaneously to in bleeding disorder cases if the immune response and clinical reaction to these vaccines are expected to be comparable by either route of injection, such as Hib conjugate vaccine, IPV, pneumococcal polysaccharide vaccine.

## IMMUNIZATION IN PREGNANCY AND LACTATION

Live vaccines are generally contraindicated in pregnant women. The yellow fever vaccine should be avoided in pregnant women as far as possible. However if travel is unavoidable, the vaccine should be given as the risks of infection outweigh the risks of vaccination (preferably in the first trimester). Measles, MMR and varicella vaccines are contraindicated in pregnancy and pregnancy should be avoided for 4 weeks after vaccination. If the vaccine is inadvertently given during pregnancy or pregnancy occurs within 4 weeks of vaccination, termination of pregnancy is not warranted. There have been no increased rates of congenital abnormalities in infants born to mothers inadvertently vaccinated in pregnancy. Measles, MMR and varicella vaccines can be safely given to contacts of pregnant women as these vaccines do not spread from vaccinee to contacts.

All inactivated vaccines may be safely given during pregnancy specially tetanus and diphtheria (Td)/tetanus toxoid (TT)/tetanus, diphtheria and acellular pertussis (Tdap) vaccines. IAP suggests immunization of pregnant women with a single dose of Tdap during the third trimester (preferred during 27 weeks through 36 weeks gestation) regardless of number of years from prior Td or Tdap vaccination. Tdap has to be repeated in every pregnancy irrespective of the status of previous immunization (with Tdap). Influenza and hepatitis B are other vaccines of importance in pregnant women. Rabies vaccine should be administered to pregnant women if indicated and is safe.

Passive immunization with Ig containing preparations is safe in pregnancy. All pregnant women should be evaluated for immunity to rubella, varicella and hepatitis B and those found susceptible should be vaccinated immediately after delivery. All pregnant women should be tested for HBsAg and if found HBsAg-positive should be followed carefully to ensure that the infant receives hepatitis B immune globulin (HBIG) and begins the hepatitis B vaccine series no later than 12 hours after birth and completes the recommended hepatitis B vaccine series on schedule.

All inactivated vaccines are safe in breastfeeding women and pose no harm to the babies. Live vaccines though may excrete poorly in breastmilk are also generally safe. Rubella vaccine may cause mild asymptomatic infection. The only exception to use of live vaccine during lactation is yellow fever vaccine as has been reported to cause infantile meningoencephalitis. If obligatory, then breastfeeding should be interrupted for the 10-day postvaccination viremic period.

## IMMUNIZATION IN PRETERM/ LOW BIRTHWEIGHT INFANTS

Generally, all vaccines may be administered as per schedule according to the chronological age. BCG and birth dose of OPV can be safely and effectively given to low birthweight (LBW) and preterm babies preferably at the time of discharge. The birth dose of hepatitis B vaccine can be administered at any time after birth in babies weighing more than 2 kg. However, in babies less than 2 kg immunogenicity of the birth dose may be low and as such preferably delayed till the age of 1 month. In babies less than 2 kg born to a hepatitis B positive mother, hepatitis B vaccine should be given along with HBIG within 12 hours of birth and three more doses at 1, 2 and 6 months are recommended. All other childhood vaccines may be given as per chronologic age and have acceptable safety, immunogenicity and efficacy. Full dose of the vaccines should be used. Since preterm and LBW babies may have low muscle mass, the use of needles with lengths of 5/8 inch or less is appropriate to ensure effective, safe and deep anterolateral thigh intramuscular administration.

## LAPSED IMMUNIZATION/PREPONED IMMUNIZATION/UNKNOWN IMMUNIZATION STATUS

Because of immune memory, there is no need to restart a vaccine sequence. Only the due doses should be given as in the original schedule irrespective of time lapse that has occurred. Doses should not be given 4 or less days from the minimum interval. In case of unknown immunization status, the child should be considered unimmunized and vaccinated accordingly. Minimum interval between the doses should be maintained and if for some reason given 5 or more days ahead of the minimum interval, the dose should not be counted. Serologic testing is also an option in patients with uncertain status but is usually not cost effective. It is better to vaccinate such children afresh to prevent missed opportunities.

## INTERCHANGEABILITY OF BRANDS

Brands of Hib, hepatitis B and hepatitis A may be safely interchanged with no compromise on immunogenicity and efficacy. However, vaccination with DTaP should be completed with the same brand as immunogenicity data different brands of DTaP is lacking. If previous brand is not known or not available any brand may be used.

## CATCH-UP IMMUNIZATION

In unimmunized or partially immunized older children any number of vaccines irrespective of live or inactivated may be given on the same day either singly or as combination vaccines maintaining a gap of 5 cm between vaccination sites (exception BCG and measles/MMR should not be given on the same day). Inactivated vaccines can be given at any time in relation to any other live/inactivated vaccines. If not given on the same day a gap of 4 weeks should be maintained between two live injectable vaccines especially MMR and *varicella* but also *yellow fever* and live-attenuated *influenza* vaccines. OPV, *rotavirus* and oral *typhoid* vaccines may be given at any time in relation to any live/inactivated vaccine. Vaccination schedule should be completed at the earliest for providing protection as early as possible.

## MORE ON THIS TOPIC

American Academy of Pediatrics. Immunization in special clinical circumstances. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS (Eds). Red Book: 2009 Report of the Committee on Infectious Diseases. 28<sup>th</sup> ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

Choudhury P, Vashishtha VM. Immunization in special situations. In: Vashishtha VM, Choudhury P, Bansal CP, Yewale VN, Agarwal R (Eds). IAP Guidebook on Immunization 2013–2014. Gwalior: National Publication House, Indian Academy of Pediatrics; 2014.

Moss W, Halsey N. Vaccination of Human immunodeficiency virus-infected persons. In: Plotkin S, Orenstein W, Offit P (Eds). Vaccines. 5<sup>th</sup> ed. US: Saunders Elsevier Publishers & Distributors; 2008. pp. 1417-30.

National Center for Immunization and Respiratory Diseases. General recommendations on immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60:1-61.

Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58: 309-18.

## IN A NUTSHELL

1. Special situations needing considerations during immunization are immunocompromised conditions, allergic disorders, bleeding diathesis and traveling to endemic areas.
2. In immunocompromised children inactivated vaccines are safe. Live vaccines are contraindicated in severe immune deficiencies but may be given in moderate or mild deficiencies conditions if benefits outweigh risks. More doses or higher potency may be needed in certain situations. Household contacts of immunocompromised patients should not receive transmissible live vaccines such as OPV.
3. All live vaccines may be given in asymptomatic HIV-infected children except BCG and OPV. In symptomatic children live vaccines are contraindicated.
4. Chemotherapy for cancer causes major secondary immune deficiency and therefore, live viral vaccines should not be given to these cases; inactivated vaccines may be considered. Three months after cancer chemotherapy patients can be vaccinated with live and inactivated vaccines. Radiotherapy has less immune deficient effect.
5. Children receiving high doses of oral corticosteroid for more than 2 weeks or other immune suppressive therapy should not receive live virus vaccines. These vaccines can be given 1 month after the therapy has been discontinued.
6. Children with asplenia or hyposplenia should be given pneumococcal Hib, meningococcal and typhoid vaccines besides all routine vaccine.
7. In patients with chronic illnesses, higher antigen content or more doses of vaccines may be needed.
8. Patients who are allergic to any component of a vaccine should not receive that vaccine. Children with history of serious egg allergy should not receive influenza or yellow fever vaccine.
9. Live vaccines should be avoided for at least 3 months after blood transfusion or any antibody containing product administration except OPV and yellow fever vaccine.
10. Live vaccines are generally contraindicated in pregnant woman. All inactivated vaccines may be safely given during pregnancy. Passive immunization with IgG is safe. All vaccines are safe in breastfeeding women.

# PART VI The Adolescent

## Section 24 ADOLESCENT DEVELOPMENT

Section Editor MKC Nair

### Chapter 24.1

### Adolescence and Adolescent

MKC Nair, Paul Russell

WHO identifies adolescence as the period in human growth and development that occurs after childhood and before adulthood, from ages 10 to 19. It represents one of the critical transitions in the life span and is characterized by a tremendous pace in growth and change that is second only to that of infancy. Today, almost one in five persons in the world is an adolescent, that's 1.2 billion people between the ages 10 and 19 globally. The state of their health is important for their lives now and in the future, for this generation and the next. There are over 1.8 billion young people in the world today, 90% of whom live in developing countries, where they tend to make up a large proportion of the population. Adolescents account for over 20% of the population of India, amounting to over 250 million adolescents in the age group of 10–19 years.

#### ADOLESCENT RIGHTS

The adolescent being a child has the basic right as envisaged in the UN child rights declaration to (i) survival: right to life, health, nutrition, adequate standards of living; (ii) protection: freedom from exploitation, abuse, neglect, armed conflicts; (iii) development: right to education, leisure and recreation, development, social security and (iv) participation: freedom of expression, thought, conscience and religion. Out of the above, the one right that is most vital for comprehensive adolescent development is the right for participation. United Nations Children's Fund (UNICEF) has given a framework and outlines for the basic approach to promoting effective adolescent participation. The key points are: (i) start early, (ii) ensure that all adolescents are in a position to participate, (iii) build young people's capabilities to participate effectively, (iv) build adults' capacity to listen and to promote adolescent participation, (v) ensure that adolescents are well informed, (vi) believe in young people and allow them to be responsible, (vii) allow adolescents to take reasonable risks, (viii) make time for participation, (ix) make space for participation, (x) connect participation to young people's interest, (xi) be transparent, (xii) be honest, (xiii) don't patronize, (xiv) be democratic, (xv) create a supportive policy environment and (xvi) pay attention to bridging the gap between policy and practice.

#### CHARACTERISTICS OF ADOLESCENCE

Adolescence is the period following the onset of puberty during which a young person develops from a child into an adult. During

this rapidly changing developmental stage adolescents can shift moods quickly, vacillating between happiness and distress and self-confidence and worry. Some of these mood changes stem from biological sources. Increased hormones and changes to the brain structure arise from normal physical growth. Also, complex social interactions such as conflicts with friends, school pressures and experimentation with romantic relationships can exacerbate the labile emotional state of adolescents. It is also a time when adolescents begin to explore and assert their personal identities and when relationships with peers begin to take precedence over relationships with the family.

The rapidly changing social, political and economic scenario in the world has not left Indian family untouched. It is going through structural and functional modifications that have a bearing on adolescent's socialization and parent-child relations. Weakening of social support from kinship, movement of women empowerment, exposure to media, increasing competitive demands of the market economy and higher standards of achievement are a few aspects that have changed the family dynamics in the recent past. The need for differential values, competencies and coping styles between parents and adolescents are a source of anxiety and stress both for adolescents and parents. The ambiguity of values that adolescents observe in the adult world, the absence of powerful role models, increasing gaps between aspirations and possible achievements, not surprisingly, lead to alienation and identity diffusion. Parents themselves appear ill prepared to cope with social change, having grown up in hierarchically structured and interlinked social and caste groups that provided stability. The conflict between parents' desire to help their adolescent children cope with the changing demands of their own rootedness in tradition expresses itself in the *cold feet syndrome* when things go wrong. Parents who apparently seem modern, but if their child breaches established social codes, intergenerational conflicts related to marriage, career choice or separate living arrangements result in the tendency to fall back on tradition.

#### THEORIES OF ADOLESCENCE

According to the *biological theory* of adolescence by G Stanley Hall, Arnold Gesell and James Tanner, the focus of the period is physical and sexual development determined by genes and biology. The *psychological theory* (Sigmund Freud) focused on adolescence as a period of sexual excitement and anxiety. The main focus of *psychological theory of Erik Erikson* is on identity formation; adolescents struggle between achieving identity and identity diffusion. The *cognitive theory* of Jean Piaget emphasized on formal operational thought; moving beyond concrete, actual experiences and beginning to think in logical and abstract terms. In the *social cognitive theory* of Albert Bandura, the main focus is

on the relationship between learning social and environmental factors and their influence on behavior. The *cultural theory* of Margaret Mead emphasized on the influence of culture in which the adolescent grows up. Maslow's hierarchy of needs explains the need to progress through biological needs, safety needs, love and belonging needs, self-esteem needs, self-actualization needs to the ultimate, the transcendental needs.

## ADOLESCENTS' NEEDS AND PROBLEMS

An individual's needs and problems influence his development to a great extent. Adolescence is a crucial period in the life of an individual with its characteristic needs and problems of adjustment. Every adolescent has certain needs, the satisfaction of which is essential to his continued physical and other aspects of development. A need is a tension within an organism which must be satisfied for the well-being of the organism. When a need is satisfied, the tension is released and the individual experiences satisfaction.

There are certain basic needs which are functioning in every individual. They are broadly classified into *physiological needs* and *psychological needs*. The fulfillment of physiological needs is inevitable because they are concerned with the very existence of the individual. The need for oxygen, need for water and food, need for rest and sleep, need for sex gratification etc. are the important physiological needs. Needs that are associated with sociocultural environment of an individual are called *secondary needs*. They are acquired through social learning and their satisfaction is necessary for the psychological well-being of the individual. The important sociopsychological needs are as follows: (i) need for security, (ii) need for love, (iii) need for approval, (iv) need for freedom and independence and (v) need for self-expression and achievement.

### Problems of Adolescents in the Indian Context

Any period of development is likely to be accompanied by many potential difficulties. Adolescence is a period of transition from childhood to adulthood that implies many development changes and associated problems. Some of the outstanding problems of Indian adolescence are the following:

#### *Perplexity with Regard to Somatic Variation*

Every adolescent has more or less difficult task of adjusting to somatic variation which may occur in connection with puberty. The flow of blood during menstruation in girls and nocturnal emission in boys creates worries and gives birth to so many fears and anxieties.

#### *Problems Related with Intensification of Sex Consciousness*

The sudden awakening of sex instinct during adolescence results in intensification of sex consciousness. Adolescents are curious to know about sex related topics and are seeking answers to their innumerable doubts in sexual matters. In our country, some of the parents are illiterate and they do not have scientific knowledge of sexual matters.

#### *Adjustment Difficulties with Parents*

Adolescents have a strong desire for freedom and independence. The conflict between parental norms of behavior and peer group relationships often leads to friction in the relationship and adolescents find it difficult to adjust to the needs and demands of parents. Failure to adjust with the parents may result in revolting against parents and authority.

### *Childhood-adulthood Conflict*

In our society, the adolescent is considered neither as a child nor as an adult. He/she has to depend on his parents and elders for his physical and emotional needs. But at the same time, he wants to hold independent views and opinions like an adult. He/she can very well manage his own affairs and resist any unnecessary interference from elders. He/she begins to feel ashamed and embarrassed for the protection and care shown by the parents.

#### *Adjustment Difficulties with School Discipline*

Most of the adolescents face a great problem in adjusting with school discipline. Sometimes school expects too much from students who must submit to teachers who may be tyrannical sometimes.

#### *Adjustment Difficulties with Community*

The adolescent is expected to find his place in a society marked by increasing social isolation and rapid technological changes. This changing world makes it difficult to anticipate and plan for adolescent life.

## COMMUNITY ADOLESCENT CARE COUNSELING PROGRAMS

A healthy adolescent is the product of a series of steps including caring for the pregnant woman, prevention of low birth weight babies, caring for the young child between 0 and 6 years, compulsory primary education for both boys and girls and care of the vulnerable adolescent period. Adolescence is a period of experimenting, experiencing and expanding, and needs parental and societal support to safeguard, protect and guide him/her safely through this rebellious period. Adolescents need help and guidance in decision making, problem solving, critical thinking, developing interpersonal skills, self-awareness, empathy, coping with stress and managing emotions.

India has a sizeable adolescent population and they constitute a vulnerable group for both mental and physical illnesses, and yet their health-care needs and delivery systems are neither well defined nor developed. Conventional health service systems did not, until very recently in India, consider adolescent health as a vital aspect of health service development in the country. The importance of adolescent health, especially enhancing the mental health as well as sexual and reproductive health has been documented. The research on child and adolescent mental health is only 3-6% of all published mental health research in the world and research base from India in this vulnerable population is negligible. Similarly, although service and delivery models have been enhanced for the Adolescent Reproductive and Sexual Health (ARSH) in India, the evidence base about the needs and interventions aimed at individual to community level is still evolving like: (i) community adolescent health care and education model, (ii) school-based family life education and counseling model, (iii) school-based adolescent care services, district model.

Many of the mental, reproductive and nutritional health needs of the adolescent population are required to be addressed and can be addressed in the primary care pediatric setting itself, if the current system of health-care can be reorganized. This restructuring will be more effective for this population if adolescent friendly approaches, public-private partnership and policy as well as sectoral linkage between the National Rural Health Mission (NRHM) and other national programs are achieved. The health program for this age group should have promotive and preventive as well as remedial and curative components. Also, improving the availability of trained personnel in these areas of health, culturally



sensitive evidence-based approaches and capacity building in the primary care approach is essential to ensure the viability of adolescent health-care in this country.

Currently, at the national level, there are efforts to develop and bring adolescent health services as part of the child health-care in India under Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCH+A) and Rashtriya Bal Swasthya Karyakram (RBSK). What we need to appreciate is that a direct approach on sexuality issues is not acceptable to Indian parents and many adolescents themselves. Hence, we need to choose a more appropriate stepwise approach of family life and life skill education, counseling for scholastic issues and reproductive issues like menstrual problems, reproductive tract infections and polycystic ovary syndrome and reserve sexuality issues for those who have completed 18 years of age.

## ADOLESCENT OFFICE PRACTICE

We need more and more general practitioners getting interested in adolescent pediatrics as a subspecialty for overall improvement in providing adolescent care and counseling. Adolescent office practice should have the following components:

### Routine Medical Care

The medical problems identified among adolescents namely, headache, refractory error, urinary tract infection, dandruff, acne, allergic rhinitis, dysmenorrhea and leukorrhea, anemia, iodine deficiency, undernutrition, overweight and obesity, body image problems, lifestyle diseases, polycystic ovarian syndrome (PCOS), acne and other cosmetology issues, dandruff and seborrhea, dental caries and problems, genitourinary infections, sexually transmitted infections, sexual abuse or empowerment issues, teenage pregnancy or contraceptives, pelvic inflammatory disease, drug therapy and individual counseling for mental health issues are problems that can be tackled by a trained adolescent pediatrician.

### Adolescent Immunization

As per Indian Academy of Pediatrics (IAP) Immunization Schedule.

### Family Life Education

Family life education should include the following topics: (i) growth, nutrition, maturation and body image, (ii) reproductive health, (iii) life skills development, (iv) improving study habits, (v) avoiding substance abuse and HIV/AIDS, (vi) adolescent mental health problems and counseling.

### Nutrition, Body Image and Prevention of Obesity

Because adolescents experience significant physical changes in their bodies during puberty, they are likely to experience highly dynamic perceptions of body image. Body image is influenced strongly by self-esteem and self-evaluation, more so than by external evaluation by others. It can, however, be powerfully influenced and affected by cultural messages and societal standards of appearance and attractiveness. In the western world, 85% of young women worry *a lot* about how they look, however, and twice as many males as females say they are satisfied with their appearance.

### Screening for Lifestyle Diseases

The rising burden of preventable risk factors for noncommunicable diseases (NCDs) among adolescents is a major public health challenge worldwide. NCDs like obesity, diabetes mellitus, hypertension, coronary artery disease, stroke in adults have been related to the prevalence of risk factors in childhood. Singh et al, documented inappropriate dietary practices (fast food consumption, low fruit consumption), low physical activity,

higher level of experimentation with alcohol and to a lesser extent smoking, high prevalence of obesity and hypertension in the school children. Khuwaja et al, reported that over 80% of the adolescents in Pakistan had unhealthy diets and 54% were physically inactive. Most adolescents were exposed to passive smoking, and 14% were also current smokers.

The *fetal origins hypothesis* proposes that NCDs including coronary heart disease, type 2 diabetes and hypertension originate through the responses of a fetus to under nutrition that permanently change the structure and function of the body. Child Development Centre (CDC) Kerala follow-up study observed that high triglyceride values and overweight/obesity were significantly more in low birth weight adolescents when compared to normal birth weight adolescents. These results may have policy implications in planning adolescent nutrition and care programs in India.

Adolescents need further evaluation if BP is more than 130/80 mm Hg. These children should also be screened for hypercholesterolemia. Indications for drug therapy (cholestyramine/niacin/statins) in those above 10 years include: (i) low density lipoprotein (LDL)  $\geq 190$  after 6–12 months of diet therapy; (ii) LDL  $\geq 160$  and family history of early coronary vessel disease; or (iii) LDL  $\geq 160$  and 2 or more risk factors like; obesity, smoking, hypertension, diabetes and inactivity.

### Screening for Reproductive Health Disorders

Health-care providers can provide important information on sexuality and reproductive health, and need to be able to communicate this information without restriction to patients in private. This includes the provision of sexuality information and healthcare to minors without parental consent or notification. Comprehensive school-based family life education that is appropriate to students' age and developmental level is an essential part of education programs for every age.

### Preventing STIs, HIV and Teenage Pregnancy

In India, although traditional norms oppose premarital sex, some studies indicate a growing trend toward premarital sexual activities among adolescents. An intervention study conducted among Lucknow slum boys has shown that approximately 15–17% of youths reported intercourse outside of marriage, including about 3% who reported intercourse with a prostitute and 3% who reported oral or anal sex with another male. After the intervention, awareness that STIs including HIV/AIDS could be acquired from women other than prostitutes increased significantly from 50% to 76% in the intervention group. However, young men's awareness that they were personally at risk of acquiring STIs changed little during the intervention.

Unmarried pregnancy is not acceptable at all to the Indian parents and there is huge social stigma attached to it. A case control study conducted in Kerala regarding risk factors for pregnancy among unmarried adolescents and young adults has shown a strong association between unmarried adolescent pregnancy and lack of parental supervision [odds ratio (OR) 8.74], poor intra-family relationship (OR 7.01), lack of knowledge on sexual and reproductive health (OR 4.95), family problem (OR 4.41) and non-engagement of adolescent in any productive activity (OR 4.41).

### Adolescent Reproductive Tract Infections among Girls

Among 427 unmarried girls seen in community adolescent clinic settings in Kerala, the mean age at menarche of the participants was 12.3 years. On clinical examination by lady gynecologist, 20.1% had vulvitis and more than 50% had mild to moderate discharge, 42.4% being normal mucoid discharge and 10.3% yellow or thick curdy discharge. On laboratory examination, 5.6% had KOH

mount positive, suggestive of candidiasis and 7% suggestive of bacterial vaginosis. More than one-third of the school going girls does not use school toilets. For majority of girls with external genital itching, apart from good menstrual hygiene, washing and drying properly the local area before going to sleep, use of local antifungal ointment or powder is adequate. However, for more serious infections with curdy white discharge and intense vulvar itching, the drug of choice is fluconazole 150 mg as a single dose which may be repeated after 1 week.

### Adolescent Counseling

Aim of adolescent counseling would be maintaining the client's adaptive patterns, modifying maladaptive patterns and enhancing motivation of the client. The counseling steps would include: (i) rapport building with the adolescent, (ii) ventilation or catharsis of adolescent's problems, (iii) prioritizing problems, (iv) understanding the context and self-role in creating the problem, (v) choices of solutions from adolescent's perspective, (vi) helping to choose and implementing the right choice, (vii) termination of the professional relationship between adolescent and the pediatrician. Counseling is further detailed in Chapter 26.2.

### Screening for Mental Health Disorders

Adolescent mental health issues have to be addressed by the general practitioners/pediatrician/physician because there are far too many adolescents with behavioral and emotional problems in the community and only limited number of psychiatrists and trained clinical psychologists available. We have to recognize early signs of psychosocial problems for better results and the pediatrician, who have been seeing the child and who knows the family well for a long time, would be the ideal person to do so. Both parents and children have to be made comfortable in a nonstigmatizing service delivery system. Many of the adult psychiatric disorders have their onset in adolescence. Half of lifetime diagnosable mental health disorders start by age 14; this number increases to three-fourths by age 24. The evidence shows that one in five adolescents experiences significant symptoms of emotional distress and nearly one in ten is emotionally impaired and the most common disorders among adolescents include depression, anxiety disorders and attention deficit hyperactivity disorder and substance use disorder.

Mental health in adolescents is dealt with in detail in Chapter 25.3.

### Premarital Counseling Services

Although ideally premarital counseling should be given to persons above 18 years, but in the Indian context, because of high prevalence of early marriages premarital counseling could be offered to any young adult over 15 years of age. The counseling sessions should include: (i) family life and life skill education, (ii) enhancing coping strategies, (iii) improving communication strategies, (iv) guidance on morality or spirituality issues, (v) self-empowerment both economic and social, (vi) prevention of intrauterine infections like rubella, hepatitis B, human papilloma virus vaccinations, (vii) screening for STIs or HIV,

lifestyle disease markers, mental health and reproductive health, (viii) medical examination including breast and external genitalia, (ix) transabdominal ultrasound examination if indicated and (x) sex and sexuality skills needed in family life including understanding needs of self as well as the partner. While examining any adolescent and particularly a female adolescent, it is a must (i) to have presence of her mother, (ii) explain what specific examination you are going to do and why and (iii) get her permission at every stage of examination in a reassuring way.

### IN A NUTSHELL

1. WHO identifies adolescence as the period in human growth and development that occurs after childhood and before adulthood, from ages 10 to 19.
2. Adolescence is a crucial period in the life of an individual with its characteristic needs and problems of adjustment.
3. The important sociopsychological needs of adolescents are: (i) need for security, (ii) need for love, (iii) need for approval, (iv) need for freedom and independence and (v) need for self-expression and achievement.
4. India has a sizeable adolescent population and they constitute a vulnerable group for both mental and physical illnesses, and yet their health-care needs and delivery systems are neither well defined nor developed.
5. Pediatricians need to incorporate care of the adolescents in their office practice including health-care, life skill education, and counseling.

### MORE ON THIS TOPIC

- Khuwaja AK, Khawaja S, Motwani K, et al. Preventable lifestyle risk factors for non-communicable diseases in the Pakistan Adolescents Schools Study 1 (PASS-1). *J Prev Med Public Health*. 2011;44:210-7.
- Nair MKC, Russell PS. Adolescent care counseling part-I. *Indian J Pediatr*. 2012;79:S1-S91.
- Nair MKC, Russell PS. Adolescent care counseling part-II. *Indian J Pediatr*. 2013;80:129-255.
- Nair MK, Mehta V. Life cycle approach to child development. *Indian Pediatr*. 2009;46:S7-S11.
- Nair M, Chacko D, Rajaraman V, et al. The diagnostic accuracy and validity of the teen screen questionnaire-mental health for clinical and epidemiological studies in primary-care settings. *Indian J Psychol Med*. 2014;36:187-91.
- Nair MKC. Adolescent mental health. Teens: a life cycle approach. *Child Adol Dev*. 2011;5:1-24.
- Moni SA, Nair MKC, Devi RS. Pregnancy among unmarried adolescents and young adults. *J Obstet Gynaecol India*. 2013;63:49-54.
- Singh AK, Maheshwari A, Sharma N, Anand K. Lifestyle associated risk factors in adolescents. *Indian J Pediatr*. 2006;73:901-5.
- UNFPA. Adolescent and Youth Demographics: A Brief Overview. From: <https://www.unfpa.org/webdav/site/global/shared/factsheets/One%20pager%20on%20youth%20demographics%20GF.pdf>. Accessed November 8, 2014.
- WHO. Developing a report Health for the world's adolescents. From: [http://www.who.int/maternal\\_child\\_adolescent/topics/adolescence/adolescent\\_health2014/en/](http://www.who.int/maternal_child_adolescent/topics/adolescence/adolescent_health2014/en/). Accessed, November 8, 2014.

## Chapter 24.2

# Sexual Development and Sexuality

Chandrika Rao

The development of reproductive organs is determined by the presence and action of sex chromosomes, sex-determining genes and a number of hormones in a coordinated manner starting early in fetal life. The development and differentiation of both internal and external genitalia are now believed to be active processes guided by genes and hormones in the presence of gonads (see Chapter 44.20 for details). Any discordance in the development may lead to disorders of sexual development (DSD).

### PUBERTY AND SEXUAL MATURITY RATING

Puberty is the phase of transition from the sexually immature child to the mature, potentially fertile adolescent and adult. The physiology of normal pubertal development in boys and girls, its regulation by the hypothalamic-pituitary-gonadal (HPG) axis as well as the physical changes associated with puberty in both genders are detailed in Chapter 44.10. The standard clinical system for describing normal pubertal development, which includes the somatic and physiologic changes in the external genitalia and breasts, is the five-stage system of sexual maturity rating (SMR) system described by Tanner and Marshall (see Chapter 44.10 for details).

### Implications of Pubertal Assessment for the Pediatrician

Assessment of puberty by SMR helps in the diagnosis of not only disorders of puberty and DSD, but also in disorders of growth and development and many systemic and genetic disorders. It should be done patiently after establishment of rapport between the adolescent and the pediatrician. Adolescents, who are uncomfortable of the examination of private areas of their body, can indicate development in a Tanner chart which can be confirmed later.

Minor asymmetry of breasts is a common normal variant in adolescent girls. The most common breast abnormality noted in adolescent girls is a mass, mostly due to a benign cyst or fibroadenoma. Tenderness with swelling of breasts especially in a cyclic pattern may occur during the premenstrual period in some girls. They need appropriate counseling to alleviate their apprehensions.

Testicular size is the earliest reliable sign of puberty and an important part of examination of boys. Testicular size is assessed by Prader orchidometer (**Fig. 1**). The beads correspond to testicular volumes of 1 mL through 25 mL. Other methods of measurement of testes include rulers, calipers and ultrasound. Ultrasound is probably the most accurate measurement method. The clinician should check for whether the testes are descended and there is hypospadias. Prepubertal boys nearly always have a testicular length of 2.5 cm or less, or volume of 4 mL or less. As puberty progresses, the increase in testicular size usually precede the increase in penis size and eventually reaches the adult size of 5.0 cm or 25 mL. To measure penile length accurately, use either a ruler pressed at the base of the penis while applying firm stretch to the penis itself. In normal prepubertal boys, the penile length ranges from 5–7 cm.



**Figure 1** Prader orchidometer

### GYNECOMASTIA

Gynecomastia is a benign enlargement of male breast. This may be unilateral or bilateral. Histologically, it contains glandular tissue proliferation of mammary tissue. In true gynecomastia, the breast enlargement is due to glandular breast tissue and in pseudogynecomastia, excess adipose tissue is the cause of the enlarged chest. It is marked by the diffuse fatty tissue infiltration of the breast and axillary areas. A detailed discussion on gynecomastia is given in Chapter 44.13.

### MENSTRUATION

The average age at menarche (the first menstrual period) has shown a secular trend in most affluent countries. In urban Indian girls it occurs at around 12.6 years, whereas for rural Indian girls it is still around 15–16 years.

The menstrual cycle usually lasts for 28–35 days, beginning from the first day of bleeding to the first day of the next cycle. The bleeding may last for 3–5 days with 50–200 mL blood loss in each cycle. The ovarian cycle consists of three phases of a *follicular phase* followed by *ovulation* and later a *luteal phase*. The uterine cycle is divided into menstruation followed by a *proliferative phase* and a *secretory phase*. The rhythm of these cycles depends on the intact hypothalamic-pituitary-ovarian (HPO) axis.

At puberty, the hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile manner which activates the HPO axis with secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Anterior pituitary releases FSH which stimulates ovarian primordial follicles into Graafian follicles. In each cycle, one Graafian follicle dominates, matures and ovulates. The Graafian follicle secretes 17 $\beta$ -estradiol which causes endometrial proliferation. During the follicular phase, estradiol suppresses the secretion of LH. As the ovum matures, the levels of estradiol reach a threshold where it stimulates secretion of LH (*LH surge*) and inhibin secretion and inhibits secretion of FSH. Estrogen secretion peaks 48 hours before ovulation and LH secretion peaks 24–36 hours before ovulation.

At ovulation, follicle ruptures and forms corpus luteum. The theca cells in ovary produce testosterone and androstenedione. Progesterone secreted by corpus luteum stimulates endometrium to undergo secretory hypertrophy and inhibits LH secretion. If fertilization is absent in that cycle, estrogen and progesterone levels gradually decline and endometrial lining is shed which causes menstruation. In an anovulatory cycle, a thin necrotic

superficial layer of endometrium is shed with vascular changes and secretion of prostaglandin E2 (PGE2). This causes myometrial contraction and vasodilatation. Prostaglandin F2- $\alpha$  (PGF2 $\alpha$ ) causes vasoconstriction. PGE2 and PGF2 $\alpha$  are responsible for dysmenorrhea while prostaglandin I2 (PGI2) causes muscle relaxation and vasodilatation and abnormal secretion can cause menorrhagia.

In about 50% of the girls, the initial cycles and those up to 2 years may be anovulatory and irregular, prolonged, scanty or excessive.

### Implications for a Pediatrician in Menstrual Disorders

Menstrual irregularities are common among school girls of 15–17 years—around 20% self-report menstrual irregularities whereas about 13% have confirmed menstrual irregularity as per the standard criteria used by a gynecologist. The most common menstrual problems reported among the school girls were dysmenorrhea (72%) followed by back pain (40%), fatigue (36%), pain over the arms and legs (28%), loss of appetite (18%), headache (14%) and vomiting (6%). The roles of the pediatrician in adolescent girl seeking counseling are as follows:

- Encourage the girl and mother to discuss menarche and menstrual cycles, and problems if any, during routine clinical contacts.
- Individual problems like irregular menstrual cycles or dysmenorrhea need to be diagnosed, counseled and treated early.
- Menstrual hygiene should be discussed.
- Need for proper diet and exercise should be stressed.
- Advice regarding hematinic and treatment of anemia—weekly dose of 100 mg of elemental iron with 500  $\mu$ g of folic acid and biannual deworming.

## DEVELOPMENT OF SEXUALITY AND GENDER IDENTITY

Sexuality deals with sexual behavior, sexual orientation, sexual interest and fantasies, attitudes toward sex and the awareness of socially defined and accepted sexual roles, values and traditions. Some of the important terms and definitions used while discussing sexuality and gender identity are described below:

### Anatomic Sex

It refers to the anatomic appearance of the sexual reproductive organs. Anatomic sex is only one component of sexuality.

### Gender Identity

It refers to the inside feeling of oneself as either masculine or feminine. Gender identity and anatomic sex sometimes do not match. For example, a person can be born as a boy but feel like a girl. This is sometimes referred to as transgender. Transgender individuals and transvestites may not have matching gender identity to the biological sex. Transgender individuals and transvestites can be heterosexual, homosexual or bisexual.

### Gender Role

It is the outward expression of maleness or femaleness. It is the public image of being male or female that a person presents to others.

### Sexual Orientation

It refers to the sexual attraction one feels toward another person. It refers to an individual's pattern of physical and emotional arousal toward other persons. Heterosexual individuals are attracted to persons of the opposite sex, homosexual individuals (often referred

to as *gay* and *lesbian*) are attracted to persons of the same gender and bisexual individuals are attracted to persons of both genders. Sexual orientation is not synonymous with sexual activity or sexual behavior. Sexual orientation is influenced by many factors including anatomic sex, gender identity and the society.

### Asexuality

It refers to having no sexual attraction to a person of either gender.

It is common for adolescents to feel confused about their sexual orientation, which is normal. These feelings may change as person matures or may persist. It is important for adolescents and adults to be comfortable with all aspects of sexuality (anatomic sex, gender identity and sexual orientation).

Adolescents may date casually without commitment. They begin as mixed-gender group friendships in preadolescence. Peer pressure, communication skills, body image issues and self-esteem play a major role here. As they grow older, group dating and later dyadic (or couple) dating with increasing levels of intimacy and commitment develop and may result in cohabitation and/or marriage. Friendship networks often play important and varied roles in the dating process. The various changes that occur in sexuality during the adolescence are listed in **Table 1**.

## Development of Sexuality

Various theories have been formulated on the development of human sexuality. They are discussed in brief below:

### Freud's Theory

According to Freud and psychoanalytic theory, the stages of psychosexual development are genetically determined. Freud believed that adolescent sexuality was influenced by behavioral, social and emotional changes and the influences on the self-

**Table 1** Sexuality in early, mid and late adolescence

Early adolescence	Middle adolescence	Late adolescence
<ul style="list-style-type: none"> <li>• Girls bolder than boys</li> <li>• Same-sex friends and group activities</li> <li>• Shyness, blushing and modesty</li> <li>• Greater interest in privacy</li> <li>• Experimentation with body—masturbation, associated with guilt</li> <li>• Worries about being normal—gay, lesbian and bisexual youth may feel differently without knowing why</li> <li>• Sexual fantasies common</li> <li>• Sexual activities are usually nonphysical</li> <li>• Early adolescents are often highly content with non-sexual interactions such as telephone calls to peers</li> </ul>	<ul style="list-style-type: none"> <li>• Concerns about sexual attractiveness</li> <li>• Frequently changing relationships</li> <li>• Movement toward heterosexuality with fears of homosexuality</li> <li>• Tenderness and fears shown toward opposite gender</li> <li>• Feelings of love and passion</li> <li>• Noncoital and coital contacts are prevalent</li> <li>• Sexual behaviors do not always match sexual identity</li> <li>• Denial of consequences of sexual behavior is typical—improving with age</li> </ul>	<ul style="list-style-type: none"> <li>• Concerned with serious relationships</li> <li>• Clear sexual identity</li> <li>• Capacities for tender and sensual love</li> </ul>



image. He also stated that the physiological changes are related to increase in negative emotions such as anxiety, tension and other forms of adolescent behavior.

### Anna Freud's Theory

She assigned greater importance to the relationship between the id, the ego and the superego. She believed adolescent conflicts depend on the strength and coping ability of id and ego of the individual.

### Erikson's Theory

He described adolescence as the period during which sense of personal identity is established and is more important than sexuality. He believed that this must be acquired through individual efforts; contact with peers and one's values all contributing to a stable identity. This influences the adolescent in adulthood. If the adolescent adopts someone else's identity or ideology, it rarely becomes satisfactory and can lead to self-doubt, role confusion and the adolescent may indulge in self-destructive activity in adolescence.

### Social Learning Theory

#### (Modeling, Imitation and Identification)

Usually, children imitate parents and later the teacher. During adolescence the peer group and selected social models like actors may form role models.

### Other Theories

Two theorists, Bandura and Hollingworth, believed that human development is a continuous process and social conditions are responsible for naming adolescence as a *transition stage* and it is not some intrinsic aspect of human development.

### Mead's Theory

It states that *in most societies adolescence is a period of reorientation*. The normal milestones of sexual play and activities are described in **Table 2**.

## ADOLESCENT HOMOSEXUALITY

Pediatricians dealing with adolescent ages may often have questions on sexual behavior and sexual orientation addressed to them. Adolescents may have doubts about sexual orientation and

may seek information from physicians about illnesses, sexually transmitted diseases or substance abuse. Health issues concerning sexual behavior are varied and are different from normal disease spectrum that pediatricians are used to. Hence, it is necessary for pediatricians to be comfortable in dealing with normal adolescents with curious questions and adolescents who go through different experiences. The pediatrician should be alert to depression, anxiety, low self-esteem and aggression. Sexual history should be done in a gender-neutral manner. It is better to phrase the question as—“*Is there anyone you are romantically interested in? Have you ever had sex with anyone?*” Counseling is necessary along with a thorough medical history, physical examination, appropriate immunizations [e.g. human papillomavirus (HPV) and hepatitis A and B], selective laboratory tests [e.g. human immunodeficiency virus (HIV), hepatitis A, B and C, sexually transmitted infections] and appropriate treatment as necessary.

## Implications for the Pediatrician Dealing with Sexuality Issues

- Assure confidentiality. Personal interview is necessary. Parents may have concerns which they are reluctant to discuss with their children and separate interviews may be desirable at time to maintain confidentiality.
- Pediatrician should keep in mind that physical maturation may correlate with sexual maturity whereas psychosocial development correlates more closely with chronologic age.
- Questions in history should be gender neutral.
- Nonjudgmental language should be used. Questions like “*Who is your boyfriend or girlfriend?*” can be better worded as “*Are you interested in anyone romantically?*”
- Information on gender, sexual orientation and resource groups in the clinic or hospital will encourage adolescents to ask questions.
- History should include questions on risk behaviors, depression and suicidal thoughts.
- The pediatrician should provide *safe sex* guidelines and information on protection to adolescents who are sexually active.
- It is ideal to counsel all adolescents about substance use (alcohol, marijuana and other drugs) and unsafe sexual intercourse.
- It may be necessary to perform investigations such as tests for sexually transmitted diseases, HIV or pregnancy depending on the clinical information.
- If adolescent has homosexual activity, urethral (or urine), pharyngeal and anal swabs for gonorrhea, urethral culture or urine for chlamydia, anal cytology and stool culture testing, ova and parasite should be done.
- Immunization to prevent cervical cancer (HPV vaccine) and hepatitis A, B should be offered.
- Information on sexual abuse and violence should be offered.
- Pediatrician and the resource personnel should not have personal bias in providing care to adolescents who have expressed their sexual orientation to the health-care providers. If nonjudgmental environment cannot be assured, adolescent should be referred to a better equipped center.

## NOCTURNAL EMISSION

Nocturnal emission is emission of semen in men or lubrication of vagina in women at night in sleep. It is common in teens and young adults. The person can sleep through it or wake up during the event. Frequency is variable and may vary to multiple episodes per month in teens to 1–2 per month in men. Multiple episodes with dizziness, weakness and insomnia are considered pathological. Local causes of abnormal emissions

**Table 2** Normal milestones of sexual play

Age group	Sexual play and activities
0–3 years	Children are egocentric
3–4 years	Boys and girls may hug, kiss and may have future plans which may not be understood by them
4 years	Awareness of differences in male and female genitalia and awareness when micturating. Play involves house play with gender roles and doctor games
5–11 years	Self-consciousness sets in. Hugging, kissing and showing may continue but decrease. Boys and girls may hate each other. Teasing occurs
Preadolescence	Jokes and secrets about sexual activities, display knowledge of sexual words, talk about sex with same sex friends
Adolescence	Exchange letters, dance, attend parties with mixed genders, kiss, have a steady partner, activities like fondling, oral-genital contact and intercourse may occur

are inflammatory diseases of the posterior urethra (urethritis), prostate (prostatitis), seminal vesicles and vas deferens (vasitis). Continued existence of inflammation in the genitals leads to constant irritation of nerve endings and the subsequent depletion of spinal ejaculation center and contribute to the emergence of pathological pelvic congestion in the pelvic fat and the pelvic organs (hemorrhoids, colitis and prolonged constipation). Management is by reassurance.

## MASTURBATION

Masturbation refers to nonpenetrative sexual stimulation of a person's genitals often to the point of orgasm. The stimulation can be performed manually, by other types of bodily contact (short of sexual contact), by use of objects or tools or by some combination of these methods. The English word *masturbation* was introduced in the 18th century based on the Latin word, *masturbari*, alongside the more technical and slightly earlier *onanism*.

Masturbation or self-stimulation of genitalia is a common human behavior and is believed to occur in 90–94% of males and 50–60% of females at some point during their life time. A study from Gujarat in 1995 in adolescent girls revealed 30% of sample indulged in masturbation.

The capacity for sexual response is present from birth. Male infants have erections and vaginal lubrication has been found in female infants 24 hours after birth. Infants have been observed fondling their genitals; the rhythmic manipulation associated with adult masturbation appears at ages 2.5–3 years. Normally, it may begin at 2 months of age and peak at 4 years of age. The practice which resembles infantile masturbation is normal and child is discovering sexuality. The concept of infantile masturbation was suggested by Still in the early part of 20th century and has been widely recognized since then by the medical fraternity. Normally, the behavior stops on its own as child learns social norms and is gradually discouraged by caretakers. As this is a normal human behavior, it needs nothing more than reassurance to the anxious parents. It is highly preferable to use the term gratification disorder instead of infantile masturbation in view of the social stigma attached to this term and to alleviate parental anxiety.

As adolescents pass through puberty, sexual arousal occurs and they may masturbate. This is considered physiologic. Today, masturbatory act is considered as a healthy practice when done in private and an offence if done in the public in most of the countries. Masturbation is considered as pathologic during the following situations:

Excessive handling of genitalia in child less than 5 years may be due to low-grade urinary tract infection. It may be due to child requiring more soothing or requiring distraction. Such a habit can also be addressed by providing other activities for the child to engage with.

Age-inappropriate sexual knowledge, sexualized play or aggression, precocious or seductive behavior and excessive masturbation may be a sign of sexual abuse where a child may have been exposed to sexual activity or was sexually abused.

Compulsive masturbation—adolescent craves to masturbate even at school or in public place.

Adolescent may blame masturbation for weakness, fatigue,

acne. It may occur due to premature exposure to sexual content, delayed cognitive development and psychiatric disorders.

## Implications for the Pediatrician

- Encourage the parent to have positive sexual attitude. The parent should not show negative gestures or emotions when children touch their genitals during bath or changing diapers. Parents can use the opportunity to teach child the body parts.
- As the child matures into adolescent, parents and doctor should introduce topics like masturbation, night emissions and high-risk behavior.
- Ensure adolescent privacy in their rooms.
- Adolescents should be encouraged to have outdoor activities.

## MORE ON THIS TOPIC

- Frankowski BL. American Academy of Pediatrics Committee on Adolescence. Sexual orientation and adolescents. *Pediatrics*. 2004;113:1827-32.
- Jeffcoate N, Tindall VR. Menstruation and other cyclical phenomena. *Jeffcoate's Principles of Gynaecology*. Butterworths; 1987. p. 76-82.
- Kaufman M. Canadian Paediatric Society, Adolescent Health Committee. Adolescent sexual orientation. *Paediatr Child Health*. 2008;13:619-23.
- Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child*. 1970;45:13-23.
- Nair MKC. Adolescent sexual and reproductive health. *Indian Pediatr*. 2004;41:7-13.
- Nair MKC. *Sexual Reproductive Health of Young People*. 1<sup>st</sup> ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2006.
- Nair MK, Chacko DS, Ranjith Darwin M, et al. Menstrual disorders and menstrual hygiene practices in higher secondary school girls. *Indian J Pediatr*. 2012;79:S74-8.
- Rosen DS. Physiologic growth and development during adolescence. *Pediatr Rev*. 2004;25:194-200.
- Ross MW. Typing, doing, and being: sexuality and the internet. *J Sex Res*. 2005;42:342-52.
- UNFPA, Save the Children. Adolescent Sexual and Reproductive Health Toolkit for Humanitarian Settings. A Companion to the Inter-Agency Field Manual on Reproductive Health in Humanitarian Settings. USA: UNFPA, Save the Children; 2009.

## IN A NUTSHELL

1. Assessment of puberty by SMR helps in the diagnosis of not only disorders of puberty and DSD, but also in disorders of growth and development and many systemic and genetic disorders.
2. Menstrual irregularities are common among school girls of 15–17 years. The most common menstrual problems reported among the school girls were dysmenorrhea.
3. It is normal for the adolescent to feel confused about the sexual orientation.
4. It is important for adolescents and adults to be comfortable with all aspects of sexuality (anatomic sex, gender identity and sexual orientation).
5. Teens should be given the opportunity to discuss issues of sexual attraction and orientation, masturbation, substance and alcohol use, safer sex, school, family and friends.

## Chapter 24.3

# Psychosocial Development

Yamuna S

Adolescents are different from children and adults in the way they respond to a stimulus from the environment. The ensuing behavior also differs, this is not species specific. Novelty seeking, risk taking, sensation seeking, peer directed activities are also common among the adolescents of other mammalian species. Such a commonality is supported by research in the neurodevelopment of brain. With the advent of finer neuroimaging modalities, study of the human brain either in response to a particular stimulus or during expression of a specific emotion has helped in identifying certain areas of the brain that respond in a unique manner during adolescence in comparison to the adult brain.

In contrary to the original belief, human brain is capable of morphological and functional transformation even in adulthood; this depends on the structural reorganization and the speed of flow of signals from one region to the other related area. Human brain makes numerous synapses in the first decade in congruence with the experiences gathered. Synaptic pruning and myelination during adolescence determine the neurodevelopment. Adolescent brain has plasticity to accommodate the experience based reorganization during adolescence to evolve into a mature adult brain which is known for its stability.

### Synaptic Pruning

All through childhood and adolescence, neural connections are made actively. Cortical regions of the brain are thickened with the synapses created. Gray matter volume peaks at 11 year in girls and at 12 year in boys. Thereafter, the synapses that are sparingly used are pruned with retention of the ones used more frequently. Thus, pruning reduces the gray matter volume by 50% and contributes toward an efficient functioning, enhances specialization of brain regions, cortical thinning progresses from back to front with the frontal lobes showing the structural changes last.

### Myelination

In addition to pruning, the nerve fibers undergo myelination that promotes faster nerve conduction from one region to a distant related region. The progress of myelination can be interpreted from the volume of the white matter; frontal and prefrontal cortex myelinate only after the teenage comes to an end.

### Role of Prefrontal Cortex

Prefrontal cortex and other frontal regions of the brain play a major role in the higher-order cognitive skills and executive functioning that are needed for goal-directed behavior like planning, response inhibition, working memory and attention. These skills allow an

individual to pause long enough to take stock of a situation, assess his or her options, plan a course of action and execute it. The connections between the frontal regions and the amygdala become denser during adolescence, thus enhancing the transmission of signals between the executive and the emotional regions of the brain. This emotional maturity is less stable during adolescence especially in the presence of social and psychological stresses that results in emotion-controlled impulsive outcomes.

Risk taking, novelty seeking and sensation seeking that are unique to mid-adolescence are being attributed to the lack of emotion-based impulse control. Risk taking escalates in the presence of peer group that endorses the same. Risk taking reduces in late adolescence with the maturity of the prefrontal cortex; adolescents become capable of response inhibition in accordance with their learning that impacts the cognition.

## THEORIES OF DEVELOPMENT

In the last century, many theorists had proposed major theories to understand the development process in a child. Few of them that stood the test of time are as follows:

### Freud's Psychosexual Theory

Sigmund Freud (1856–1939) proposed that the personalities of the children would be determined by the way their respective parents handle the initial sexual desires in early childhood. Freud based his proposal on the sexual activity and the pleasurable sensations associated with certain body areas. He categorized human life in five stages: oral, anal, phallic, latent and genital (**Table 1**).

Another part of Freud's theory focused on the consciousness. All basic instinctual, selfish urges that demand immediate gratification are termed as id; when their needs are not met, the babies develop a more realistic approach which determines the *ego*; when the babies internalize the parental rules and values, the *super ego* evolves. Thus, the battle between the high moral super ego and basic urge Id is moderated by the ego that sculpts a child into an adult with actions approved by self. In an adolescent, wanting to see a movie with friends is the desire of the Id, but going to a movie by cutting classes is against what is expected by parents is dictated by the super ego; thus, the adolescent is ready to go for a movie with friends without cutting classes is determined by the ego. When the Id and super ego clash, the adolescent is disturbed until his emotional maturity is achieved.

### Erik Erikson's Psychosocial Theory

Erikson proposed the development of the human through the entire lifespan from infancy to adulthood. He downplayed the role of sex and the unconscious mind but focused more on the social, interpersonal and cultural influences across the lifespan. He suggested that a child has eight developmental stages from birth to death (**Table 2**) with each stage having a unique challenge which

**Table 1** Freud's psychosexual stages and their features

Stage	Period of life	Features
Oral	Infancy	Pleasures associated with sucking, biting, etc. with the mouth; an infant mouths the objects that come on its way or at least sucks his own fingers for pleasure
Anal	Toddler	Focus shifts to anus when toilet training begins; vigorous toilet training results in habitual constipation
Phallic	Preschooler	Associated with genital stimulation and the sexual identification; genital exploration and self-stimulation are common activities between 2 and 6 years of age
Latent	School going kid	Sexual urges and interest were temporarily nonexistent; attention on acquisition of skills takes priority
Genital	Adolescence and later	Adult sexual interests and activities dominate; adult gender role and sexual behavior is either carried out or fantasized

**Table 2** Erik Erikson's psychosocial stages of development

Stage	Psychosocial crisis	Basic virtue	Age	Remarks	Example
1	Trust vs mistrust	Hope	Infancy (up to 1.5 years)	Stability and consistency of care makes the infant develop trust on the caretaker. Bowlby's theory of attachment is also similar where the bonding between the infant and the caretaker is qualified based on the availability of care and attention	An infant, who has trust on the parents at this stage, usually continues to communicate with them even during adolescence
2	Autonomy vs shame	Will	Early childhood (1.5–3 years)	Child is more mobile and gathers skills for self-care. If given time to learn skills like wearing one's shoes, the child feels independent; the absence of such a learning ends in shame	A child with self-care individualizes well during adolescence
3	Initiative vs guilt	Purpose	Preschool (3–5 years)	Children usually move out of home to interact with other children and other adults. They initiate conversation and plan games and activities. Parents may stop the child in a view to limit boundaries which can be perceived by the child as a <i>source of nuisance to others</i> with guilt	A child who has achieved this phase of development evolves as an independent adolescent capable of forming new friendships, associations and relationships with members outside the family
4	Industry vs Inferiority	Competency	School going kid (5–12 years)	Children gather skills and seek approval from others for the same. A balance between accomplishment and modesty is necessary. But frequent disapproval during this phase results in inferiority	An adolescent who enters his teenage years with a sense of accomplishment at least in one area of life is able to enter the search for his identity with a better self-esteem
5	Identity formation vs role confusion	Fidelity	Adolescence (12–18 years)	This is a major stage when an adolescent explores himself to find his identity in multiple domains like physical stature, academic, athletic, social, sexual, financial areas of life. He defines his role for adulthood based on the understanding gained after the search. The lack of formation of identity either due to delayed pursuit or due to absence of the quest results in role confusion	Every adolescent should go through this search and then conclude his strengths and weaknesses. If not, he either forecloses his identity based on inputs from others or continues to search with no end in sight
6	Intimacy vs isolation	Love	Young adult (18–40 years)	Young adults share their emotions, feelings and ideas with others with whom they enjoy commitment and attachment. Such intimate association promotes meaningful relationships. Absence of intimacy results in isolation, loneliness and depression	Good attachment with caretakers during infancy promotes a better understanding of the needs of an intimate relationship as the youth is capable of not only receiving but also giving love and affection
7	Generativity vs stagnation	Care	Adulthood (40–65 years)	This is the stage when adults give back to the society in a productive manner after completion of commitments to the immediate kin. Contribution to the society takes the upper hand	Involvement in useful activities outside home forms the major part of their daily routine. Only those youngsters who have enjoyed the previous stages are capable of reaching this stage. A person who has no strength to feel proud of might get stuck at the stage of identity formation with confusion about self
8	Integrity vs despair	Wisdom	Maturity (65 years and above)	Here the productivity comes down and counting the accomplishments maintains integrity. A look back on one's life is seen as success if the fulfillment is high; the absence of which makes the person feel hopeless with only meager time at hand	A well lived adult enjoys this phase with contentment

he termed as crisis. The way these crises are overcome determines the identity of the person.

### Kohlberg's Theory of Moral Development

According to Kohlberg, moral reasoning develops in three levels with six stages; each level being more capable of handling the dilemmas in real life than the previous one (**Table 3**). This is again a lifespan approach. Not all individuals are capable of reaching the highest stage of reasoning. This has been discussed in detail in Chapter 21.1.

### Piaget's Stages of Cognitive Development

Piaget (1896–1980) was the first to suggest that children are not less intelligent than adults, but they think differently from adults. Children are *little scientists* who constantly explore the world around them and understand the same. They progressed through four stages of cognitive development (**Table 4**).

#### Formal Operational Stage

This is the fourth and the final stage of cognitive development that begins with the onset of adolescence and lasts into adulthood.



**Table 3** Kohlberg's stages of moral development

Levels	Stages	Term	Features	Examples
Level 1 Preconventional morality (childhood)	Stage 1	Obedience or punishment orientation	Children follow rules to avoid punishment. Rules are seen as absolute and fixed. This is the stage where young children begin with. Few adults remain in this stage of moral reasoning	If I do not wear my uniform, I will be punished
	Stage 2	Self-interest orientation	As children grow older, they see that other people have their own goals. They question, "By doing this what do I gain? Will I be rewarded?"	Will I be appreciated for wearing my uniform?
Level 2 Conventional morality (adolescence)	Stage 3	Social conformity orientation	Social expectations and norms are understood by adolescence. Conforming to the expectations determines the good <i>boys, nice girls</i> label	Good boys and good girls wear uniforms to school
	Stage 4	Law and order orientation	By the time individuals reach early adulthood, they follow rules to maintain law and order and to respect authority	School authorities expect us to wear uniform, so we wear uniform every day
Level 3 Postconventional morality (adulthood)	Stage 5	Social contract orientation	At this stage, people understand that there are differing opinions about what is right and wrong; laws are there to maintain a social contract; if the rules do not concur with the value system, adults may not follow the same	Wearing uniform on all days is the norm; but wearing our religious dress on our festival days is not wrong
	Stage 6	Universal ethics orientation	Very few people develop this level of moral reasoning. They are empathetic and practice principles based on universal ethics regardless of rules and laws	School should have a code of conduct, so even if it is a festival, my principle would be to adhere to the code of conduct as I prefer doing it that way. I will wear uniform to school

**Table 4** Piaget's stages of cognitive development

	Stage	Age	Key features
1	Sensorimotor	0–2 years	Acquire knowledge through sensory experiences and manipulating objects, object permanence
2	Preoperational	2–7 years	Can view the world only with their point of view. Cannot take other's view and struggle with logic. Pretend play
3	Concrete operational	7–11 years	Capable of thinking with logic but rigid. Struggle with abstract and hypothetical concepts
4	Formal operational	11 upward	Enhancement of logic, able to use deductive reasoning, understand abstract ideas

Abstract thought process, logical thought, deductive reasoning, systematic planning emerge during this stage.

### Logic

Deductive logic is the ability to use a general principle to determine a specific outcome especially in hypothetical situations like study of Algebra.

### Abstract Thought

Adolescents are able to see and plan beyond the *here and now*; capacity to consider possible outcomes and consequences of current action evolves. For instance, smoking during adolescence can increase the chances of lung cancer in adulthood makes sense to an adolescent with abstract thought process.

### Problem Solving

Problem solving using a methodical logical way emerges; will be able to choose from multiple options keeping in mind the probable outcome. Let us consider a girl of 17 who is troubled by eve teasing on a regular manner while going to college. She would be able to see the options before her like either going with a group of friends or request her parent to accompany her or might think about taking another route and then choose the best option.

## PSYCHOSOCIAL, MORAL AND COGNITIVE DEVELOPMENT

Having recollected the theories behind psychosocial, moral and cognitive aspects of human development, let us see the specific issues that determine the adolescence. From the above it is clear that the adolescents are in the psychosocial stage of *identity formation, level of conventional morality and cognitive stage of formal operation*. The stage of identity formation would be dealt with in detail while the moral and cognitive development during adolescence has been addressed in the respective sections above. Let us also explore if the existing studies suggest methods to promote positive youth development.

As postulated by Erik Erikson in his theory on psychosocial development with eight stages covering the lifespan, youth should resolve two crises before evolving into a mature adult: (i) identity formation versus role confusion during adolescence and (ii) intimacy versus isolation in late adolescence and early adulthood.

### What is Identity?

Identity is a core construct in psychology because it refers to how a person addresses the question, "Who am I?" Identity is a social

science concept. S Sharma and M Sharma said, *identity is an umbrella term used throughout the social sciences to describe an individual's comprehension of him or herself as a discrete, separate entity*. Proponents of theories on identity (Erik Erikson, Marcia and Higgins) proclaim that identity is learnt, well organized and continues to be dynamic; personal introspection of one's identity has emotional consequences. Inculcation of clear and positive identity after a thorough exploration during adolescence builds self-esteem and promotes self-definition, thereby reducing the self-discrepancies, paving way to a smoother path to adulthood.

Identity can be organized into general, physical, psychological, social, sexual and spiritual domains; identity formation is a dynamic process that spans the entire life; processes involved in the development of identity are influenced by external factors like childhood experiences, environmental changes, parenting styles and biological factors (**Table 5**).

*Identity crisis* occurs when adolescents seriously question their essential personal characteristics, their views of themselves, their concerns about how others view them or their doubts about the meaning and purpose of their existence. The outcome of the exploration could either be healthy or may lead to confusion.

### Marcia's Identity Status Theory

It proposed two dimensions namely exploration and commitment that influence the identity formation. She suggested four identity statuses as possible outcomes of exploration of active questioning and search for adult roles and values (**Table 6**). Commitment to the decisions taken with the personal goals in mind including all domains of life determines the path to adulthood.

Exploration has two components that give opportunity to redefine as shown in **Flow chart 1**. While in depth exploration

**Table 5** Impact of early childhood experiences on the development of identity in an adolescent

Early experiences	Consequences	Remarks
Attachment with parents/parent figures	Securely attached children are capable of making sustained friendships and relationships. Children with insecure ambivalent and avoidant types of attachment have trouble in making and sustaining friendships and relationships	Contributes to social identity
Parenting styles	Authoritarian parenting results either in submissive adolescents or rebellious young people. Recipients of permissive parenting style lack direction and discipline. Adolescents who have been brought up with authoritative parenting style evolve into self-confident, self-disciplined individuals	Self-esteem, communication style, interpersonal relationships are related to the parenting style practiced at home. Determines the self-efficacy of the adolescent
Environmental chaos	Domestic violence, trauma due to emotional, verbal, physical and sexual abuse has long-term implications in the adolescents. Quality of parents' marriage, type of family either joint family or nuclear family or broken/separated family has specific consequences in adolescents. Socioeconomic status, dwelling places influence the acquisition of skills and practices	Emotional competence, emotional regulation, self-regulation, self concept, emotional efficacy are established in response to the diverse environmental influences
Biological factors	Whether the adolescents are living with biological parents or foster parents, illnesses and disorders including specific learning disorders, predisposition to mental illnesses like schizophrenia, bipolar disorders, physical challenges like club foot, hemiparesis, flaccid paralysis of limbs or diseases like asthma, thalassemia, etc. are significant in determining the process of identity formation in the adolescents	Illnesses stall the identity achievement

**Table 6** Marcia's four identity status

Dimensions	High exploration	Low exploration
High commitment	Identity achieved	Identity foreclosure
Low commitment	Identity moratorium	Identity diffusion

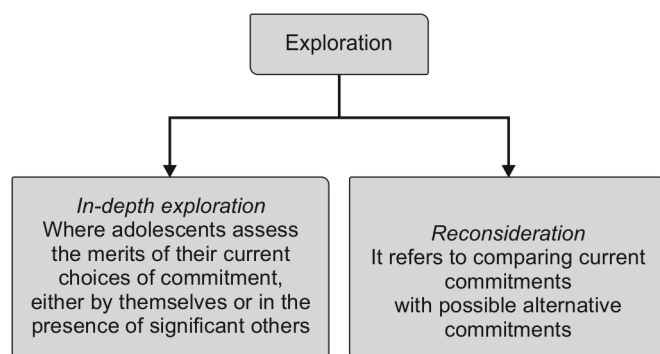
helps in self-understanding; reconsideration may result in confusion due to emergence of new alternatives. For example, an adolescent who moves into the university goes through reconsideration of his self-concept on friendships to make social associations in the new environment. Reconsideration helps in the adaptation to new developments in the environment in which we live.

### Higgins' Self-Discrepancy Theory

It focuses on the discrepancies that arise between the self domains and the standpoints from which they are viewed. Self domains are: (i) *actual self* (actually possess), (ii) *ideal self* (like to possess) and (iii) *ought self* (should possess). The standpoints from which they are viewed are: (i) *own* and (ii) *significant others* like parents and teachers. This results in six self-state representations: (i) actual/own, (ii) actual/other, (iii) ideal/own, (iv) ideal/other, (v) ought/own and (vi) ought/other. The nature and the extent of the discrepancies between the different selves affect the person's emotional vulnerabilities. For example, the discrepancies between:

- Actual/own and ideal/own are associated with *disappointment* and *dissatisfaction*

**Flow chart 1** Components of exploration in adolescents



- Actual/own and ideal/other are associated with *shame, embarrassment*
- Actual/own and ought/other are associated with *fear* and feel *threatened*
- Actual/own and ought/own are associated with *worthlessness* and *weakness*.

Some discrepancies are inevitable during the process of self-exploration as they help in formulating strategies to identity formation.

### Theory of Possible Selves

It focuses on those elements of self-concept that individuals could become, would like to become or are afraid of becoming. The latter is also known as *fear possible selves*. Empirical research has supported the idea that possible selves could be self-regulatory and can serve as roadmaps for one's behavior.

### Benzonsky's Identity Style Model

This model postulates that three processing styles can be depicted in adolescent identity formation.

1. The *informational style* involves the active searching and evaluation of identity-relevant information.
2. The *normative style* refers to the adherence to conventions, and dependence on the expectations and feedback of significant others when confronted with identity issues.
3. The *diffuse-avoidant style* denotes a tendency to procrastination in the handling of identity issues.

### Assessment of Identity

**Table 7** helps us in knowing the current level of identity formation in the adolescent. These measures not only facilitate discussion but also ensure transparency for other professionals to take over in the event of transition of care.

The results of the assessment would give a clear understanding about which aspect of identity formation should be focused during intervention. For example, choosing a career at 17 years of age; confusion between cinematography and information technology can be handled with in depth exploration of the adolescent with respect to preference of indoors versus outdoors, love for a desk job versus field activity, etc. This assessment helps in resolving the confusion with commitment to the choices made after exploration.

Physical deformity like a hemiparesis not only affects the psychosocial progress in the domains of autonomy and industriousness of childhood but also prevents the establishment of identity in certain domains due to discrepancies between actual/own and ideal/own, and actual/own and ought/own. The adolescent with *diffuse-avoidant identity style* with procrastination might postpone the process and stay confused, thus not be ready for intimacy during adulthood.

### Self-Efficacy

A person's behavior is under the reciprocal influence of the environment and his personal thought processes (cognitions) is the basis of the concept of *triadic reciprocity* as proposed by Bandura in the *Social Cognitive Theory* in 1990. Thus, an adolescent's academic performance (behavior) is influenced by his beliefs (cognitions) that are affected by the support provided by his parents, teachers and peers (environment).

Self-efficacy reflects one's beliefs about one's capacity to plan organize and execute a course of action to produce outcome. Thus, according to Bandura, *self-efficacy beliefs determine how people feel, think, motivate themselves and behave*. Self-efficacy can be seen in two ways: (i) task self-efficacy denotes the perceived ability to perform a particular behavior and coping self-efficacy denotes the perceived ability to prevent, control or cope with potential difficulties that might be encountered when engaged in a particular performance.

Self-efficacy can be assessed using quantitative and qualitative methods to understand the self-doubts in a person (**Box 1**).

#### BOX 1 Case vignette

*A student of class XII aspiring for a seat in a medical college through All India Premedical Test is preoccupied about his future and has not been able to focus on his preparation. On exploration he said, "I am very sure of my performance in the board exams as I am good in subjective approach to examination. I don't feel confident about the objective examination at AIPMT with multiple choice questions. So, I am pushing myself to accept the disappointment in the same." Thus, he is trying to use the coping self-efficacy to handle his self-doubt.*

### Emotional Competence

The capacity to understand one's emotions, others' emotions and handle the same in a socially approved manner is a topic of great interest, especially in the context of helping adolescents who have frequent anger outbursts. *Emotional intelligence* is related to one's innate potential to manage emotions which are related to traits like temperament and personality. *Emotional competence* is seen as a set of developed skills based on the early childhood experiences, emotional regulation of the family and also influenced by the self-discrepancies in identity which have a major emotional impact on the person. Competence can also mean that the skills can be inculcated with practice.

Saarni proposed eight skills. Consider a student of class XII on the day of his first examination; he is very abusive of his parents for nagging him to study and not being supportive. The features in the case mentioned are given within parentheses:

- Being aware of one's own emotions (anxiety, fear)
- Discerning and understanding others' emotions (parents' worry about his future)
- Using the vocabulary of emotion and expressions (I am anxious, please understand me)

**Table 7** Assessment of identity

Aspects of identity	Features	Example
Levels and domains of identity	Identity on a personal and social level. Domains such as physical appearance, athletic competence, scholastic competence, social acceptance, behavioral conduct, and global self-worth	Chinese Adolescent Self-Esteem Scales (CASES) to assess the self-esteem of Chinese adolescents in terms of seven aspects: social, academic, appearance, moral, family, physical/sport and general self-esteem
Identity statuses	One of four possible identity statuses: diffusion, foreclosure, moratorium and identity achievement	Quantitative and qualitative methods (like the identity status interview)
Identity dimensions	In-depth exploration, commitment and reconsideration	Utrecht-Management of Identity Commitments Scale (U-MICS)
Identity styles	Informational style, normative style and diffuse-avoidant style	Identity style inventory (revised)

- Having the capacity for empathic involvement (poor parents are worried about my future, after all I am their only son, they want to see me well settled).
- Differentiating internal, subjective emotional experience from external, emotional expression (I am absolutely anxious and panicky within, but I am showing it as anger, am I right?)
- Coping adaptively with aversive emotions and distressing circumstances (let me calm myself, so that I can approach the exams with a clear mind)
- Being aware of emotional communication within relationships (I can also cry on the parents' shoulder for relieving my anxiety)
- Possessing the capacity for emotional self-efficacy (I am sure I can handle the anxiety with deep breathing exercises over a period of time).

### HEADSS SCREENING TOOL

Adolescents are screened using the HEADSS tool (Goldenring and Cohen, 1998) to understand the psychosocial environment in which they live. **H**ome and environment; **E**ducation and employment; **A**ctivities; **D**rugs; **S**exuality; and **S**uicide/depression are the areas probed using a standard set of questions. Open-ended questions that encourage elaborate conversations are used to gather information. Closed-ended questions like, "*Do you live with parents?*" usually end either with a yes or no for an answer which gives very little information about the quality of the home environment.

### IN A NUTSHELL

1. Adolescence is a dynamic phase of life.
2. Identity formation is the key psychosocial concept during this phase.
3. Self-efficacy and emotional competence would help adolescents to scale through the phase with ease.
4. Pediatricians with the above understanding would be able to facilitate the adolescent to explore and reinvent himself.

### MORE ON THIS TOPIC

- Hornberger LL. Adolescent psychosocial growth and development. *J Pediatr Adolesc Gynecol.* 2006;19:243-6.
- Johnson SB, Blum RW, Giedd JN. Adolescent maturity and the brain: the promise and pitfalls of neuroscience research in adolescent health policy. *J Adolesc Health.* 2009;45:216-21.
- Kroger J. Identity Development: Adolescence through Adulthood. 2<sup>nd</sup> ed. USA: Sage; 2006.
- Lawrence Kohlberg's Stages of Moral Development. From: <http://www.usefulcharts.com/psychology/kohlberg-stages-of-moral-development.html>. Accessed November 7, 2014.
- Spear LP. Adolescent Neurodevelopment. *J Adolesc Health.* 2013;52:S7-13.
- Sanders RA. Adolescent psychosocial, social, and cognitive development. *Pediatr Rev.* 2013;34:354-8.
- Tsang SK, Hui EK, Law BC. Positive identity as a positive youth development construct: a conceptual review. *Scientific World Journal.* 2012;2012:529691.
- Tsang SK, Hui EK, Law BC. Self-efficacy as a positive youth development construct: a conceptual review. *Scientific World Journal.* 2012;2012:452327.



# Section 25 HEALTH ISSUES IN ADOLESCENCE

Section Editor MKC Nair

## Chapter 25.1

### Factors Influencing Adolescent Health

Sukanta Chatterjee

The consideration of factors influencing adolescent health should include factors affecting physical health, mental health and social health, if not beyond. In comparison to other age groups, in the adolescent population, mental and social health issues are more important than physical health issues. The importance is not only in the incidence but also in the possibility of late detection of these health issues and their long-term impacts. In this context it needs to be mentioned. Lack of easy recognition between the normal variation and the disease state in nonphysical health issues is responsible for late intervention, both at family level and at health sector. Therefore, a clear understanding of the determinants or factors affecting adolescent health will be of great help to the readers in promoting health of the adolescents and also making detailed evaluation and treatment of their health problems.

The factors influencing adolescent health may be either unique for this age group, e.g., schooling or some of them may be common with other age group as we see them influencing health of adults, e.g., stress in human relations. The impact on health of any particular factor might differ in adolescents with a maturing mind and body in comparison to that seen in adults with a mature tolerant mind and an already matured body, e.g., an emotional stress might affect mental health more seriously in adolescents. In the discussion first of all, we shall mention the factors that operate on the health of an adolescent and thereafter the impact of each determinant along with interactions when more than one factor are operating simultaneously. The factors might influence health with positive impact called 'protective factors' or with negative impact or harmful effect called 'risk factors.' Finally the influencing factors may operate at different levels or situation like individual level, family, peers, school and society. Therefore, the factors affecting adolescent health to decide the ultimate outcome are complex:

- Factors operating at different level or situation, e.g., the individual, school, family and social situation
- Risk or protective factors
- Interaction of multiple factors both risk and protective for different duration and at different stages of mental and physical maturation.

In the entire write up the focus will be on these three points but the most ill understood is the last one that is interaction of

multiple factors which finally decides the health status. Therefore, the achieved health outcome may not be exactly predictable. Attempt is made to provide the evidence based information from the literature in less predictable situations rather than offering a conclusion. There is increasing evidence in research that the role of protective factors are major determinant to adolescent health outcome when they are getting more and more exposures to the risk factors in the process of modernization of the society.

#### FACTORS OPERATING AT DIFFERENT LEVELS

**Figure 1** shows the distance of different influencing factors acting on adolescent health. Closer the factor plotted here from the adolescent individual higher is the influence on the health that means, peers influence health of the adolescent more than the school or community. Each level has both risk and protective factors mentioned in details here:

- A. *Adolescent as an individual* The factors operating at individual level may be either protective or risk factors
  1. *Protective factors* Self-efficacy, self-esteem, spirituality/religiosity.
  2. *Risk factors* Gender and caste discrimination, off-time sexual maturation, substance abuse, absence of parents, feeling of hopelessness, mental depression, suicidal thought or attempts, physical or mental retardation, aggressive temperament, involvement in violence, homosexuality and slum dweller.
- B. *Peers* They play great role in shaping the adolescent health
  1. *Protective factors* Peer education, peer affiliation or acceptance, youth participation, youth organizations and many friends.
  2. *Risk factors* Negative peer culture, peer pressure or victimization, deviant friends and social isolation.
- C. *Family* The influence of family on adolescent health is traditionally recognized.
  1. *Protective factors* Family connectedness, appropriate parenting skill, monitoring 'how was the day' or taking report of the daily events and participation in family programs.
  2. *Risk factors* Overcrowding, addicted parent, parental conflict and violence, single parent particularly absence of father, hopelessness or mental illness in the family.
- D. *School or Work* Teachers and school environment offers significant influence on the health, particularly mental and social health of this population. Similarly employer, colleagues and work environment influence nonschool going working adolescent.
  1. *Protective factors* Positive counseling and parenting skills of teachers, school connectedness, good academic achievement.

	Health influencing factors
Adolescent	→ Peers → Family → School/Work → Community → Policy/Country

**Figure 1** Closer the distance from the adolescent, stronger is the influence on health

2. *Risk factors* Poor academic achiever, school drop outs, child labor, unemployed youth, excessive discipline, sexual abuse, physical violence, female gender and limited opportunities of sports and recreational activity organized by school.
- E. *Community* The modern society or community is presenting a host of opportunities and risks to the adolescents. Exposure with these opportunities depends on the awareness and affordability of the parents. The risk factors naturally attract adolescents if their influence is not protected by parental guidance.
  1. *Protective factors* Understanding and tolerant society, supportive environment for adolescents, interaction with previous generation, cultural heritage, scope of adolescent participation, optimal health and educational opportunities.
  2. *Risk factors* Nonsupportive community for holistic development of adolescent, permissive society for night clubs and pubs, sex and violence in media, lack of sports and recreation, migration, negative environment of lack of moral values and exploitation.
- F. *Policies and legislatures of the country* The influencing factors at this level are corruption, poor resources, transitional society, lack of existing policy for promoting adolescent health and invest on it.

Box 1 summarizes important health risk behaviors in adolescents.

#### BOX 1 Health risk behaviors in adolescents

1. **Food habit:** Skipping meals, overeating, junk food.
2. **Substance use:** Smoking, drinking, use of addictive drugs.
3. **Exercise and sports:** Inactivity, sedentary life style, risky sports.
4. **Violence and injuries:** Peer violence, sexual violence, keeping weapon, bike racing, no use of helmet and drunk driving.
5. **Sexual/Reproductive:** Dating, loss of romantic partner, early sexual debut, more than one sex partner, no use of condom.
6. **Social:** Conflict with law, police custody, and school dropout.

### Protective Factors in General

1. *Physical* Regular sports and physical activity, avoiding injury prone life style, healthy diet, early treatment of health risk factors and diseases.
2. *Emotional* Health conscious or awareness of positive health keeping, sense of happiness in mind, not feeling sad, no mental health difficulties, no evidence of mental health diseases like depression and no suicidal thought or attempt.
3. *Social* Satisfactory scholastic achievement, good peer relation, feeling connected with family, participation in social activity.

We shall now discuss few of the factors and situations mentioned above in details, e.g., relation with parents, teachers and peers, social status, mass media, education, gender, habits, lifestyle, behavioral issues, policies and legislation.

## FACTORS INFLUENCING HEALTH OF ADOLESCENTS

### Parents

Childhood relation with parents is all disclosure and dependent but the adolescent do not like to share everything due to confidentiality and privacy senses developing within them. Hence existing parent child relation changes to partial disclosure and partial hindrance. If there is anxiety and guilt feeling for this inevitable change of existing parental relation then it acts as a risk factor. Smooth adaptation to this situation leading to good personality development needs parental support in creating opportunities to discuss this normal transition for everyone.

The parenting style will also influence adolescent health. The four different types of parenting styles are mentioned here for understanding its influence.

### Authoritative Parenting

Here the parental expectation about child's performance is high but they provide opportunity to the child to discuss about the expectations and difficulties in performing it. The task and discipline imposed on the adolescent are explained properly and accepted logically to maintain by both. This is considered the ideal type of parenting. This parenting style helps the adolescent to understand about the effort and its outcome, ability in right decision making and be self-sufficient or independent.

Adolescents brought up in authoritative parenting style are mostly seen successful in expressing their opinion, happy with themselves, and supportive to others. They are liked and respected by their friends and become all-rounder adults.

### Authoritarian Parenting

The expectation of parents regarding the performance is high and the task and discipline imposed on the adolescent is rigid and noncompliance, which could be threatening. They do not get the opportunity to discuss the reason of the rule which even changes according to the wish and necessity of the parents, and hence the adolescent fails to understand what is expected and gets frustrated. Adolescents raised by this style live in a state of fear. They become less self-confident and socially withdrawn. They might defying the parents, leave home, consume drugs or alcohol, may initiate sexual behavior early, marry a partner whom parents do not approve and may prefer to live separately from their parents reaching adulthood.

### Permissive Parenting

Here the love and affection is more with lack of expectations to follow the discipline and indifferent of adolescent's performance or achievement. Parents always try to fulfill the demand of the child without attaching responsibility with it. They are very much emotional attached with the adolescent to see that their demands do not remain unfulfilled but do not take stock of activities in school or with peers. Adolescents brought up with this parenting style cannot control their emotion and unable to bear the responsibility of their work. They tend to become home sick or home dependent to continue with the environment of achievement on demand without performance. They often blame others without recognizing their own fault.

### Neglectful Parenting

It is one step forward of permissive parenting. The parents provide basic needs of the adolescent but do not care for their activity or performance. They are not emotionally attached with the adolescent and are indifferent of what has happened in the life of the adolescent throughout the day. At the end of the day they never ask the adolescent—"how was the day". The neglected adolescent might face serious problems at home or outside but parents are not aware till something tragic has happened. The adolescents often grow up with feeling of anger with the parents and might be less attached to home. They are more prone to sexual exploitation, addiction, violence and conflict with law.

### Teachers and School

The protective role of a teacher is to develop a good school connectedness by the adolescent. School connectedness is a state of happy feeling of the student that the teachers and other staffs of the school are interested and concerned in their studies and wellbeing. Teacher's indifferent role may act as a risk factor.

A school connected student is less prone to get involved in group violence, substance use like tobacco or alcohol, sexual debut or other risk taking activities. On the other hand they are better academic performers, have higher school attendance and involve themselves more in the school organized activities.

### *How to Promote School Connectedness?*

Six principles may be adapted by the stake holders of the school, the parents and the society to increase the feeling of attachment to the school by the students: (1) Provide an environment of involvement in decision making by the students, parents and the society in scholastic performance along with capacity building among staffs; (2) Offer educational and non-educational opportunities to ensure active participation of parents in the school life and studies of their children; (3) Empower pupils to understand and enjoy studies to stimulate their zeal of achieving academic excellence and impart the social and emotional skills required for active engagement in the school; (4) Offer a positive teaching learning method in the classroom to promote effective learning; (5) Provide the teaching and nonteaching staffs with quality training and resources required to promote the all-round development of the students not only in academics but also in social, emotional and cognitive domain; (6) Provide a supportive and trusted relationship among students, teachers, administrators, nonteaching staffs, parents and the society to encourage free exchange of opinion.

### **Peer Relations**

The relation with friends can have direct effect on health of an adolescent by influencing the behavior and attitude of peers, e.g., getting involved in drinking with friends or indirect effect by the perception of the adolescent about their friends' behavior and attitudes, e.g., initiate sexual activities thinking that others are doing it.

There are multiple components of peer relation which regulates an adolescent's interpersonal relation to regulate the mental health are: (a) general peer relations which imparts both positive impact (peer crowd acceptance or affiliations) or negative impact (peer victimization); (b) best friendship relations can also have both positive and negative impact, and (c) romantic relationship will have stronger positive or negative influence, e.g., break in romantic relation leads to greater negative impact on the health of the adolescent. Negative impact from above relations may lead to social anxiety and depression. An environment of peer crowd acceptance or affiliation, existence of satisfactory romantic relation and stable best friend relations help to develop confident personality and act as protection against depression. Failure to obtain acceptance from peer groups in general, strong differences in best friendship relations may lead to social anxiety on the other hand break in romantic relation, loss of best friendship relations or victimization by peers are more likely to lead to depression.

### *'Peer Crowds' and 'Best Friends'*

There are scientific publications indicating influence of peer relations in internalization of feeling of social anxiety and depression in the developing mind of adolescent. The term "peer crowds" means social relation of adolescent that happens within the peer group at large or the bigger group of adolescents with whom an individual relates regularly. Peer crowds may be a reputation-based group of similar individuals who might or might not mix together very often. An adolescent may mix with a peer crowd to seek support and acceptance from them. Peer crowd may be a high-profile, good image group known as *Hot Shots*, a sports-oriented group or *Athletes*, an academically accredited group or *Brains*, a group that protests against social norms called

*Nonconformists*, a defiant behavior group having conflict with law, e.g., *Burnouts* or *Druggies* and a group of misfits who remain indifferent or *Loners*. *Hot Shots*, *Athletes* and *Brains* represent high-status groups or crowds, whereas *Burnouts*, *Nonconformist* and *Druggies* represent low-status groups or crowds. Peer crowds are different from adolescents' smaller peer network or best friendship. Almost all teenagers have one or few best friends who mix with the same peer crowd.

### *'Peer Pressure' and 'Peer Affiliations'*

Peer victimization may be overt victimization like threats or physical violence, or relation victimization like spreading rumors, discontinuation of friendship and social boycott. Overt victimization is more commonly seen in boys than in girls although the occurrence of relational victimization is more common than overt victimization among adolescents. At early adolescence overt victimization affects mental health more than relation victimization; however, in older adolescents relation victimization might influence mental health more than overt victimization leading to loneliness, low self-esteem and depression. Peer affiliation may be sought from peer crowd or from best friends.

### *How to Overcome Peer Pressure?*

1. Encourage adolescents to develop positive self-esteem and good peer relation to withstand or neutralize the impact of negative peer relations or pressure.
2. Establish good relation with adults who are important in the life of the adolescent like teachers, parents, relatives and family friends.
3. Encourage diverse relationships and support group among friends, at school and in society, by involving them to play and work together.
4. Organize parent education programs along with their adolescent children.
5. Teach adolescents the skill to cope with negative impact of behavior and take right decisions.
6. Teach adolescents how to say 'no' in peer pressure retaining the relation in future.

### *Best Friendships*

Successful establishment of intimate friendship relations increases the interpersonal skill to develop good relationship in the society and reduces the negative impact of diminished acceptance among peer crowd. Main source of support in the society to an adolescent is his friends. It is seen that close friendship with support and empathy act as protective factor for mental health for adolescents by reducing social anxiety. Good psychosocial development and a positive self-esteem come up through best friends' support. Friendship relation can have its negative effect also like conflict, violence, peer victimization or relationship termination. They may lead to problem of school adjustment, increases interpersonal conflicts, feeling of stress, anxiety and depression.

### *Romantic Partners*

During late adolescence, adolescents in late teens develop more interest and inclination towards romantic relations than with close friends, parents, and relatives. An established romantic relation acts as a strong positive factor for mental health of adolescents. On the other hand, stress in romantic relation will increase the incidences of depressive symptoms than that of adolescents without having romantic partners. Break of romantic relation will have higher negative impact on adolescent's mental health than that seen in break of best friendship relation. An adolescent with depression finds it difficult to develop romantic relations.

### Competitive and Cooperative Relations

The current modern society presents a competitive relation among schoolmates in adolescents. The competition remains healthy with attempts of individual achievement with cooperation and sharing of resources without restricting the interest of others. Compromising the access to resources for peers in the interest of competitive achievement leads to selfish and jealous personality. These adolescents fail to develop trusted relations with the contemporary members of the society. An atmosphere of cooperation rather than unhealthy competition leads to greater individual achievements and friendship relations.

### Social Status

With the increase of available opportunities in the society, the risk factors are equally accompanying them. Education, social relations and employment options may be the major ones looked after by the adolescents. Risk of not getting the best education may be economy or lack of awareness of parents of it. Risk involved in developing relations and getting employment are becoming complex difficult to handle by the adolescents themselves. Low socioeconomic status offers adolescents less opportunities or protective factors and more risk factors since parents may not be aware of them or may not be able to provide quality time to negotiate the counseling skill to present a risk prone situation in a protective manner. Parents may have more stressors in the society to earn their livelihood and may adopt an authoritarian parenting at home to minimize stress at home leaving less scope to understand when their offspring are exposed to more risk factors. Higher socioeconomic status provides them more opportunities or protective environment due to parental awareness about the resources and affordability. The risk factors are minimized since the less stressed parents are more likely to be connected to the adolescents. Although this is the trend as evidenced in the research but not the rule since multiple factors influence to decide the health outcome.

### Social Learning and Social Control

There are evidences that social learning has greater impact on adolescent health than that of social control system. Social learning means what adolescent learn to adapt by seeing others doing it whereas social control means the restrain imposed by others which is not practiced by the imposer. If friends are involved in smoking or alcohol use or the same experience comes from the family, e.g., father is a smoker then adolescent are more likely to adapt these habits in spite of restrain or control efforts from the society. Social or family control to prevent these negative practices is statistically less effective when adolescents are exposed to negative learning situation in the family or with friends. It is seen that the attachment to mother and father and regular monitoring by parents reduces the risk of substance use in adolescents significantly but this influence is statistically less significant if compared with the influence of learning experience by the adolescent in the similar field. Similarly, a westernized or modern urban society which is permissive to pubs and dating culture for adolescents provides more learning experiences for alcohol use and sexual experimentations hence family restrictions may be less effective to protect them.

### Mass Media

Access to mass media, particularly electronic media including internet, is rapidly increasing amongst adolescents. It may significantly affect the physical, mental and social health by influencing their behavior. Commercial mass media usually excite the bioemotional desire of the individual. Social norms, religion and culture restrain it. A given type of stimulus from mass media,

commercial or sexual, may have more serious effects on the immature adolescent mind than that of an adult mind. Exposure to media is inevitable and also desired since it provides many protective factors in the form of knowledge. Adolescents having media literacy understands the motive of the publication sponsor thereby develop the capacity to minimize the risk at exposure.

### Media Literacy

Getting adolescents to actively analyze and think about the media regarding their motive, commercial interest and its trustworthiness develops awareness of the potential harmful or beneficial effect a media. This is media awareness or literacy. There are media awareness development websites hosted by noncommercial professional organizations such as the American Academy of Pediatrics and Canadian Pediatric Society such as [www.cps.ca](http://www.cps.ca) or [www.media-awareness.ca](http://www.media-awareness.ca)

### How to Minimize the Risk from Media Exposure?

1. Encourage family members to watch the media together and look for or create opportunities to discuss with the adolescents the positive and negative aspects of it. Parents can facilitate in their children the skill of critical analysis to understand the difference of reality and fantasy in context of what is being shown, e.g., product advertisement, violence and sex.
2. Placement of media displayer like television, computer with net, video game devices, etc. at a central place in the house having physical and password access to all.
3. A home rule of only 2 hours of television and computer access by the adolescents should be maintained by parents and other adult care givers.
4. Teenagers should be given the opportunity to make choices of programs to be accommodated in this 2 hours slot in consultation with parents. This will regularly offer the scope of helping the adolescents make their right choices through discussion, why some programs are not suitable for them. Praising them on making good choice brings confidence in adolescents to make similar choices in future.

### Education

Education empowers adolescents. It reduces risk exposure and increases protective behaviors. There is no evidence in the literature that sex education increases the early sexual experimentation or unwanted pregnancy. Adequate sex education will increase the capacity of protection for the sexual and reproductive health. Good academic grades delays sexual debut in contrast to school dropout or detainers.

### Gender

Sex is biologically determined; gender is attributed by the society. Gender indicates the behavior, roles and responsibility expected to be observed by a man or a woman in the society. Hence it may differ from country to country or amongst localities, e.g., a womanly behavior of a conservative family of rural India may not match with that of a family of a metro city. The gender role constructed by the religion, culture, family values and further modified by mass media, economic and political factors. In Indian context boys and girls in adolescent age are allowed to have different sets of exposures and opportunities in the family and the society. This makes them receptive to variable risk and protective factors due to gender alone. Therefore, all components of health like physical, mental and social health may have a different health outcome in boys and girls although they are brought up in the same family. Access to health services and control over health resources that help in protection and promotion of health, may also be controlled by gender. It affects the health of the women and also the children born of and brought



up by them. The sexual behavior is also regulated by the balance between the preset gender standard or expectation and the existing permissibility of the society. Bioemotional instinct of human try to distort the society set gender specific behavior. Mass media helps to increase the social permissibility for this desired distortion to set an accepted new standard. That is how gender behavior changes with time in the same society. Girls are more vulnerable than boys by social and biological reasons. On the other hand, boys in India are having less family and socially accepted opportunity to access the existing sexual and reproductive health services in contrast to girls.

Gender equality means equal access to and distribution of available benefits and resources irrespective of being men or women. It does not take care of the difference in the need for men and women. Gender equity, on the other hand, recognizes that men and women have differences in their health needs, therefore, it is rational for better health outcome that these differences be addressed while allocating resources and access to services in relation to the gender. It means that men and women should be treated with gender equality where they have common needs but where differences in need exist it should go by gender equity. Gender discrimination leads to behavior restrictions, less education, nutrition deprivation, early marriage, domestic violence and sexual offence on girls. Factors promoting gender discrimination in favor of male are seeing pornography, belief that their friends are sexually active, addiction, possession of weapon and doing job. Factors influencing gender discrimination negatively in girls are absence of father, unstable family.

### Gender Tool

To ensure the gender equity where the difference in the health needs exist among adolescent boys and girls, World Health Organization developed an action strategy called *Gender Tool* for healthcare providers and policy makers.

### Habits

Habits are long-term practices maintained by an individual usually offering pleasant experience. Adolescent habits in eating, physical activity, risk taking, substance uses are going to influence health. Taking adequate balanced diet regularly and doing optimum sports and activities act as protective factor. Over eating, junk food, lack of physical activity, risky sports and behaviors, getting involved in violence and alcohol or tobacco use will have negative impact.

### Lifestyle

Medical world has already recognized the term *lifestyle diseases* indicating causal relationship of disease and lifestyle, e.g., sedentary lifestyle may lead to obesity. Adolescent lifestyle may have early or immediate health impact in the adolescent age, e.g., physical injuries or it may have long-term impact in adult life, e.g., acquiring AIDS, obesity and hypertension. Lifestyle may affect all components of health like physical health, mental health and social health; each component can have short-term or long-term impact. Lifestyle of a teenager may be influenced by his food habits and nourishment, sports and activities, body weight, addiction, mental health and sexual health. Lifestyle is regulated by the family and social opportunities and restrains along with individual instinct. Therefore family practices, education environment and social exposure along with adolescent's choice act as regulators to decide the final outcome regarding lifestyle. Each setting can have either positive or negative impact on health.

### Behavioral Issues

Unhealthy behaviors are often acquired in adolescence and leads to adult life morbidity. Common health risk activities seen

in Indian adolescents are adventurous sports, substance use like tobacco, alcohol, drugs and sexual experimentation. Risky sexual behaviors and substance use often accompany each other. There are many intervention strategies developed to combat an individual risky behavior of the adolescent but strategies that work to combat the influence and interaction of multiple risk behaviors need to be worked out. The wider social determinants of health (protective and risky behaviors and their interaction) must not be overlooked. These are beyond the microenvironments or the singled out risk behaviors mentioned above. Therefore, it is important to remember the multiple determinants prevailing in broad social environment that influence the behavior of adolescents while framing government policies and intervention strategies. There is little evidence that increasing the price of alcohol reduces binge drinking on the other hand, smoking initiation is reduced by increasing the price of tobacco. The impact of intervention programs at mass media on prevention of smoking initiation or cessation among adolescents is good and evidence based but alcohol consumption and risky sexual behaviors are little influenced by mass media programs.

### Policies and Legislations

Comprehensive adolescent health policy needs to be developed by the legislative authority. There is enough evidence that investment on adolescent health, both at preventive and promotional strategies at national and policy level helps in obtaining positive results on adolescent health. Sales restriction of tobacco and alcohol does not reduce the substance use since adolescents buy them through illegal route.

#### IN A NUTSHELL

1. Mental and social health issues in adolescents are more important than physical health issues yet the healthcare providers are traditionally trained and comfortable to deal with the physical health problems rather than the mental health or social health issues.
2. Lack of easy recognition between the normal variation and the disease state in nonphysical health issues is responsible for late intervention, both at family level and at health sector.
3. The impact on health of any particular factor might differ in adolescents due to a maturing mind and body in comparison to that seen in adults with a matured body and tolerant mind.
4. The factors might influence health with positive impact called *protective factors* or with negative impact or harmful effect called *risk factors*.
5. There are increasing evidence that the role of protective factors are major determinant to adolescent health outcome when they are getting more and more exposures to the risk factors in the process of modernization of the society.
6. The authoritative parenting styles is considered ideal for adolescents.
7. Peer crowd affiliation and romantic relation, work as strong protective factor.
8. *School connectedness* acts as a protective factor. It is the belief by students that adults and peers in the school care about their learning as well as about them as individuals.
9. Social learning has greater impact on adolescent health than that of social control system.
10. With the increase of available opportunities in the society, the risk factors that are accompanying them also increase.

- Bagchi NN, Ganguly S, Pal S, Chatterjee S. A study on smoking and associated psychosocial factors among adolescent students in Kolkata, India. *Indian J Public Health*. 2014;58(1):50-3.
- Blum RW, Nelson K. Risk and Protective Factors Affecting Adolescent Reproductive Health in Developing Countries. Baltimore: Department of Population and Family Health Sciences Johns Hopkins Bloomberg School of Public Health; 2005.
- Centers for Disease Control and Prevention. School Connectedness: Strategies for Increasing Protective Factors among Youth. Atlanta: US Department of Health and Human Services; 2009.

- Das S, Ghosh M, Sarkar M, et al. Adolescents speak: why do we smoke? *J Trop Pediatr*. 2011;57(6):476-80.
- Jackson CA, Henderson M, Frank JW, Haw SJ. An overview of prevention of multiple risk behavior in adolescence and young adulthood. *J Public Health (Oxf)*. 2012;34(Suppl 1):i31-40.
- Kanikar A. Parenting of adolescents. In: Nair MKC. Trainers Module on Adolescent's Care in Office Practice. Adolescent Health Academy, IAP; 2011. pp. 17-32.
- La Greca AM, Harrison HM. Adolescent peer relations, friendships, and romantic relationships: do they predict social anxiety and depression? *J Clin Child Adolesc Psychol*. 2005;34(1):49-61.
- Nair MKC. Adolescence and Family Life Education. Bengaluru: Prism; 2002.

## Chapter 25.2

# Adolescent Nutrition

Preeti M Galagali

Nutrition is a key determinant for ensuring optimal health in adolescence. Adolescence is one of the most rapid periods of growth, second only to infancy. Hence, the nutritional requirements are greatest in this phase of life. Psychosocial developmental changes in the form of autonomy, identity issues, body image concerns, experimentation and peer affiliation have a significant effect on dietary intake in adolescence. Adequate nutrition in adolescence can ensure a healthy transition into adulthood. Adolescent malnutrition; both over and undernutrition has deleterious effects on health over the entire life span. It even has an intergenerational effect on the health of the future progeny.

With the change in the socioeconomic milieu in India, there has been a change in lifestyle of the population. Population explosion, demographic changes, rapid urbanization, globalization and media boom have resulted in significant changes. These lifestyle changes include *nutrition transition* from traditional whole grain diet to adopting modern processed, refined ready to eat diet and increase in sedentary activities like television and computer usage. Aggressive advertising of junk food and beverages especially targeted at the youth has also contributed to an increase in their consumption. Habits formed in adolescence persist into adulthood. Unhealthy nutritional practices are one of the important contributors to the emerging epidemics of obesity, anemia, hypertension, hyperlipidemia, hypercholesterolemia, type 2 diabetes mellitus, eating disorders, caries and osteoporosis in the young.

## ADOLESCENCE: A NUTRITIONALLY VULNERABLE PERIOD

Adolescence is a nutritionally vulnerable period as the physiological increase in nutritional demands may not be met adequately. This is because dietary choices and lifestyle in adolescence are influenced to a great extent by external factors like quality and quantity of food available, peers and media. In addition, adolescents may make unhealthy dietary choices due to immaturity of the prefrontal cortex of the brain that is responsible for judgment and decision making.

Adolescence is characterized by hormonal surges and sexual maturation resulting in dramatic changes in height, weight, muscle mass and fat distribution. A poor dietary intake in adolescence results in delayed sexual maturation, decreased lean body mass and stature, decreased cognitive ability and poor school performance. The following anabolic changes in physical growth during adolescence require increased intake of energy and nutrients.

- Gain of 15% of adult height and 50% of adult weight
- Growth spurt with an average annual increase of 9–10 cm in height and 8–10 kg in weight
- Gain of 45% of adult skeletal mass
- In boys, testosterone promotes an increase in lean body mass while in girls, increase in estrogen and progesterone result in increased fat deposition. In adolescent boys, body fat accounts for 15% of total body weight and in girls, 19–23%. Also, an increase in growth hormone and insulin like growth factor-1 result in *physiological* insulin resistance during puberty that leads to increased adiposity.

With emergence of autonomy and independence in early and middle adolescence, the influence of family decreases and the dietary and physical activity patterns are determined to a large extent by peer attitudes, behavior and by media messages. In this period, concrete thinking is the predominant cognitive ability that compromises the ability to link current healthy behavior to future adult health. Immediate rewards in the form of improved body appearance, peer acceptance and taste preferences govern food choices and behavior. If proper guidance and nutritional counseling are not given to adolescents, unhealthy eating behavior and habits may easily set in. In later adolescence, as the identity consolidates, abstract thinking develops and peer influence wanes away, lifestyle choices are made according to one's own values and attitudes.

## NUTRITIONAL STATUS OF ADOLESCENTS

Globally, 85% of adolescents live in developing countries of South East Asia and Sub-Sahara. Stunting, undernutrition and micronutrient deficiencies in adolescents are common in these regions due to poverty, inadequate nutrition, helminthiasis and poor growth in early childhood. Undernutrition in early life is mainly due to protein energy malnutrition and infections. Early marriage and pregnancy further compromise the nutritional status of adolescent girls. This in turn triggers the intergenerational cycle of malnutrition as the undernourished adolescent girl gives birth to a low birth weight or premature baby who is susceptible to increased morbidity and mortality throughout the life span. According to 2011 census, the median age of marriage in India is 21 years. Fifty percent of adolescent girls in rural areas and 33% in urban areas are married. Low birth weight accounts for 22% of all newborn births. A change in dietary practices in the form of increased consumption of energy dense, nutrient depleted fast food especially amongst the higher socioeconomic strata has led to an increase in overnutrition in adolescence in the developing countries. Decrease in physical activity has also contributed to an increase in obesity.

## Stunting

Stunting is defined as height less than 3<sup>rd</sup> percentile on height chart for that particular age. Stunting in adolescents indicates chronic energy and nutritional deficiency. It results in decreased physical ability and risk of obstetric complications like obstructed labor due to contracted pelvis. In developing countries, the prevalence of stunting in adolescence ranges from 12% to 67.3%. According to National Nutrition Monitoring Bureau Report 2000, 39% of the Indian adolescents are stunted and 24.1% of the married adolescent girls had a height less than 145 cm. It is controversial as to whether increased nutritional intake in adolescent period would spur up the peak height velocity during adolescence and allow for *catch up* growth. It is proposed that height in adolescence and adult period is determined by genetics and adequate nutrition in the first 2–3 years of life that are critical to growth. Increased intake in adolescence for those who are undernourished may in fact promote the onset of obesity. In the undernourished adolescents, there is usually a delayed onset of menarche and this may perhaps permit more time for *catch up growth*. Secular trends over twenty years from 1975 to 1996 indicate that there has been an increase of 2.5–3.5 cm in height and 1–1.5 kg in the mean weight of Indian adolescents.

## Underweight

According to WHO, the best indicator for *thinness* in adolescence is a body mass index (BMI) that is less than 5<sup>th</sup> percentile for that particular age. Demographic and Health Surveys (DHS 2002–2007) indicate that prevalence of underweight in girls aged 15 to 19 years is from 27% to 47% in the South east Asian and Sub

Saharan regions. The prevalence of undernutrition in Indian adolescents is given in **Table 1**. Overall prevalence in adolescence is 53%. More boys than girls are underweight and the prevalence of undernutrition decreases with age in adolescence. According to National Nutrition Monitoring Bureau (NNMB) 2000 report, 77.6% of 11-year-old boys were undernourished compared to 44% at 17 years. In girls, 62.7% of 10-year-olds were undernourished compared to 16.4% at 17 years.

### Micronutrient Deficiency

Globally, iron deficiency is the most common nutritional deficiency and cause of anemia in adolescence. In the developing countries, the prevalence of anemia in adolescent girls aged 15–19 years, ranges from 49% to 68%. The prevalence of anemia in Indian adolescents is given in **Table 2**. The overall prevalence is 55%. It is more in girls than boys. Anemia is more prevalent in the married adolescent girls and those living in rural areas and belonging to scheduled castes and tribes. Gender discrimination, poor dietary intake and early pregnancy contribute to increased prevalence of anemia in girls. Nutritional anemia directly contributes to nearly 24% of maternal mortality. In 2007, a review of 11 studies from India evaluating nutritional status of school children from 6 years to 18 years from middle and high socioeconomic strata revealed that even overnutrition coexisted with micronutrient deficiencies. In this review 19–88% of the study population was anemic and nearly 100% had folate deficiency while prevalence of riboflavin, niacin, vitamin C, vitamin A and vitamin B<sub>12</sub> ranged from 40% to 60%.

### Overnutrition

Rapid urbanization of the developing world has concomitantly resulted in an increased prevalence of overweight and obesity. Overweight is defined as being between 85<sup>th</sup> and 95<sup>th</sup> centile on BMI sex and age related charts and obesity as being above 95<sup>th</sup> centile. The prevalence of obesity in the Indian adolescents is given in **Table 1**. Secular trends reveal that prevalence of obesity has increased from 9.8% in 2006 to 11.7% in 2007 in urban adolescents aged 14–17 years. There was a two fold increase in risk of obesity in those watching television for more than 3 hours per day. The risk increased by four fold in the high socioeconomic strata. Adolescents who indulged in outdoor games for more than 6 hours per week or did household activities for more than 3 hours per day had a lower prevalence of overnutrition. In the 2007 review, the

prevalence of overweight varied from 8.5% to 29% and of obesity from 1.5% to 7.5% in urban adolescents.

### Energy and Nutrient Intake

National Nutrition Monitoring Bureau 2006 report states that most Indian adolescents consume 66% of the recommended caloric intake and 32–45% of recommended dietary allowance (RDA) of iron leading to widespread prevalence of undernutrition and anemia. Sixty six percent were consuming less than 70% of RDA for riboflavin and vitamin A. The adolescent diets were also deficient in protein. A 2007 study done in six rural blocks revealed that in adolescent girls, the intake of milk and milk products, pulses, vegetables and fruits was grossly inadequate. Higher socioeconomic strata consumed an energy rich diet with increased intake of fats and sugar and decreased dietary fiber. Over the past two decades (from 1975 to 1995), the extent of severe deficit with respect to energy (< 50% of RDA) has decreased from 21% to 9% in adolescent boys and 14% to 5% in girls.

### DIETARY RECOMMENDATIONS FOR ADOLESCENTS

Adolescent dietary recommendations include daily energy and nutrient requirements to maintain health and to support ongoing growth and development. Recommendations also address how food and beverages should be chosen to fulfill the normal dietary requirements. Macronutrients namely carbohydrates, proteins and fats provide energy while micronutrients like vitamins and minerals are important components of enzymes and hormones. Recommended dietary allowances (RDAs) are the quantitative levels that meet the needs of nearly 98% of individuals in a particular life stage and sex group. Nutritional requirements in adolescence vary according to current weight, age, sex, pubertal stage and physical activity level. Current RDAs for Indian adolescent boys and girls along with recommended dietary portions are given in **Tables 3 to 5**. National Institute of Nutrition, Hyderabad in 2010 framed the Dietary Guidelines for Indians. These guidelines recommend eating a variety of food from different food groups, increasing the intake of fruits and vegetables, moderating the intake of edible oils, salt, ready to drink beverages and processed foods and on doing regular exercise (See Section 22). The guidelines also recommend 60 min of moderate physical activity for adolescents on a daily basis.

### Energy

To maintain optimal weight, energy intake must be balanced with expenditure. Energy is expended in doing daily activities, for growth and for maintaining basic metabolic rate. As adolescent boys have a higher increase in height, weight and lean body mass compared to girls, their energy needs are greater. Energy intake increases with increased levels of physical activity.

### Micronutrients

The requirements for iron, zinc and calcium are higher during adolescence compared to second decade of life when the growth is almost complete. Vitamin needs steadily increase from childhood into adolescence.

### Iron

Iron needs are increased in adolescence as there is a higher production of myoglobin and hemoglobin due to an increase in lean muscle tissue and red cell mass. In girls, iron is also required to cover monthly menstrual losses of approximately 30–40 mL. Diet rich in iron include green leafy vegetables, legumes, dry fruits, meat, fish and poultry. Bioavailability of iron is poor from plant

**Table 1** Nutritional Status of Indian adolescents aged 15–19 years

Nutrition status (BMI)	Undernutrition (< 18.5)	Normal	Overnutrition (> 25)
Female	46.8%	50.8%	2.4%
Male	58.1%	40.2%	1.7%

Abbreviation: BMI, body mass index.

Source: National Family Health Survey-3 (NFHS-3), 2005-06.

**Table 2** Prevalence of anemia in Indian adolescents aged 15–19 years

Severity	Mild anemia*	Moderate anemia*	Severe anemia*	Any anemia
Girls	39.1%	14.9%	1.7%	55.7%
Boys	16.7%	12.1%	1.4%	30.2%

\*Anemia defined as mild, moderate, severe, and any as follows:

Girls (Hemoglobin: 10–11.9 g/dL, 7–9.9 g/dL, < 7 g/dL, < 12 g/dL) and

Boys (Hemoglobin: 12–12.9 g/dL, 9–11.9 g/dL, < 9 g/dL, < 13 g/dL).

Source: National Family Health Survey-3 (NFHS-3), 2005-06.



food. Eating food rich in vitamin C like *amla*, guava and citrus fruits along with an iron rich diet increases the intestinal absorption of iron. Tannin in tea inhibits the absorption of iron and is to be avoided especially immediately before, after or during meals. Poor dietary intake results in anemia that impairs growth and cognition and leads to fatigue and increased risk of infections.

### Calcium Intake

Calcium intake is important as there is maximum bone mineral accretion in adolescence and nearly half of the peak skeletal mass is accumulated in this phase. Increased calcium needs must be entirely met by dietary intake. Poor dietary intake will result in long-term risk of osteoporosis. Calcium is found in dairy products,

**Table 3** Recommended dietary allowances for adolescents

Age (years)	Girls						
	Calories	Proteins (g)	Fat (g)	Calcium (mg)	Iron (mg)	Zinc (mg)	Magnesium (mg)
10–12	2010	40.4	35	800	27	9	160
13–15	2330	51.9	40	800	28	11	210
16–17	2440	55.5	35	800	26	12	235
Age (years)	Boys						
	Calories	Proteins (g)	Fat (g)	Calcium (mg)	Iron (mg)	Zinc (mg)	Magnesium (mg)
10–12	2190	39.9	35	800	21	9	120
13–15	2750	54.3	45	800	32	11	165
16–17	3020	61.5	50	800	28	12	195

Source: National Institute of Nutrition, ICMR Guidelines 2010.

**Table 4** Recommended dietary allowance of vitamins for adolescents

Age (years)	Girls								
	Vit A (μg)		Thiamin (mg)	Riboflavin (mg)	Niacin equivalent (mg)	Pyridoxin (mg)	Ascorbic acid (mg)	Dietary folate (μg)	Vit B12 (μg)
	Retinol	βcarotene							
10–12	600	4800	1.0	1.2	13	1.6	40	140	0.2–1.0
13–15	600	4800	1.2	1.4	14	2.0	40	150	0.2–1.0
16–17	600	4800	1.0	1.2	14	2.0	40	200	0.2–1.0
Age (years)	Boys								
	Vit A (μg)		Thiamin (mg)	Riboflavin (mg)	Niacin equivalent (mg)	Pyridoxin (mg)	Ascorbic acid (mg)	Dietary folate (μg)	Vit B12 (μg)
	Retinol	βcarotene							
10–12	600	4800	1.1	1.3	15	1.6	40	140	0.2–1.0
13–15	600	4800	1.4	1.6	16	2.0	40	150	0.2–1.0
16–17	600	4800	1.5	1.8	17	2.0	40	200	0.2–1.0

Source: National Institute of Nutrition, ICMR Guidelines 2010.

**Table 5** Number of portions constituting a balanced diet for adolescents

Food Group	Cereals & millets	Pulses	Milk & milk products	Roots & tubers	Green leafy vegetables	Other vegetables	Fruits	Sugar	Fat/oil (visible)
g/portion	30	30	100	100	100	100	100	5	5
Age (year)	Girls								
10–12	8	2	5	1	1	2	1	6	7
13–15	11	2	5	1	1	2	1	5	8
16–18	11	2.5	5	2	1	2	1	5	7
Age (year)	Boys								
10–12	10	2	5	1	1	2	1	6	7
13–15	14	2.5	5	1.5	1	2	1	4	9
16–18	15	3	5	2	1	2	1	6	10

Source: National Institute of Nutrition, ICMR Guidelines 2010.

fish, spinach, ragi, broccoli, turnip, custard apple and almonds. Along with calcium, adequate Vitamin D, parathyroid hormone and doing weight bearing exercises are essential to maintain bone mineral density. Contraceptive usage, alcohol abuse and excessive soft drink consumption in adolescence impairs calcium absorption.

### Zinc

Zinc has an important role in protein synthesis and general growth and maintenance of tissues. Dietary sources include meat, dairy products, nuts and whole grains. Inadequate intake results in growth failure, delayed sexual maturation, loss of taste and appetite and mental lethargy.

### Folate and Vitamin B<sub>12</sub>

Folate and Vitamin B<sub>12</sub> are required for formation of red blood cells. Folate is obtained from green leafy vegetables, legumes, whole grain cereals and liver. Vitamin B<sub>12</sub> is obtained from non-vegetarian food, eggs and dairy products. Deficiency of Vitamin B<sub>12</sub> and folate in adolescence results in megaloblastic anemia. Folate is essential for replication and translation of DNA and thereby for cell division and protein synthesis. Its deficiency in the periconceptional period results in neural tube defects in the fetus. Vitamin B<sub>12</sub> deficiency also results in neurological damage.

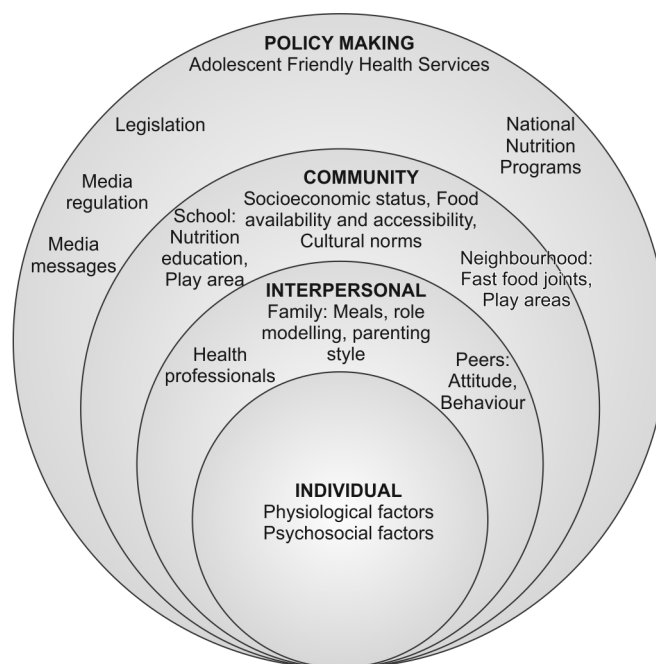
Pregnant and lactating adolescents have increased requirements of all micronutrients. Only 51% of households in India consume iodized salts. Iodine deficiency disorders contribute to 90,000 still births and neonatal deaths annually. They also result in mental retardation and impaired cognition. Adolescents who follow a strict vegan diet and those on drugs like alcohol and tobacco may require dietary supplements. Vegetarians may be at an increased risk of protein, vitamin B<sub>12</sub>, vitamin D, iron, zinc, calcium and omega-3 fatty acid deficiencies.

## FACTORS AFFECTING ADOLESCENT NUTRITION

Recent research has proved that socioecological factors affect adolescent health and behavior including dietary intake, level of physical activity and media usage. The socioecological determinants of adolescent nutrition are shown in **Figure 1**. Knowledge of these factors is important in policy making and planning of effective nutritional health programs at the individual and the community level. These determinants operate at multiple levels and are as follows.

### 1. Individual Level

Both physiological and psychosocial factors work at the individual level to determine dietary intakes. Physiological factors include sex, stage of adolescent development, disease and health status. Boys have larger appetite than girls and have also increased physical activity levels. Mid adolescents get easily influenced by the peer group. Those with poorly controlled chronic diseases like tuberculosis, asthma, depression or connective tissue disorders may have poor appetite. Those with diabetes mellitus may have dietary restrictions. Psychosocial factors such as knowledge, attitudes, and beliefs related to food, existing meal and dieting patterns and body image concerns influence dietary patterns. Adolescents especially girls who are excessively concerned about maintaining a *zero figure* may have low energy and nutrient consumption. Many adolescents are in the habit of skipping meals especially breakfast and a few prefer to eat only sweet or oily food. Increased media usage promotes sedentary behavior and weight gain.



**Figure 1** Socio-ecological model of determinants of adolescent nutrition

### 2. Interpersonal Level

Family peers and health professionals influence dietary intake in adolescence. Authoritative parenting style, parental encouragement and modeling, emotional connectedness, family meals, home resources for healthy eating and physical activity and cooperative siblings promote adequate dietary intake. Peer groups that promote intake of unhealthy junk food, fast food, in between meal snacking, soft drinks, colas and alcohol influence the adolescent in adopting the same. Fad diets, excessive dieting and dissatisfaction with current body image may also be reinforced by friends. In middle adolescence, the effect of family wanes and the influence of peers on behavior increases. Health professionals can negate the effect of such influence by imparting science based anticipatory guidance and counseling to adolescents.

### 3. Community Level

Availability and accessibility of processed food and junk food determines its intake. Adolescents belonging to lower socio economic status and in rural areas consume diets poor in energy, proteins and minerals. The consumption of junk food by adolescents increases if their college and school canteens supply such food items. Educational institutions that provide effective evidence based nutrition education play a big role in promoting healthy eating habits and attitudes. A large number of cheap fast food joints in the immediate neighborhood encourage consumption of energy dense nutrient poor food and beverages. Glossy junk food promoting media messages especially by celebrities should be banned or censored. Many media messages encourage the adolescent to adopt unhealthy body images like *thinness* in girls or *muscularity* in boys. Media literacy is the need of the hour. Social norms like celebrating *achievements and successes* by holding high caloric feasts and meals may also influence dietary consumption of adolescents. Safe playing areas would promote physical activity. Availability of adolescent friendly health facilities in the vicinity, facilitates appropriate management of nutrition related health issues.

#### 4. Governmental and Political Level

Due importance should be given to adolescent health at the highest political and governmental level. This in turn helps in framing adolescent friendly policy, rules, regulations and legislations. Increased taxes on junk food, sweetened beverages, alcohol and tobacco would decrease their intake and cheaper fruits and vegetables would increase their consumption. Law against junk food availability like those for tobacco in educational institutions would result in its decreased intake. Making food labels compulsory for all ready to eat items and beverages is another important policy decision. Media messages regarding unhealthy eating and body image should also be regulated. The Government of India's *Rashtriya Kishore Swasthya Karyakaram* launched in 2014 has adolescent nutrition as one of the important focus areas. The various national programs framed toward achieving nutritional sufficiency amongst adolescents are listed below.

##### *National Iron + Initiative*

The guidelines for control of iron deficiency anemia over the entire life-span were published by the Government of India in 2013 and was named as National Iron + Initiative. Evidence based strategies and comprehensive action plans were outlined to eliminate anemia in the target groups comprising of children, adolescents, pregnant and lactating women and all women of reproductive age groups. For school and out of school adolescents, the weekly iron and folic acid supplementation (WIFS) program was initiated. WIFS has the following components:

- Supervised intake of weekly iron (100 mg) and folic acid (500 µg) tablets to all adolescents in school and in *Aganwadis* (for out of school adolescents)
- Biannual intake of albendazole tablet (400 mg)
- Screening of all adolescents for anemia and referral for treatment
- Information and counseling regarding dietary intake, hygiene and prevention of worm infestation.

For pregnant adolescents and women, 100 mg of elemental iron and 50 µg of folic acid are recommended for 100 days each in the antenatal and postnatal period. They are also provided with insect repellent treated bed nets for their personal use. Weekly iron supplementation is given by ASHA workers to all women of reproductive age group (15–45 years).

##### *SABLA Program for Adolescent Girls*

Under the SABLA program, adolescent girls are given a take home ration of fresh prepared food that provides 600 calories with 18–20 g of protein along with micronutrients.

#### Screening and Assessment of Nutritional Status in Adolescents

Apart from an annual screening, adolescents should be screened for their nutritional status at every health visit. Nutritional intake and concerns about body image form an important part of routine psychosocial screening using the HEADSS tool (Chapter 24.3). Food frequency questionnaires, 24 hour dietary recall and food diaries can also be used for a detailed dietary assessment. Physical activity levels, details of current or past weight control behavior and media usage should also be evaluated. Height, weight, BMI and blood pressure should be plotted on appropriate charts. Obesity, hypertension, anemia or undernutrition that are detected on examination require detailed investigations and appropriate management.

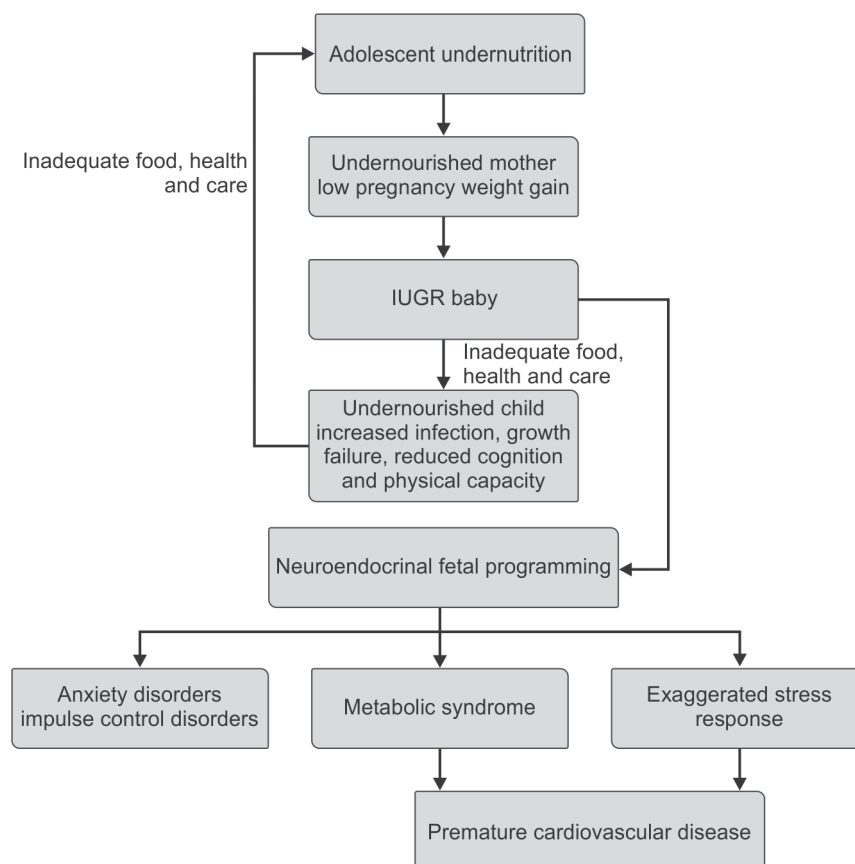
#### ADOLESCENT NUTRITION AND LIFESTYLE DISORDERS

According to WHO, 33% of disease burden and almost 60% of premature deaths among adults can be attributed to causes that begin in adolescence like poor dietary habits, tobacco, alcohol use and risky sexual behavior. Improving adolescent nutrition especially those of girls will play a major role in achieving Millennium Development Goal (MDG) 1 (eradicate extreme poverty and hunger), MDG 4 (reduce child mortality) and MDG 5 (improve maternal health).

Recent research has proven that maternal undernutrition and anemia have not only adverse effects in utero, but also epigenetic effects that can be transmitted from one generation to another. Effect of maternal undernutrition is shown diagrammatically in **Flow chart 1**. These are explained in detail below:

- Maternal undernutrition results in low birth weight babies and premature births. These babies, especially those with intrauterine growth restriction have increased mortality and morbidity. Poverty leads to poor health, inadequate nutrition and poor child care. This in-turn causes childhood undernutrition, inadequate catch up growth, stunting, increased susceptibility to infections and impaired cognition that continues into adolescence and adulthood.
- According to Barker hypothesis and developmental origin of adult health and disease hypothesis, maternal undernutrition and anemia cause fetal neuroendocrine programming. This includes reduced insulin sensitivity and pancreatic beta cell mass, low nephron number, poor muscle mass, altered arterial structure and increased cortisol secretion. There is an up regulation of hypothalamic pituitary axis and sympathetic nervous system leading to in utero susceptibility to develop obesity, hypercholesterolemia, diabetes mellitus and hypertension in later life. When these undernourished babies are exposed to a high caloric energy dense diet in childhood, they put on weight rapidly and develops metabolic syndrome in adulthood.
- Fetal exposure to toxic stress in form of maternal undernutrition has an effect on the brain development by increased exposure to cortisol levels. It alters brain neuronal connectivity, cortical thickness, white matter fiber tracts and size and shape of gray matter structures like amygdala and hippocampus. This results in an exaggerated stress response, poor memory, impaired cognitive ability and predisposes to anxiety and impulse control disorders due to faulty development of the orbitofrontal neural tracts. It also leads to an increase in lifelong susceptibility to coronary artery disease.

As mentioned before in this chapter, overnutrition among adolescents is on the increase. This has led to an increase in metabolic syndrome in adolescence. Metabolic syndrome increases the likelihood of developing stroke and heart attack by two to three times and type 2 diabetes mellitus by five times compared to normal population. Hence, it is very important to identify and manage adolescents who are *at risk* of developing metabolic syndrome. In 2007, the International Diabetes Federation (IDF) published the consensus definition of metabolic syndrome in children and adolescents. Abdominal obesity, clinically determined by measuring the waist circumference at the umbilicus is an essential feature of the definition. The presence of the essential feature plus any two of the other four factors defines the syndrome. The other four factors include hypertriglyceridemia, low HDL, hypertension and impaired fasting glycemia. Early detection, followed by treatment in form of

**Flow chart 1** Effect of adolescent undernutrition on life cycle

lifestyle related intervention and possibly, pharmacotherapy with metformin form an important part of management of metabolic syndrome. Polycystic ovarian syndrome, the most common endocrinopathy seen in female adolescents is also attributed to increased prevalence of obesity and insulin resistance. Obesity has also lead to an increase in type 2 diabetes mellitus and hypertension among adolescents.

According to Diagnostic and Statistical Manual of Mental Disorders (DSM-5), feeding and eating disorders include binge eating, anorexia nervosa, bulimia nervosa, pica, rumination and avoidant/restrictive disorder. Currently, with media's emphasis on equating beauty to thinness, the incidence of eating and feeding disorders are on the rise amongst adolescents. An Indian study published in 2007, estimated the prevalence of eating disorders in adolescents as 1.25%. A 2012 survey from Bengaluru revealed that Indian psychiatrists have noted a recent increase in clinical cases of eating disorders. Anorexia is characterized by failure to maintain a minimal normal weight along with intense fear of gaining body weight and distorted body image. Bulimia is characterized by recurrent episodes of binge eating and purging behavior in the form of emesis or use of laxatives. Both these psychiatric disorders are discussed in detail in Section 21.

Optimal and adequate adolescent nutrition determines health of a nation. All stakeholders including government, community leaders, educational institutions, health care professionals, parents and adolescents themselves have a major role to play in ensuring appropriate adolescent nutrition at all levels of health care.

### IN A NUTSHELL

1. Adolescence is a nutritionally vulnerable period.
2. Adequate nutrition and physical activity in adolescence are essential for current, future and intergenerational health.
3. India is facing the double jeopardy of adolescent undernutrition and overnutrition. Lifestyle disorders are on the increase.
4. Micronutrient deficiencies are common in Indian adolescents.
5. Adolescent nutrition is determined by multiple socio-ecological factors.
6. Nutritional status of adolescents must be assessed at every health visit.
7. Girls are especially vulnerable to nutritional deficiencies.
8. Nutritional well-being has to be ensured over the entire life span to break the intergenerational cycle of undernutrition and poor health.

### MORE ON THIS TOPIC

- Chandra PS, Abbas S, Palmer R. Are eating disorders a significant clinical issue in urban India? A survey among psychiatrists in Bangalore. *Int J Eat Disord*. 2012;45(3):443-6.
- Cusick SE, Kuch AE. Determinants of undernutrition and overnutrition among adolescents in developing countries. *Adolesc Med State Art Rev*. 2012;23(3):440-56.
- Dietary guidelines for Indians. A manual, 2<sup>nd</sup> edition. Hyderabad: National Institute of Nutrition. Indian Council of Medical Research; 2010.
- Gupta DK, Shah P, Misra A, et al. Secular trends in prevalence of overweight and obesity from 2006 to 2009 in urban asian Indian adolescents aged 14-17 years. *PLoS One*. 2011;6(2):e17221.



- International Institute for Population Sciences (IIPS) and Macro International National Family Health Surveys (NFHS-3), 2005-06, India: Key Findings. Mumbai:IIPS; 2007.
- Larson N, Story M. Adolescent Nutrition and Physical Activity. In: Fisher MM, Alderman EM, Kreipe RE, Rosenfeld WD. Textbook of Adolescent Health Care. USA: American Academy of Pediatrics; 2011. pp. 127-147.
- Laxmaiah A, Nagalla B, Vijayraghvan K, et al. Factors affecting prevalence of overweight among 12- to 17-year-old urban adolescents in Hyderabad, India. *Obesity (Silver Spring)*. 2007;15(6):1384-90.
- Mammen P, Russell S, Russell PS. Prevalence of eating disorders and psychiatric comorbidity among children and adolescents. *Indian Pediatr*. 2007;44(5):357-9.
- Srihari G, Eliander A, Muthaya S, et al. Nutritional status of affluent Indian school children: what and how much do we know? *Indian Pediatr*. 2007;44(3): 204-13.
- Strategy Handbook. Rashtriya Kishor Swasthya Karyakram. New Delhi: Adolescent Health Division, Ministry of Health and Family Welfare, Government of India; 2014.
- UNICEF. Adolescence: an age of opportunity. State of the World's Children. February 2011. Available from URL: [http:// www.unicef.org/sowc2011/index.php](http://www.unicef.org/sowc2011/index.php). Accessed April 28, 2014.
- WHO. Adolescent nutrition: a review of the situation in selected South East Asian countries. 2006. Available from URL: [http://www.searo.who.int/EN/Section38\\_11624.htm](http://www.searo.who.int/EN/Section38_11624.htm). Accessed April 28, 2014.

## Chapter 25.3

# Mental Health

Priya Mary Mammen

Mental health is defined as the *successful performance of mental function, resulting in productive activities, fulfilling relationships with other people, and the ability to change and to cope with adversity*. Poor mental health is not synonymous with mental illness. Mental disorders refer to conditions that are characterized by alterations in thinking, mood, or behavior associated with distress and/or impaired functioning. Global estimates of the prevalence of psychiatric disorders in adolescence have reported that almost one in five adolescents has a diagnosable psychiatric disorder and about 10% of these have severe disturbances. In India it is documented that the prevalence of psychiatric disorders among adolescents under 16 years is 12.5%. In addition, almost half of the mental illnesses diagnosed in adults have their onset in the adolescent period and those with onset in childhood are invariably found to persist into adolescence. Mental health issues in adolescents have far reaching effects in their development, leading to a host of other problems which affect the individual, family and society at large. This chapter will deal with poor mental health (e.g., peer pressure, bullying and stress) and few specific disorders seen in adolescents.

### DETERMINANTS OF MENTAL HEALTH IN ADOLESCENTS

Three main determinants have been identified: *Individual attributes, social circumstances and environmental factors*. These three determinants can act and interact as adverse factors which pose a risk to mental wellbeing, or as protective factors which enhance positive mental health. There are many factors which adversely affect the mental health of an adolescent; some of these have been enumerated below.

#### 1. Peer Pressure

Eric Erikson's theory on psychosexual development mentions adolescence to be the stage of identity versus role diffusion. An adolescent is in a struggle to develop an ego identity and group identity. Adolescence is a period when individuals spend considerable time with peers as compared to their families. Peer influence can have both positive and negative effects. These effects have been already discussed in the Chapter 25.1 on factors influencing the adolescent health. Adolescents who usually conform to the norms of their peer group are usually better accepted socially. Rejection by peers has been found to have higher associations with school drop outs, delinquency and substance use. However, peer group values can often be in conflict with one's internalized value systems. The pressure on the adolescent to be socially accepted by conforming to the peer group norms and peer pressure, can at times give rise to significant problems. Peer pressure has been found to have the maximum influence in early and middle adolescence. Peer pressure can occur either through direct influence, modeling or by perceived norms. Adolescents who are most vulnerable to the effects of peer pressure are those with low self-esteem, under assertive traits, have family backgrounds which are disturbed or parents who are uninvolved. Peer pressures can be spoken or unspoken—spoken peer pressures are those where friends directly tell an adolescent what to do while the unspoken pressures are those that the adolescent observes in their peer and wishes to imitate.

#### Substance Abuse

A large number of individuals, who go on to develop substance use disorders, have a history of initiating substance use in their adolescence. It has been found that one of the strongest predictors of alcohol and tobacco use in teenage years has been social motivation. Studies done across India, have reported that peer pressure has been one of the most commonly cited reasons for initiating substances like alcohol, tobacco and inhalant substance use in 35–45% of adolescents. Peer pressure has been found to have a stronger influence on adolescent substance use, than the presence of substance use disorder in a parent or sibling.

#### Sexuality

Adolescence is a period of sexual maturation and developing a sexual identity. Sexual peer norms, peer sexual behavior and peer pressure to have sex have been strongly associated with premarital sex in adolescence. Peer pressure is especially significant in adolescents who report poor quality of parental relationship with parental inhibition in discussing these issues with their child.

#### Body Dissatisfaction

With hormonal influences and bodily changes that occur in this stage, an adolescent is understandably preoccupied with appearance. It is therefore not surprising that disorders like anorexia nervosa and bulimia usually have their onset in this age group. Many studies have shown however, that *appearance-related social pressure* from peers is one of the most crucial factors for body image concerns in both adolescent boys and girls. Peer interactions and comparisons for thinness have been associated with weight concerns and dieting in adolescent girls, while peer comparisons for physical stature and musculature have been reported as significant for body dissatisfaction in adolescent boys.

#### Other Risk Taking Behaviors

Coercive behaviors and reinforcement of these by peer groups have been associated with high risk behavior in adolescents. Truancy from school, vandalism, traffic offences and weapon use are commonly associated with peer group influence.

Peer influence plays a major role in one's development especially in vulnerable individuals. It is therefore recommended that preventive interventions need to address peer pressure influence through social and life skills training programs.

#### 2. Bullying

Bullying is defined as *an intentional and repetitive aggressive behavior from one person that causes harm to a vulnerable peer*. The definition of bullying implies certain characteristics namely: a hostile intent, causes distress to the victim, implies a power imbalance between the bully and the victim and tends to be repetitive. There are various forms of bullying: physical, verbal and social aggressive/relational. While physical and verbal types are more direct forms of bullying, social aggressive in the way of gossip, rumor circulation and being ostracized from peer groups, is an indirect form. Physical (hitting, kicking) and verbal (teasing, name-calling) aggression is commonly described in male adolescent bullies; female adolescent bullies tend to resort to more socially aggressive bullying tactics. Over the past few years with the advent of social media platforms, classic forms of bullying have been replaced by newer forms like cyberbullying.

#### Prevalence

Bullying has been widely reported across the world, however prevalence rates are varied across countries. Prevalence studies of bullying in school populations have reported low rates of 5%

in some Scandinavian countries to higher rates of 13–24% in USA and England. Few studies which have looked at the prevalence rates in Asian countries like India and Taiwan, have reported much higher rates like 50–60%. These reports also state that male adolescents bully more than females especially with regard to physical aggression. There also appears to be a reducing trend in the prevalence of bullying by late adolescence. Three groups of individuals who are involved in bullying have been identified, namely bullies (perpetrators), victims and bully-victims (both perpetrator and victim).

### *Risk Factors in Victims*

While bullying has been reported as a universal phenomenon, the risk factors for the same are multifactorial. Important risk-factors at individual, family, school and community level are listed below:

1. *Individual factors* Low self-esteem, poor social skills, physical and intellectual disability, aggressiveness.
2. *Family factors* Domestic abuse, authoritarian parenting, inadequate parental supervision, broken homes.
3. *School factors* Overcrowding, socioeconomic disparities, inadequate teacher supervision, aggressive peers.
4. *Community factors* High crime areas, overcrowding, lower socioeconomic status.

### *Outcome of Bullying*

All three groups directly involved in bullying develop mental health concerns. Both internalizing and externalizing disorders are reported in victims of bullying. *Internalizing disorders* like anxiety, depression, post-traumatic stress disorder and suicide are more prevalent. Cross-sectional studies on bullies have found higher rates of *externalizing disorders* like conduct disorder and attention deficit hyperactivity disorder, delinquency, substance abuse, interpersonal difficulties and school failure. While the bully-victim is the least prevalent among the three groups, they have the highest levels of psychopathology, with both externalizing and internalizing disorders. Numerous studies that have looked at the effects of bullying have emphasized the need to address this issue in preventive programs.

### *Interventions*

Antibullying programs have been initiated in schools. One of the earliest structured programs was the Olweus Bullying Prevention Program (OBPP) which was introduced in schools across Sweden and Norway and the KiVa which was initiated in Finland. The program was geared toward the 5–15 year age group and had interventions addressing the problem at an individual, parent and school administrative level. Controlled trials of these preventive intervention programs have found decrease in self and peer reported bullying. A systematic review which looked at the effectiveness of antibullying interventions, found an overall reduction of 20–23% in bullying across schools where these were implemented. These programs have not yet been implemented in India.

## **3. Stress**

Stress is defined as a *state of mental or emotional strain resulting from adverse or demanding circumstances*. While stress can affect mental health, low levels of stress have been found to have beneficial effects and are associated with better performance. Stressors can be acute or chronic. Acute stress is usually characterized by sudden onset, is more severe, but time limited. Many life events fall in this category. In contrast, chronic stress occurs over a longer duration of time, is generally less severe and gradual in onset. However, both types of stress are known to affect adolescent mental health, though correlates may differ. While almost every adolescent

undergoes stress in some form or the other, not all of them develop mental health concerns. This brings into light the mediating effect of resilience and coping in the context of adversity. Resilience can be determined by both internal factors such as high intellect, good self-esteem and problem based coping styles, and external factors like strong social support, involved/supportive parents and peers. Therefore, interactional effects of the stressor and an adolescent's resilience will determine the perception of the stress and its effect on mental health. Studies that have looked at perceived stress have found gender differences, with higher prevalence in girls. Adolescence has been reported as the most vulnerable period for stress to affect functioning, as compared to early childhood, or in adults.

### *Common Stressors in Adolescents*

School/academic pressure; relationship issues; peer pressure and bullying; more responsibilities; future career and financial concerns; and chronic physical illnesses, family conflict, sexual or physical abuse.

### *Associations Between Perceived Stress and Mental Health Issues*

Higher levels of perceived stress in adolescents have been linked to nonspecific health concerns like physical complaints, fatigue and sleep disturbances, to more specific disorders like anxiety, depression and post-traumatic stress disorder (PTSD). While acute, sudden and intense trauma has been associated with PTSD and anxiety disorders, chronic adversity has been commonly linked to later development of depression and personality problems. However as mentioned, individual vulnerabilities interacting with negative life events would finally determine these outcomes.

## **MENTAL HEALTH PROBLEMS IN ADOLESCENCE**

World Health Organization has identified specific disorders which are commonly seen and can be managed in primary care pediatric settings based on the findings of epidemiological studies on the prevalence of psychiatric disorders in adolescents. Among these, depression, anxiety, substance use and behavior disorders are the most prevalent. We have already discussed anxiety and conduct disorders in Section 21. Others are detailed below.

### **Depression**

Depressive disorders are the most common psychiatric disorders seen in adolescents. While historically reactive and endogenous types of depression have been described, current classificatory systems have classified these under major depressive disorders (MDD) and adjustment disorders respectively. Adjustment disorders with transient and mild depressive symptoms which are temporally correlated with a recent stress are highly prevalent in adolescents and usually require only brief nonpharmacological interventions. MDD however needs to be diagnosed and treated appropriately. The diagnostic criteria for MDD are given in **Box 1**. There are several other subtypes of MDD which are out of the scope of this discussion.

### *Epidemiology*

Global community studies on depression have reported prevalence rates ranging from 0.2% to 17%, with a median prevalence of 4% in the adolescent age group. While pre and early adolescent MDD rates are similar in both genders, a female preponderance is noted following puberty, with M:F ratio of 1:2. A significant proportion of adolescent youth with MDD have comorbid anxiety disorders (30–40%), conduct disorders (15–30%) and substance use disorders.

**BOX 1 ICD-10 Diagnostic criteria for major depressive disorder**

- A. Depressive symptoms lasting at least 2 weeks
- B. At least two of the following three symptoms:
  1. Depressed mood present most of the day
  2. Loss of interest in pleasurable activities
  3. Decreased energy
- C. Additional symptoms (four or more):
  1. Decreased self esteem
  2. Excessive guilt
  3. Suicidal thoughts or behavior
  4. Decreased concentration
  5. Psychomotor agitation or retardation
  6. Sleep disturbance
  7. Change in appetite and weight

**Etiology**

A combination of genetic vulnerability and environmental factors has been implicated in the etiology of depression. Having a parent with depressive disorder has been associated with a two times higher chance of developing an MDD. One of the most cited biological theories regarding depression have reported low levels of monoamines and serotonin in individuals with MDD.

**Clinical Features**

Clinical symptoms encompass groups of cognitive, affective, biological and behavioral symptoms which are characteristically seen in depression and are listed below:

- *Cognitive* Cognitive triad of helplessness, hopelessness and worthlessness; guilt and suicidal ideation
- *Affective* Low or irritable mood
- *Biological* Changes in sleep, appetite and libido
- *Behavioral* Suicidal behavior, crying spells, psychomotor retardation/agitation.

**Assessment**

Common medical conditions which may present with depressive symptoms need to be ruled out. This would include hemoglobin, leukocyte counts, ESR, thyroid function tests and creatinine. Psychological assessments in the form of rating scales to rate the severity of depression at baseline and for monitoring can be administered. Some of the common rating scales used are the Beck Depression Inventory (BDI), the Childhood Depression Rating Scale (CDRS) and the Hamilton Depression Rating Scale (HDRS).

**Management**

Treating an adolescent with depression will need to take the following factors into consideration:

- *Severity of episode* May require inpatient admission in case of severe psychomotor retardation, suicide risk or catatonic symptoms.
- *Presence of psychotic symptoms* Will require initiation of an antipsychotic medication along with the antidepressant, which will need to be continued through the acute phase of treatment and then tapered.
- *Presence of past hypomanic/manic episodes* Will require antidepressants under the cover of a mood stabilizer at adequate therapeutic dose, to prevent the likelihood of a switch.
- *Presence of recurrent depressive episodes* Will require prophylactic antidepressant treatment (continuation of medications for 2–5 years).

**Nonpharmacological treatment** Nonpharmacological treatments have been recommended as first line treatment in mild and moderate depressive episodes. Cognitive-behavior therapy (CBT),

interpersonal therapy (IPT), psychodynamic therapy and family based therapies have been used; the evidence is most in favor of CBT and IPT in adolescent depression.

**Pharmacological treatment** Various classes of antidepressants can be used, however most guidelines recommend Serotonin Specific Reuptake Inhibitors (SSRIs) as the first line medications. These medications are easily available, have easy dosing schedules and relatively better side effect profiles and are therefore easy to prescribe at a primary care pediatric setting. Common SSRIs and their dosing schedules are described in **Table 1**.

Tricyclic antidepressants can be used as second line medications. However, are not usually prescribed in view of their side effect profile. For the first episode of depression, the treatment is divided into two phases: an acute phase lasting for 2–3 months and a continuation phase lasting for 6 months after the acute phase of treatment. The antidepressant needs to be continued through the two phases of treatment and is usually maintained at the dose required for acute control. While the above treatment regimens are recommended at primary care levels, it is recommended that more severe forms of depression with psychotic, catatonic, high suicide risk, bipolar or recurrence features, be referred to tertiary centers for further management.

**Substance Abuse**

The use of psychoactive substances by adolescents is a universal phenomenon. Substance use has been considered by the United States Substance Abuse and Mental Health Services Administration as *minimal or experimental use* with minimal consequences and *substance abuse* as regular with more severe and serious consequences. Both the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) have defined criteria for substance abuse and dependence, with current revisions further made in the DSM-5. The ICD-10 classifies substance use disorders into acute intoxication, harmful use, dependence syndrome, withdrawal states, psychotic states and amnesic syndrome. While substance use and acute intoxication are highly prevalent in adolescents, substance abuse and dependence in this age group is relatively uncommon. The features of substance abuse/harmful use and substance dependence as mentioned in the ICD-10 are listed below.

**Substance Abuse/Harmful Use**

A pattern of substance use that is causing damage to physical and mental health without other features are suggestive of dependence. The term *abuse* has been similarly used in the DSM-IV, which also includes the social, legal and occupational consequences of this pattern of substance use.

**Substance Dependence**

A cluster of physiological, behavioral and cognitive phenomena characterized by three or more of the following over a one year period—tolerance, physiological withdrawal, inability to control, preoccupation with substance use, continued use in spite of harmful consequences and craving.

**Table 1** Dose and dosing for the common serotonin specific reuptake inhibitors

Drug	Dose/day
Fluoxetine	20–40 mg od
Citalopram	20–40 mg od
Escitalopram	10–20 mg od
Sertraline	50–100 mg od



Most adolescent substance use is usually experimental (more out of curiosity) or recreational (during social gatherings).

### Epidemiology

Prevalence rates of substance use in adolescents vary widely with extremely high rates of 50–75% for alcohol reported in the UK and 40–42% of illicit drug use in the UK and USA. Prevalence estimates of substance abuse and dependence however have ranged from 3.3% to 9.8% in 17–19 year olds in western studies. Global trends show that alcohol and nicotine are the most commonly used substances among adolescents. Among illicit drugs, cannabis and opiates are the most frequently abused, followed by cocaine and amphetamine. One of the largest national studies done in India, 'National Survey on Extent, Pattern and Trend of Drug abuse in India' was sponsored by the Ministry of Social Justice and Empowerment, Government of India (MSJE, GOI) and the United Nations Office on Drugs and Crime, Regional Office for South Asia (UNODC, ROSA). The results of this survey published in 2004, reported that the most prevalent substance of abuse was alcohol (21.4%) and tobacco, followed by cannabis (3%) and heroin (0.2%). While the population prevalence for opiate use was low, higher prevalence of opiate use was seen in treatment clinics. The highest prevalence of substance use was seen in the northeast region. Most of the individuals with substance use disorders also reported associated high risk behaviors like sharing of needles or unsafe sex practices.

### Risk Factors for Substance Use

Risk and protective factors have been identified in substance use disorders. The most common risk factors are listed here:

- **Genetic factors** Family history of substance use or mood disorder in 1st or 2nd degree relatives
- **Environmental factors** Substance abusing peers, cultural and religious sanction for substance use, easy availability of drugs, media influence, poverty
- **Individual factors** Psychiatric disorders like conduct disorder, depression and ADHD, traits of impulsivity, aggression and risk-taking, low self-esteem, low intelligence
- **Family factors** Family conflict, poor parental supervision, drug abusing parent, child abuse, permissive or authoritarian parenting.

### Assessment

It is important to identify an adolescent with substance use early on and make an assessment of the pattern of substance use before planning intervention strategies. There are screening questionnaires which have been used to identify substance use disorders. One of the common used screening measures, recommended by the American Academy of Pediatrics committee for substance use in adolescents is the CRAFFT which is a mnemonic acronym of 6 questions (**Box 2**). A few other screening measures for use in adolescents are the Adolescent Drinking Index (ADI), Drug Use Screening Inventory Revised (DUSI-R) and the Teen Addiction Severity Index (T-ASI).

#### BOX 2 Items of the screening questionnaire for substance use

##### The CRAFFT questionnaire

- C – Have you ever ridden in a *car* driven by someone (including yourself) who was *high* or had been using alcohol or drugs?
- R – Do you ever use alcohol or drugs to *relax*, feel better about yourself, or fit in?
- A – Do you ever use alcohol/drugs while you are by yourself, *alone*?
- F – Do you ever *forget* things you did while using alcohol or drugs?
- F – Does your family or *friends* ever tell you that you should cut down on your drinking or drug use?
- T – Have you gotten into *trouble* while you were using alcohol or drugs?

### Interventions

A complete physical and mental status examination is needed to look for signs of intoxication, withdrawal or physical and psychiatric comorbidities or sequelae of the substance use. Most adolescents with substance use disorders which are not of a dependent pattern will require the following interventions:

- **Psychoeducation** The harmful effects of substance use and the associated consequences are enumerated
- **Motivation enhancement therapy** An adolescent's perception of the advantages and disadvantages of substance use are assessed and challenged using motivational interviewing techniques.
- **Family and community based interventions** Parent based therapies which focus on improving parent-adolescent relationship; addressing better parenting styles and conflict resolution are implemented. Multisystemic therapy models which target family, school and peer functioning have been found to be effective.
- **Assertiveness training** Learning to be assertive in situations where peer pressure has contributed to substance use.
- **Assessment and management of comorbid psychiatric conditions** like conduct disorder, depression or ADHD.

Adolescents who have a pattern suggestive of dependence will most often require inpatient care with detoxification and de-addiction strategies specific to the substance being abused.

### Preventive Interventions

Substance use in adolescents has been associated with other high risk behaviors and has incalculable costs in the form of morbidity and mortality, academic underachievement, family dysfunction, legal consequences and economic implications. Preventive interventions are therefore needed to address this complex issue. Highly intensive programs are recommended for adolescents at risk. Many school based programs have started intervening at the primary school level. Most preventive programs consist of psychoeducation on drug use listing its consequences, life skills education addressing problem solving, assertiveness and handling peer pressure, self-esteem enhancement, managing leisure and other forms of recreation, and education on high risk behaviors.

### Personality Disorders

Personality disorders (PD) generally refer to an enduring and persisting pattern of maladaptive behavior, usually implicated as being consistent over time, place and circumstance. As childhood and adolescence are invariably considered as a stage of constant developmental change, the concept of stability of personality cannot be considered here. Personality disorders are by and large therefore conceptually not diagnosed below 18 years of age.

Both the ICD-10 and the DSM classificatory systems have listed various types of personality disorders which are mentioned in **Table 2**. Personality disorders in both the ICD-10 and DSM IV-TR classifications had used a categorical approach to classifying these disorders. The DSM-5 has been modified to include both a categorical and dimensional approach in diagnosing personality disorders but the categories essentially remain the same.

Child and adolescent approaches to the development of personality have addressed the theories of temperament and attachment in early childhood, to the constellation of personality traits in adolescence. While personality disorders are therefore not diagnosed, early childhood and adolescent traits in these domains and their association with the later development of personality disorders have been described. Certain disorders diagnosed in children and adolescents like conduct disorder, have been suggested as *prodromal personality disorders* in view of their continuum with adult antisocial personality disorder. Personality development is ultimately an interaction between genetic and environmental influences and the development of a disorder is

**Table 2** Summary of the personality disorders in ICD-10 and DSM-5 classificatory systems

DSM-5	ICD-10
1. Paranoid	Paranoid
2. Schizoid	Schizoid
3. Antisocial	Dissocial
4. Borderline	Emotionally unstable
5. Histrionic	Histrionic
6. Obsessive-compulsive	Anankastic
7. Avoidant	Anxious/avoidant
8. Dependent	Dependent
9. Narcissistic	-
10. Schizotypal	-

invariably related to the quality of these interactional processes. Maladaptive ways of interpreting situations and people can have both a biological influence (e.g., in disorders like autism) and an environmental influence (e.g., a life event like abuse).

### Childhood Predictors of Development of Personality Disorders in Adulthood

- **Early temperamental traits** Impulsivity, behavioral disinhibition, low frustration tolerance associated with antisocial and borderline PDs.
- **Attachment problems** Disorganized attachment patterns linked to borderline PD.
- **Childhood psychopathology** Disruptive behavior disorders linked to antisocial PD; anxiety disorder linked to paranoid, histrionic and obsessive compulsive PD.
- **Personality traits in adolescence** Paranoid, borderline and narcissistic traits linked to antisocial behavior in adulthood.
- **Environmental factors** Physical, sexual, verbal abuse and neglect in early childhood, low socioeconomic status.
- **Family factors** Single parent families, death of parent, family conflict.
- **Parenting factors** Parental psychopathology, parent substance abuse and criminal behavior, maternal over control or lack of closeness to parent.

### Delinquency

The term *delinquent* typically refers to a juvenile (a person below 18 years of age) who has committed an act which would be considered a criminal offence. While the term delinquency seems synonymous with crime and the legal system, it is important to remember that *delinquent acts* are quite commonly seen in adolescents. Adolescence is a period of accomplishing the task of autonomy versus dependency. In the process of establishing their self-identity, adolescents can often become rebellious and commit delinquent acts. Delinquency therefore needs to be considered in the context of its frequency, severity and persistence in an adolescent. While studies have shown that about 60–80% of adolescents may have engaged in some sort of juvenile offence, most of these offences are nonviolent or status offences which may have occurred infrequently and only during the adolescent period. However, delinquent acts can also be violent in the form of weapon use, physical aggression, homicide, arson and sexual offences.

### Epidemiology

While prevalence rates of delinquent acts in youth have been documented in other countries, the same in India have not been clearly studied. It has however been seen that when compared to the high prevalence of the behavior, only a small number have been violent offences (approximately 10%), with a higher prevalence of these being in male adolescents. Western studies

have shown higher prevalence in certain noncaucasian youth and ethnic minorities. Most of the reports on delinquency have found peak incidences in late adolescence.

### Risk Factors

Multiple risk factors have been implicated in the development of antisocial behaviors at individual, family and community levels. While numerous socioeconomic variables have been identified with implications for policy initiatives, there is also a higher prevalence of psychiatric disorders which have been associated with delinquency.

These include conduct disorders, ADHD, learning disability and substance abuse. While other psychiatric disorders like mood disorder and psychosis have been identified in delinquency, their overall prevalence is low compared to the disorders listed above. Other risk factors identified include lower socioeconomic status, high crime neighborhoods, male gender, negative life events/childhood trauma, poor social support, poor parental supervision and domestic violence.

### Interventions

Ideal interventions for delinquency should be able to address the issue at primary, secondary and tertiary levels of care.

- **Primary level** Interventions at the primary level would be those that would reduce the incidence of delinquent behavior in those who had not yet developed it. Most primary level interventions would therefore involve policy initiatives addressing social risk factors, parenting based training programs and school based programs involved with life skills training.
- **Secondary level** Intervening with adolescents who have started getting into delinquent patterns of behavior through school and parent based programs. Most of the evidence for these is from multisystemic interventions at individual, family and community levels.
- **Tertiary level** Interventions at this stage address juveniles who have been convicted by the legal system. The primary legal framework for juvenile justice in India is the Juvenile Justice Act 2000, which addresses the prevention and treatment of juvenile delinquency and also provides guidelines for the protection and rehabilitation of children who are under the juvenile justice system.

Mental health is an often neglected area of adolescent health. According to a recent UNICEF report, nine out of ten of the 1.2 billion adolescents in the world live in developing countries and 20% are from India. While there are many factors which affect the mental health of adolescents, these need to be addressed through preventive interventions in a large way in developing countries in order to reduce the overall morbidity and mortality associated with disorders which can subsequently develop.

### IN A NUTSHELL

1. Mental health is defined as the successful performance of mental function, resulting in productive activities, fulfilling relationships with other people, and the ability to change and to cope with adversity.
2. *There are 3 main determinants of mental health* Individual attributes, social circumstances and environmental factors. These three determinants can act and interact as adverse factors or as protective factors.
3. Adolescent mental well-being is affected by peer pressure, bullying, and stress.
4. Major mental health problems in adolescents include depression, anxiety, substance abuse and behavior disorders.
5. Mental health problems need to be addressed through preventive interventions to reduce the overall morbidity of these problems in adolescents.

## MORE ON THIS TOPIC

- Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. *Psychiatr Clin North Am.* 2009;32(3):483-524.
- Gowers SG. *Adolescent psychiatry in clinical practice.* 1<sup>st</sup> ed. London: Arnold; 2001.
- Griswold KS, Aronoff H, Kernan JB, Kahn LS. Adolescent substance use and abuse: recognition and management. *Am Fam Physician.* 2008;77(3):331-6.
- Henggeler SW, Sheidow AJ. Empirically supported family-based treatments for conduct disorder and delinquency in adolescents. *J Marital Fam Ther.* 2012;38(1):30-58.
- Lal R. *Substance Abuse Manual for Physicians.* New Delhi:AIIMS; 2005.
- Leiner M, Dwivedi AK, Villanos MT, *et al.* Psychosocial profile of bullies, victims, and bully-victims: a cross-sectional study. *Front Pediatr.* 2014;2:1.
- Malhi P, Bharti B, Sidhu M. Aggression in Schools: Psychosocial Outcomes of Bullying Among Indian Adolescents. *Indian J Pediatr.* 2014.
- Merikangas KR, Nakamura EF, Kessler RC. Epidemiology of mental disorders in children and adolescents. *Dialogues Clin Neurosci.* 2009;11(1):7-20.
- Tsitsika AK, Barlou E, Andrie E, *et al.* Bullying behaviors in children and adolescents: "an ongoing story." *Front Public Health.* 2014;2:7.
- World Health Organization. Risks to mental health. Available from: URL:[http://www.who.int/mental\\_health/mhgap](http://www.who.int/mental_health/mhgap). Accessed Aug 1, 2014.

## Chapter 25.4

# Injuries, Violence and Suicide

Srikanta Basu

Every year, millions of children all over the world die from preventable causes. Injuries and violence are responsible for a large majority of these causes. Causing more than five million deaths every year, violence and injuries account for 9% of global mortality and as many deaths as HIV, malaria, and tuberculosis combined. Young people are among the most vulnerable. Injury death rates are significantly higher in low and middle-income countries, which already account for more than 95% of the world's deaths from injuries and violence.

### IMPACT OF INJURIES

Worldwide, eight of the fifteen leading causes of death for people aged 15–29 years are injury related, including road traffic injuries, suicides, homicides, drowning, burns, war injuries, poisonings, and falls (**Table 1**). According to findings of 2010 Global Burden of Disease Study, injuries cost the global population some 300 million years of healthy life every year, causing 11% of disability-adjusted life years (DALYs) worldwide. Road-traffic crashes were the number one killer of young people and accounted for nearly a one-third of the world injury burden—a total of 76 million DALYs in 2010, up from 57 million in 1990.

**Table 1** Leading causes of death in children, both sexes, World, 2004

Rank	10–14 years	14–19 years
1.	Lower respiratory infections	Road traffic injuries
2.	Road traffic injuries	Self-inflicted injuries
3.	Drowning	Violence
4.	Malaria	Lower respiratory infections
5.	Meningitis	Drowning
6.	HIV/AIDS	Tuberculosis
7.	Tuberculosis	Fire-related injuries
8.	Diarrheal diseases	HIV/AIDS
9.	Protein-energy malnutrition	Leukemia
10.	Self-inflicted injuries	Meningitis

Source: WHO (2008), Global Burden of Disease: 2004 update.

Apart from the high death toll, injuries during childhood and adolescence are also associated with high morbidity—for every injured child who dies, several thousand more survive with varying degrees of disability. The impact on the society is tremendous—everyday, thousands of families are robbed of their children and thousands of children have to learn to cope with the consequences of their injury, which, in some cases, can be both long-lasting and profound.

### UNDERSTANDING INJURIES

#### Definitions

Injuries have traditionally been regarded as unavoidable *accidents*. Accident is defined as an unintended, unplanned event, independent of human will power. Whereas, injury may happen out of unintentional or intentional harm and is a degree predictable and largely preventable. Injuries are defined as *acute exposure to physical agents such as mechanical energy, heat, electricity, chemicals, and nonionizing radiation interacting with the body*

*in amount or rates that exceed the threshold of human tolerance*. Injuries are broadly classified into two types—as intentional (deliberately inflicted) or unintentional injuries (**Box 1**).

#### BOX 1 Classification of injuries

##### I. Intentional injuries

- Self-inflicted injuries (suicide)
- Interpersonal violence (homicide, sexual, child abuse)
- Collective violence (war)
- Other intentional injuries (legal intervention)

##### II. Unintentional injuries

- Road traffic injuries
- Drowning
- Poisoning
- Falls
- Burns
- Other unintentional injuries (firearm injuries)

### Setting of Injuries

Both intentional and unintentional injuries can also be categorized according to the place where they occurred, i.e., on the road, at home, at a leisure/sport facility, at school or in the workplace, or according to the circumstances in which they occurred, e.g., during working hours (occupational injury) or during leisure time.

### Indian Scenario

Injuries account for 9–10% of total mortality in India. The common causes of unnatural accidental deaths are—road traffic injuries (37.2%), poisoning (7.8%), drowning (7.8%), railway accidents and rail-road accidents (7.7%), and fire related deaths (6.8%). Age-wise, 6.9% of such victims were up to 14 years of age. There are hardly any published data on injuries and violence in the age group 10–19 years in India.

### Etiology

#### Why are Adolescents at Risk from Injuries?

Overall rates of injury and death increase dramatically from childhood to late adolescence. Due to developmental and social factors, such as time spent without adult supervision and increasing independence, adolescents are more likely to engage in risk-taking behaviors than either younger children or adults.

*Developmentally*, research over the past decade has found that parts of the frontal lobe, in particular, the prefrontal cortex which governs judgment, decision-making, reasoning and impulse control—appears not to fully mature until the age of 20 or 25 years making adolescents more likely to engage in risk-taking behaviors.

#### Risk-taking Behavior

Nearly 50% of the morbidity and mortality in adolescents stems from four behaviors: sexual activity, substance use and abuse, motor vehicle use, and interpersonal violence. These behaviors have their origin in adolescence, and is common among all age, socioeconomic and ethnic groups. All of these behaviors have a probability for negative outcome and share one common thread, i.e., risk taking tendency of the adolescents. Moreover, these behaviors continue in adult life and are responsible for some of the major causes of morbidity and mortality and are largely preventable. While young children may inadvertently take risks because they lack appropriate skills to do otherwise, older children and adolescents may actively seek out risk. Risk-taking behavior may allow adolescents to feel a sense of control over their lives or else to oppose authority. Research shows that there are high



levels of sensation-seeking behavior among young adults and that there exists a need to maintain a heightened level of physiological arousal. Young people consequently seek new situations and experiences to maintain this level, irrespective of the risks inherent in the experience.

Such sensation-seeking frequently focuses on risky behaviors, while driving a vehicle or crossing a road. Sensation-seeking has been shown to rise between the ages 9 years and 14 years, peaking in late adolescence or in early adulthood, and declining steadily with age. Risk-seeking behavior is a significant predictor of involvement in road traffic injury among child pedestrians as it is for young adolescent drivers aged 16–17 years. Across all ages and particularly among the young, sensation-seeking is more common among boys than among girls. Boys as young as 11 years have a greater affinity for speed, risk-taking and competitive behavior, all of which place them at an increased risk of road traffic injury. But it is also pertinent to remember that though injuries are a frequent and sometimes devastating outcome of risk taking, risks are also inherent in the environment in which adolescents live, work and play.

### Peer Influence

As young children become adolescents, they begin to discover and assert their independence. For many young people, peers are of significant importance and can be the primary source of the social norms with which they strive to conform. Social norms, including peer pressure and the emphasis placed on rebellion in the culture of young people, can affect the manner in which young people drive a vehicle. Research has shown that young drivers experience higher peer pressure than older drivers to commit traffic violations such as speeding, driving under the influence of alcohol and dangerous overtaking.

### Gender

Most studies show a strong male bias, with the male-to-female ratio ranging between 3:1 and 5:1. This relationship holds true across different regions of the world and applies to fatal and nonfatal injuries.

### Road Traffic Injuries

Speeding, drunk-driving, nonusage or improper usage of helmets, seat-belts and child restraints are the five most important risk factors that is consistently associated with fatalities and are largely preventable. An examination of the factors that contribute to injuries reveal that alcohol may be the single most important factor. Drinking and driving increases the risk of being involved in a crash, as well as the severity of resulting injuries. Driving may be impaired at very low levels of alcohol consumption, with the risk of crash involvement growing rapidly, as consumption increases. The effects of alcohol impairment are magnified when combined with fatigue. The other factors which might affect safe driving are consumption of other intoxicants, sleep deprivation, use of mobile or other gadgets. Use of mobile telephones while driving, increases the risk of crash four-fold. The risk is similar for both the hand held and hands free mobile set. Other factors, that may divert the attention of adolescents and have the potential to impact the safe driving texting, in-vehicle internet use, and on-board navigation systems. Two wheeler drivers (motorcyclists and bicycle drivers) are at increased risk of severe head injuries resulting from traffic injuries. Motorcyclists comprise a one-third of all road traffic deaths in the South-East Asia. Head and neck injuries are the main cause of severe injury, disability and death among motorcycle users.

The high incidence of adolescent traffic-related injury is due in part to lack of experience and lack of maturity. The fatal crash rate per km driven for 16–19-years-old is three times the risk for older drivers (age 60+), and fatal crash risk is highest at age 16. Crash

risk for both males and females is particularly high during the first months of driving and drops as young drivers accumulate more experience behind the wheel. One has to understand that many years of experience may be needed for adolescents to become proficient in driving. For example, young drivers may also lack experience to recognize, assess, and respond to the situation or hazards. They may be willing to accept higher levels of risks while walking, riding a bike, or driving a car or motorcycle. These risks may be fueled by emotions, peer pressure, and other adolescent stressors. These problems are further compounded by adolescent alcohol use.

### Drowning

Drowning is the process of experiencing respiratory impairment from unintentional submersion/immersion in liquid. Apart from mortality it may also result in nonfatal injury which may lead to brain damage and long term disability. Around 96% of unintentional drowning deaths take place in low- and middle-income countries. China and India have particularly high drowning mortality rates and together contribute 43% of the world's drowning deaths and 41% of the total global DALYs lost related to drowning. In India, the drowning deaths could be due to boat capsizing, swimming, recreational (during picnics and other outing). Males are especially at risk of drowning, with twice the overall mortality rate of females. Studies suggest that the higher drowning rates among males are due to increased exposure to water and riskier behavior such as swimming alone, drinking alcohol before swimming alone and boating. Increased access to water is another risk factor for drowning.

### PREVENTION OF INJURIES

The traditional model of injury prevention and control rests on managing three Es: *enforcement, education and engineering*. Multipronged strategies are required to control injuries and these strategies complement each other thereby amplifying the final effect. It involves changing the environment, individual behavior, products, social norms, legislation, policy, and ecology related to injury. Broadly it can involve several approaches.

#### Structural Strategies

Involve product modifications (such as machinery guards) and environmental changes (such as adding lifeguarding to pools and recreational water bodies, and building bike lanes, pool fencing) often afford the greatest protection to the population. *But the adolescent's individual choices and behaviors can often override these protections and in the end they do not have a desirable effect.* Moreover, these measures are costly or may not be feasible to implement.

#### Behavioral Approaches

Injury prevention education is the process of changing people's health directed behavior to reduce unintentional injuries. It is a very important component of the effective structural, automatic, environmental, or engineering protections. Effective injury prevention always involves both behavioral (active) and environmental (passive) countermeasures—it is never an either/or proposition. However, behavior education has its limitation as it is difficult to bring about a desired change and the successful outcome is difficult to measure.

#### Legislation and Policy Approaches

Although adolescent behaviors can be changed by introducing a law or policy that mandates compliance—such as requiring protection when operating industrial machinery or requiring helmet use—legislation must be *supported by the public and enforced by local authorities*. Enforcement of legislation indicates state awareness of

the importance and urgency of problem. However in LMICs, laws around the injuries are inadequate and rarely proactive. Other policy approaches that have proven effective for preventing motor vehicle injuries among adolescents as well as other drivers include primary seat belt use laws (where one can be cited for nonuse as a primary offense), enhanced police enforcement, blood alcohol level laws, minimum legal drinking age 21 laws, sobriety checkpoints, and zero tolerance laws for young and inexperienced drivers. Policy changes that discourage early adolescent driving, such as rising insurance costs, expensive driving schools, and GDL laws, have already reduced the proportion of 16-year-olds who hold a driver's license from nearly 43.8% in 1998 to 29.8% in 2006 in US.

### Ecological Approaches

The most effective injury prevention efforts are structured within an ecological framework, focusing on individual modifiable factors, family, peer group, work site, and community and sociocultural factors simultaneously. For example, legislation requiring bicycle helmet use should be accompanied by an educational campaign for children and parents, police enforcement in the community and discounted sales of helmets by local merchants. Ecological approaches emphasize tailoring specific interventions to the cognitive and physical skills of adolescents and to the social world in which they live. Local enforcement of laws designed to protect adolescents is an important ecological factor in prevention. Significant overlap exists among these strategies. Ecological changes have an influence on legislation and behavior; structural changes have an effect on behavior and ecology. Legislative changes affect behavior, structures, and ecology and they work best when combined.

### Preventing Road Traffic Injuries

As per the Global action plan for road safety, 2013 designed by UN general assembly, the 5 pillars that guide national road safety plans and activities over the decade of action are— Road safety management; Safer roads and mobility; Safer vehicles; Safer road users; and Post-crash response.

A significant proportion of patients who sustain a road traffic injury incur permanent disability, through amputation, head injury or spinal cord injury. Access to pre-hospital services and quick evacuation and transport to hospital can save many lives and limit disability, since majority of these who die do so before they reach a hospital. Moreover, health care providers should be appropriately trained in emergency medical care, which is not the case in many low- and middle-income countries (LMICs) including India.

A number of effective strategies would, if implemented, reduce motor vehicle-related injuries in adolescents. Among the most important strategies are graduated licensing, safety belt and helmet use. Wearing a standard, good quality motorcycle helmet can reduce the risk of death by 40% and the risk of serious injury by over 70%. Seat belt usage protects the driver and the occupants from severe crash injuries. It reduces the risk of a fatal injury by up to 50% for front seat occupants, and up to 75% for rear seat occupants. Proper use of bicycle helmets can eliminate 65–88% of bicycle-related brain injuries and 65% of serious injuries to the face. Building a culture of safety for seat belts and helmet-wearing among adolescents with enforcement and education, has proven to be the most effective strategy.

One proven method for helping teens to become safer drivers is graduated driver licensing (GDL) which is prevalent in many developed countries. GDL systems work because they directly target the risk factors by giving newly licensed adolescent drivers experience under low-risk driving conditions. Many of these strategies have been successfully implemented within the context of parent management of teen driver intervention conducted within driver education.

### Prevention of Drowning

Victims of drowning have a very slim chance of survival after immersion. The victim loses consciousness after approximately 2 minutes of immersion and irreversible brain damage can take place after 4–6 minutes. Therefore, prevention strategies are more important.

Drowning prevention strategies should be comprehensive and include— engineering methods which help to remove the hazard, legislation to enforce prevention and assure decreased exposure, education for individuals and communities to build awareness of risk and to aid in response if a drowning occurs. Availability of properly-fitted and appropriate personal flotation devices, non-consumption of alcohol while boating and swimming appear to be effective drowning prevention strategies. Individual and community education on drowning awareness, risks associated with drowning and learning water survival skills appear promising strategies to prevent drowning. Similarly, ensuring the presence of lifeguards at swimming areas also appears to be a promising strategy to prevent drowning. Ensuring immediate resuscitation by increasing the capability of first responders to provide first aid in cases of drowning can decrease the potential severity of outcomes.

### VIOLENCE

Violence by young people is one of the most visible forms of violence in society. The main victims and perpetrators of such violence, almost everywhere, are adolescents and young adults. The World Health Organization defines violence as: *The intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation.* The definition used by the World Health Organization associates intentionality with the committing of the act itself, irrespective of the outcome it produces.

Youth violence deeply harms not only its victims, but also their families, friends and communities. The problem of youth violence cannot be viewed in isolation from other problem behaviors. They also often display other problems, such as truancy and dropping out of school, substance abuse, compulsive lying, reckless driving and high rates of sexually transmitted diseases. However, not all violent youths have significant problems other than their violence and not all young people with problems are necessarily violent. There are close links between youth violence and another forms of violence. Witnessing violence in the home or being physically or sexually abused, for instance, may condition children or adolescents to regard violence as an acceptable means of resolving problems. Prolonged exposure to armed conflicts may also contribute to a general culture of terror that increases the incidence of youth violence. Understanding the factors that increase the risk of young people being the victims or perpetrators of violence is essential for developing effective policies and programmes to prevent violence.

### Epidemiology

In 2000, an estimated 1.6 million people worldwide died as a result of self-inflicted, interpersonal or collective violence, for an overall age-adjusted rate of 28.8 per 100,000 population. Nearly half of these 1.6 million violence-related deaths were suicides, almost one-third were homicides and about one-fifth were war-related. Though there is paucity of data on violence, especially in adolescents in India it has been reported in some studies. A school study from Chandigarh illustrates these facts: two-third of adolescents witnessed violence in life, 80% witnessed someone being bullied, 28% witnessed violence being caused by rods or sticks; 27% of subjects were victim of violence; 13% of subjects were perpetrators of violence. National study on child abuse (2007) found

that nearly every other boy and girls faced sexual abuse at least once. There is gross under-reporting of violence in our set up, though it is being reported almost daily in media in every part of India.

### Nonfatal Violence

Studies of nonfatal violence reveal that for every youth homicide there are around 20–40 victims of nonfatal youth violence receiving hospital treatment. As with fatal youth violence, the majority of victims of nonfatal violence treated in hospitals are males. The rates of nonfatal violent injuries tend to increase dramatically during midadolescence and young adulthood. Compared with fatal youth violence, nonfatal injuries resulting from violence involve substantially fewer firearm attacks and a correspondingly greater use of fists and feet, and other weapons, such as knives or clubs.

### Gender Based Violence: Indian Context

Girls are subjected to worse form of violence as documented by some of the Indian studies (**Box 2**). Violence against girls may range from emotional, (teasing, spreading rumors, humiliating, threatening) physical (slapping, beating, burning, murder) sexual (by manipulation, threats or physical force). Many of these forms of violence are under reported as they may take place amongst families or close relationship. Violence against girls can have serious health consequences to the girl or her future generation. It has been shown that young women who has experienced physical or sexual violence in married life has 1.5 times more chance of aborting compared to one who had not had similar experience.

#### BOX 2 Violence against girls in India

- 1 in 5 girls aged 15–19 who experienced sex before marriage were forced to engage in sexual behavior
- 1 in 3 married girls aged 15–19 have experienced emotional, physical and sexual violence from their husbands
- 2 in 5 women who were commercially exploited were minor girls.

### Forms of Violence

Violence can be *nonphysical*, i.e., verbal harassment, bullying or intimidation, verbal coercion, or expression in the form of body language, staring, glaring, gesturing, blocking access to entry or escape). The other form is *Physical*—sexual (abuse, incest, assault, rape), on sexual (hitting, kicking, biting, choking, punching, grabbing, pulling hairs or other body parts, with a weapon in the form of object like gun, knife, and stick or with hand, feet head, etc.

The WHO report places youth violence in a model within the context of three larger types of violence: self-inflicted, interpersonal, and collective. *Interpersonal violence* is subdivided into violence largely between family members or partners and includes child abuse. *Community violence* occurs between individuals who are unrelated. *Collective violence* incorporates violence by people who are members of an identified group against another group of individuals with social, political, or economic motivation. The types of violence in this model have behavioral links, in that child abuse victims are more likely to experience violent and aggressive interpersonal behavior as adolescents and adults. Overlapping risk factors exist for the types of violence, such as firearm availability, alcohol abuse, and socioeconomic inequalities. The benefit of identifying common risk factors for the types of violence lies in the potential of intervening with prevention efforts and gaining positive outcomes for more than one type of violent behavior. The model further acknowledges four categories that explore the potential nature of violence as involving *physical, sexual, or psychologic force, or deprivation*. Whereas, no model violence is universally acceptable, but WHO model does provide a useful

framework for understanding the complex patterns of violence taking place around the world, as well as violence in the everyday lives of individuals, families and communities.

### Etiology

Aggressive behavior and violence are interlinked. Some children exhibit problem behavior in early childhood that gradually escalates to more severe forms of aggression before and during adolescence.

### Life-Course Persistent Offenders

This group of adolescents commit the most serious violent acts and often continues their violent behavior into adulthood. Several longitudinal studies have shown that childhood aggression is a good predictor of violence in adolescence and early adulthood. In other words, those who are relatively more aggressive at a given age also tend to be relatively more aggressive later on, even though their absolute levels of violence may vary. There may also be progressions over time from one type of aggression to another. For instance, in a longitudinal study in Pittsburgh, PA, United States, of over 1500 boys originally studied at 7, 10 and 13 years of age, Loeber et al. reported that childhood aggression tended to develop into gang fighting and later into youth violence.

### Adolescence-limited Offenders

This group is relatively common. These young people engage in violent behavior over much shorter periods and show little or no evidence of high levels of aggression or other problem behaviors during their childhood. Majority of the violent youths belong to this group and they tend to discontinue their violent behavior after 1–3 years.

### Factors Contributing to Violence

Violence is learned behavior and cultural and social influences play a significant role in many of these intentional injuries. Some of the important factors contributing to violence in youth are enlisted in **Box 3**. The link between severe mental disorders and violent behavior are more closely linked for those with co-occurring alcohol or substance abuse or dependence. Moreover, inability to maintain proper social skills like establishment and maintenance of positive family and peer relations and poor resolution of conflict may put adolescents with these mental disorders at a high risk of physical violence. Some of the psychiatric disorders like *conduct disorder* and *oppositional defiant disorder* are also associated with violent behavior.

### Approach and Management

The medical personnel dealing with adolescents need to know how to screen, identify, treat and refer violence victims. Additionally, they should be familiar with the community programs available in the locality. The assessment of adolescent at risk or with history of violent behavior or victimization should be a part of the health maintenance visit of all adolescents. If there is any history of involvement in physical fight, carrying a weapon or if there are concerns about safety issues (HEADSS questionnaire), one should do more in depth analysis. The FIST's mnemonic (**Box 4**) is a very useful assessment tool for these kind of cases. One should not hesitate to take the help of a mental health professional if there is presence of any of these risk factors: substance use, physical or sexual abuse, consistent poor school performance, multiple incidents of trauma or encounter with law, or feature suggestive of mental health disorders.

The primary responsibilities of the attending clinician is two-fold: firstly to provide immediate medical care and secondly to ensure the safety and welfare of the adolescent. It has been broadly outlined in **Box 5**. Overall it requires lot of careful handling, sensitivity, empathy, and skill to manage these kind of cases. A very good description in structured format is given in the *job aids*



manual by WHO which can be accessed at [http://www.who.int/maternal\\_child\\_adolescent/documents/9789241599962/en/](http://www.who.int/maternal_child_adolescent/documents/9789241599962/en/).

Apart from initial stabilization after injury, the other steps in the management are evaluation and treatment of injury, evaluation

### BOX 3 Factors contributing to violence

- Poverty
- Gender
- Developmental issues (preoccupation with oneself, own appearance and image)
- Environment (violence at home, school)
- Interpersonal relations with family, friends and peers
- Poor school performance
- Absence of role models/mentors
- Substance abuse; childhood abuse
- Past history of violence or victimization
- Poor family functioning
- Media violence
- Mental health disorders (mental retardation, learning disabilities, ADHD and mood disorders)
- Other risk factors (use of anabolic steroids, gang tattoos, belief in one's premature death, preteen alcohol use, placement in juvenile delinquent centers)

### BOX 4 FISTS mnemonic to assess adolescents at risk of violence

**F: Fighting** (how many fights you had in last year? Which was the last?)  
**I: Injuries** (have you ever been injured? Have you ever injured someone else?)  
**S: Sex** (Has your partner hit you? Have you hit your partner? Have you ever been forced to have sex?)  
**T: Threats** (Has someone with a weapon threatened you? What happened? Has anything changed to make you feel safer?)  
**S: Self-defense** (What will you do if someone tries to pick a fight? Have you carried weapon in self-defense?)

Adapted from Knox L: American Medical Association 2002.

### BOX 5 Management of violence and assault in adolescents

- Prepare yourself and health facility to manage adolescents who have been assaulted
- Take a history
  - General medical history; detailed history of assault
  - Gynecological history (in case sexual assault in females)
- Physical examination
  - General physical examination
  - Genitoanal examination (in case sexual assault in males and females)
- Provide treatment
  - Physical violence
  - Sexual violence
- Record your findings and treatment provided
- Assess and ensure ongoing safety
- Provide information on findings of examination and treatment
- Arrange counseling and social support
- Arrange referrals if needed
- Arrange for follow-up visit

Adapted from adolescent job aid—a handy desk reference tool for primary level health workers: WHO; 2010.

of assault circumstances, psychological evaluation and support, treatment plan at discharge that is directed to protect the teenager from similar injuries, and minimize development of psychological disability. One has to remember that victims as well witness of violence are at risk for post-traumatic stress disorder, and future aggressive or violent behavior.

Apart from being sensitive toward the adolescent, the physician should be aware of the legal aspect of managing these cases as well, and if required should inform police as required by law. Depending upon the situation, the family, or the care taker, or the child welfare committee of the district or the child helpline can be contacted. Precautions should be taken while dealing with an adolescent who is a victim of violence including sexual violence. A detailed verbatim hand written history from the child and accompanying person mentioning the date, time, place, witness and other details of other history should be taken. For medical examination, a consent should be taken from the child or the parents and it should be done preferably by the doctor of same sex. Diagrammatic representation of anatomic parts and the injuries should be recorded along with the detailed general physical examination. Appropriate samples should be collected depending on the form of violence/abuse. The record should be kept confidential at a secured place. The cases of sexual or child abuse should be dealt by specially trained teams. The medical officer (MO) should be aware of Protection of Children from Sexual Offences Act 2012 (POSCO) while dealing with the cases of child abuse. For persistent violent and aggressive behavior multiple treatment modalities varying from cognitive behavioral therapy involving the individual and the family and pharmacotherapy are used simultaneously.

## Prevention

The most common interventions against youth violence seek to increase the level of protective factors associated with individual skills, attitude and beliefs. As per WHO report, broadly four types of approaches viz: individual, relationship, societal and community can be used for prevention.

- **Individual approaches** Concentrate on children as well as youths who have already displayed some violent tendencies by changing their attitudes and behaviors to avoid aggressive and violent behavior.
- **Relationship approaches** Focus on the family members of the victim, especially those with the potential to trigger aggressive or violent responses.
- **Community-based approaches** Raise public awareness in an effort to stimulate action by community members to reduce violence and protect vulnerable community members.
- **Societal approaches** Include broader advocacy and legislative actions, as well as societal and cultural environmental changes. Ideally prevention should start from the beginning and these are age group directed preventive measures as advised by WHO.

## SUICIDE AND SELF-HARM

Self-harm and suicide are major public health problems in adolescents, with rates of self-harm being high in the teenage years and suicide being the second most common cause of death in young people worldwide. Pediatricians and primary care providers should ask about depression and suicidal ideation at each adolescent visit and must be comfortable assessing suicide risk and knowing when to refer children and adolescents for mental health care.

### Self-Harm

Self-harm refers to intentional self-poisoning or self-injury, irrespective of type of motive or the extent of suicidal intent. Methods of self-injury are heterogeneous, including acts such



as self-cutting, jumping from heights and self-battery ingestion, with some authors also including nonrecreational risk taking. Self-harm (and suicide) in adolescents are the end products of a complex interplay between genetic, biological, psychiatric, psychological, social, and cultural factors (**Box 6**). Although international variation exists, findings from many community-based studies show that around 10% of adolescents report having self-harmed, of whom some will report some extent of suicidal intent underlying their self-harm. Such studies consistently show that self-harm is more common in female adolescents than in male adolescents. Presentation to hospital occurs in only about one in eight adolescents who self-harm in the community, being more common in those who take overdoses.

#### BOX 6 Risk factors for self-harm and suicide in adolescents

##### Sociodemographic and educational factors

- Sex (female for self-harm and male for suicide)—most countries\*
- Low socioeconomic status\*
- Lesbian, gay, bisexual, or transgender sexual orientation
- Restricted educational achievement\*

##### Individual negative life events and family adversity

- Parental separation or divorce\*
- Parental death\*
- Adverse childhood experiences\*
- History of physical or sexual abuse
- Parental mental disorder\*
- Family history of suicidal behavior\*
- Marital or family discord
- Bullying
- Interpersonal difficulties\*

##### Psychiatric and psychological factors

- Mental disorder\*, especially depression, anxiety, attention deficit hyperactivity disorder
- Drug and alcohol misuse\*
- Impulsivity
- Low self-esteem
- Poor social problem-solving
- Perfectionism
- Hopelessness\*

All the factors in the panel have been shown to be related to self-harm.

\*Shown to be related to suicide.

Adapted from Self-harm and suicide in adolescents By Hawton K, Saunders KEA, O'Connor RC. Self-harm and suicide in adolescents the lancet.com. 2012;379:2373-82.

## Epidemiology

World Health Organization estimates that nearly 900,000 people worldwide die from suicide every year, including about 200,000 in China and 170,000 in India. Global figures for suicide in the age group of 10–24 show that suicide is the second most common cause of death after road-traffic accidents—it is the third most common cause of death in male adolescents (after road-traffic accidents and violence). Globally, suicide is the most common cause of death in female adolescents aged 15–19 years. Suicide is uncommon before 15 years of age but increases in prevalence through adolescence (19.2 deaths per 100,000 male adolescents aged 15–24 years) and into adulthood (28.3 deaths per 100,000 men aged 25–34 years). A recent study by Patel et al. on *suicides in India* published in *Lancet* in 2012 present some interesting facts: About 3% of the surveyed deaths (2684 of 95,335) in individuals aged 15 years or older were due to suicide, corresponding to about 187,000 suicide deaths in India in 2010 in these ages. For suicide deaths at ages 15 years or older, 40% of suicide deaths in men (45,100 of 114,800) and 56% of suicide deaths in women (40,500 of 72,100) occurred at ages 15–29 years. A

15-year-old individual in India had a cumulative risk of about 1.3% of dying before the age of 80 years by suicide; men had a higher risk (1.7%) than did women (1.0%), with especially high risks in south India (3.5% in men and 1.8% in women). About half of suicide deaths were due to poisoning (mainly ingestions of pesticides), followed by hanging, burns and drowning. Overall the reported cases of suicide are just the tip of the iceberg, the actual number may be much higher.

## Etiology

Experts emphasize the presence of few predisposing factors, viz biological (e.g., serotonin imbalances), personality (e.g., perfectionism, impulsivity), and cognitive vulnerabilities (e.g., impaired social problem solving) combined with exposure to negative life events, including both early and recent life adversity, and psychiatric disorders to increase risk of self-destructive behaviors across the lifespan. The outcome could be due to further interplay between factors associated with the development of thoughts of self-harm or suicide (e.g., feeling defeated and trapped) and those that increase the likelihood that such thoughts will be translated into actual suicidal behavior (e.g., impulsivity, exposure to self-harm by others).

## Management

The vast majority of children and adolescents who complete suicide have some form of psychiatric illness. Assessment of suicidal ideation should be a part of each health visit in adolescence (HEADSS questionnaire). There is no evidence that discussing suicide with patients increases the likelihood that they will harm themselves. There is evidence that suicidal persons who seek medical care do not discuss suicidal thoughts, symptoms of depression, or patterns of drug use, unless specifically asked.

The first step of *suicide assessment* is that suicidal ideation should not be taken lightly. If a suicidal threat is labeled manipulative, power or control becomes a major issue influencing behavior, and the risk of suicide may increase. In the case of the adolescent who is seen after a suicide attempt, a thorough history regarding ingestion (including drug and alcohol) is necessary, and aggressive management of poisoning must be implemented as indicated.

The next step of suicide assessment is that the child or adolescent must be understood within the framework of biopsychosocial factors. A careful psychiatric history and a mental status examination are necessary to assess the risk of suicide completion. Pediatricians who are uncomfortable with psychiatric assessment should seek immediate consultation with a mental health professional. Signs and symptoms of mood disorders, conduct problems, chronic anxiety, or substance abuse suggest the need for intervention and indicate a risk of eventual suicide completion. Previous suicide attempts should also be documented. To identify precipitating events, the physician should carefully explore, in detail, the child's life during the 2–3 days before either the threat or the suicide attempt. When a suicidal patient has been seen in the physician's office, the physician should inform the parents and a psychiatric consultation should be obtained (*no-suicide contract* comes to play) with the patient. The parents should be notified. As many clients resist psychiatric consultation, the pediatrician should try and schedule a psychiatric consultation as early as possible. If possible, the patient should be admitted and adequate evaluation should be made of the patient's frame of mind and the family or environmental circumstances. The physician must pay careful attention to how the family and friends have responded to the patient's act. A hostile and angry family, as is frequently seen, necessitates a different disposition or resolution than a supportive, sympathetic, and understanding family. Some families may completely deny the seriousness of the behavior; this can be discouraging and provocative to the patient, whose act has been an attempt to compel a different response. Family members

should be counseled to examine their roles in the interactions that preceded the attempt, without being made to feel overly guilty. Psychiatric hospitalization is indicated when the individual continues to be actively suicidal, when he or she is found to have a major psychiatric disorder, or when major family problems complicate his or her ongoing protection.

### Prevention

Approaches (**Box 7**) to prevent self-harm and suicide can be divided into population-based measures, which are aimed at all young people (e.g., educational initiatives), and measures aimed at high-risk groups (e.g., individuals with a history of abuse, those who self-harm). Restriction of access to means for suicide is a key suicide prevention strategy in adolescents, especially because of the often impulsive nature of the behavior. For example, safe storage of pesticides in rural areas of developing countries, where ready availability means that suicide by pesticide ingestion is common.

#### BOX 7 Approaches to prevent self-harm and suicide in adolescents

##### Population measures

- School-based psychological well-being and skills training programmes
- Gatekeeper training (e.g., school teachers, peers)
- Screening to identify those who might be at risk
- Restriction of access to means used for self-harm and suicide
- Improved media reporting and portrayal of suicidal behavior
- Encouragement of help-seeking behavior
- Public awareness campaigns
- Help-lines
- Internet sources of help
- Reduction of stigma associated with mental health problems and help seeking.

##### Measures for at-risk populations

- Psychosocial interventions for adolescents at risk of self-harm or suicide (e.g., depressed adolescents, abused individuals, runaway children)
- Screening of those at risk (e.g., young offenders)
- Psychosocial interventions for adolescents who have self-harmed
- Pharmacotherapeutic interventions for adolescents at risk of self-harm or suicide.

Adapted from Hawton K, Saunders KEA, O'Connor RC. Self-harm and suicide in adolescents the lancet.com. 2012;379:2373-82.

### IN A NUTSHELL

1. Violence and injuries account for 9% of global mortality causing more than five million deaths every year.
2. Nearly 50% of the morbidity and mortality in adolescents stems from four behaviors: sexual activity, substance use and abuse, motor vehicle use, and interpersonal violence.
3. Adolescents are more likely to engage in risk-taking behaviors because judgment, decision-making, reasoning and impulse control do not fully mature until 20–25 years of age.
4. Adolescents are the prime population involved in road traffic injuries. Speeding, drunk-driving, improper usage of helmets, not wearing seat-belts are the most important risk factors.
5. Youth violence deeply harms its victims, and their families, friends and communities.
6. Girls are subjected to worse form of violence as documented by some of the Indian studies.
7. Adolescents are frequently involved in interpersonal and self-inflicted violence (including suicides).
8. Suicides in adolescents are the end products of a complex interplay between genetic, biological, psychiatric, psychological, social, and cultural factors.
9. The medical personnel dealing with adolescents need to know how to screen, identify, treat and refer violence victims.
10. The most common interventions against youth violence seek to increase the level of protective factors associated with individual skills, attitude and beliefs.

### MORE ON THIS TOPIC

- Accidental Deaths and Suicides in India. New Delhi: Crime Records Bureau, Ministry of Home Affairs, Government of India; 2010.
- Global Status Report on Road Safety: Supporting a Decade of Action. Geneva: World Health Organization; 2013.
- Hawton K, et al. Self-harm and suicide in adolescents. Lancet. 2012;379: 2373-82.
- World Report on Child Injury Prevention. Geneva: World Health Organization; 2008.

## Chapter 25.5

# Menstrual Disorders and Polycystic Ovary Syndrome

Amita Suneja, Richa Aggarwal

Menstrual disorders are a common problem in adolescents. Studies have shown worldwide that approximately 25% of girls have significant menstrual dysfunction affecting life activities and resulting in school absence. These disorders are often the source of anxiety for the patients and their families. The common menstrual disorders in adolescents include amenorrhea, abnormal/excessive uterine bleeding, dysmenorrhea and polycystic ovary syndrome (PCOS). In the adolescent clinic of our hospital in Delhi which is a tertiary center, 68% of girls attending the clinic presented with menstrual disorders, of which amenorrhea was the most common complaint (22% with primary amenorrhea and 11% with secondary amenorrhea), followed by oligomenorrhea (28%), menorrhagia with or without polymenorrhea accounted for 24% of cases, 10.6% of patients had dysmenorrhea and 2.8% girls presented with cryptomenorrhea.

### AMENORRHEA

The absence of menses in a girl of reproductive age is defined as amenorrhea, and is divided into *primary* and *secondary* types. Recently, the definition of primary amenorrhea has changed and an evaluation should be considered in the conditions given in **Box 1**. Secondary amenorrhea is defined as the absence of menses for 6 months in girls with previously irregular menstrual pattern, or in girls before the completion of the second gynecologic year. In girls with formerly regular cycles of 21–45 days, secondary amenorrhea is defined as the absence of menses for three consecutive months. The distinction between primary amenorrhea and secondary amenorrhea is somewhat arbitrary and there is a great deal of overlap. Any cause of secondary amenorrhea (including pregnancy) can also be a cause of primary amenorrhea. In general, however, for a patient with primary amenorrhea the suspicion should be high for the possibility of a chromosomal or structural abnormality.

#### BOX 1 Indications for evaluation of an adolescent for primary amenorrhea

- An adolescent who has not had menarche by 15 years of age
- An adolescent who has not attained menarche and more than 3 years have elapsed since thelarche
- An adolescent with no periods and no secondary sexual development by 13 years of age
- An adolescent with no periods by age 14 years
  - There is a suspicion of an eating disorder or excessive exercise
  - There are signs of hirsutism
  - There is suspicion of genital outflow obstruction

### Etiology

The common causes of amenorrhea in adolescents are listed in **Box 2**. In clinical practice, hypothalamic amenorrhea and PCOS are the most prevalent causes of amenorrhea in adolescents. However, the most common cause of primary amenorrhea in our series was tuberculosis which accounted for 20% of cases.

### Approach to Diagnosis

#### History

Presence of secondary sexual characteristics should be asked for specifically. History of any chronic illness, weight gain or loss,

#### BOX 2 Etiology of amenorrhea in adolescents

- *Hypothalamic*
  - Eating disorders
  - Immaturity of the HPO axis
  - Exercise-induced amenorrhea
  - Medication-induced amenorrhea
  - Chronic illness
  - Stress-induced amenorrhea
  - Tumor, irradiation
  - Kallmann syndrome
- *Pituitary*
  - Hyperprolactinemia
  - Prolactinoma
  - Craniopharyngioma
  - Isolated gonadotropin deficiency
- *Thyroid*
  - Hypothyroidism
  - Hyperthyroidism
- *Adrenal*
  - Congenital adrenal hyperplasia
  - Cushing syndrome
- *Ovarian*
  - Polycystic ovary syndrome
  - Gonadal dysgenesis (Turner syndrome)
  - Premature ovarian failure Ovarian tumor Autoimmune oophoritis
  - Surgical removal, chemotherapy, irradiation
- *Uterine*
  - Pregnancy
  - Androgen insensitivity Uterine adhesions (Asherman syndrome)
  - Müllerian agenesis
  - Genital tuberculosis
  - Cervical agenesis
- *Vaginal*
  - Imperforate hymen
  - Transverse vaginal septum
  - Vaginal agenesis

Abbreviation: HPO, Hypothalamic-pituitary-ovarian axis.

and exercise habits should be elicited. Sexual history should be obtained confidentially, because pregnancy is a rare but possible cause of primary amenorrhea and the most common cause of secondary amenorrhea.

Social stressors may contribute to primary or secondary amenorrhea, and should be sought. Patient should be asked specifically about the medications she is taking, including any antipsychotic medication, contraceptive use, and illicit drug use. The review of systems should include discussion of acne or unwanted hair growth, weight changes, mood changes, disordered eating attitudes and behavior, change in bowel habits, abdominal pain, headaches, visual changes, galactorrhea, athletic participation and vaginal discharge. Family history should focus on any potential endocrine disorders in first-order relatives, including thyroid disease, diabetes, PCOS, and infertility and any constitutional delay of menses in siblings.

### Physical Examination

The physical examination of the girl presenting with amenorrhea begins with a general assessment including height, weight and body mass index (BMI calculation). Girls who are overweight are more likely to have an endocrinopathy (hypothyroidism, Cushing syndrome), whereas underweight patients may have a deficit of calories (eating disorder or bowel disease such as inflammatory bowel disease or celiac disease). The patient with exceptionally short stature with or without other features such as webbed neck,

widely spaced nipples, shield chest, and high arched palate, and primary amenorrhea points toward Turner syndrome (45,X) or mosaicism (46,XX/45,X).

Palpation of thyroid gland and Tanner staging of breast development and pubic hair has to be done. Breasts should be examined for presence of galactorrhea. A brief neurological examination may include an assessment of the ability to smell, fundoscopic examination and screening visual field tests by confrontation. The presence of hirsutism, acne and acanthosis nigricans should be looked for.

The gynecological assessment involves inspection of the external genitalia to determine if the girl has clitoromegaly and a normal hymenal opening and whether there is estrogen effect on the hymen and anterior vagina. Normal breast development and an estrogenized vagina implies ovaries are producing estrogen. To assess the patency and length of the vagina in a virgin patient, a saline moistened cotton-tipped applicator can be gently inserted into the hymen opening to assess the depth of the vagina (7–8 cm is average for a postpubertal young woman). In a patient with vaginal agenesis, the applicator can be inserted only 0.5–2 cm. If there is any question of anatomic abnormality, pelvic ultrasonography should be performed at an experienced center.

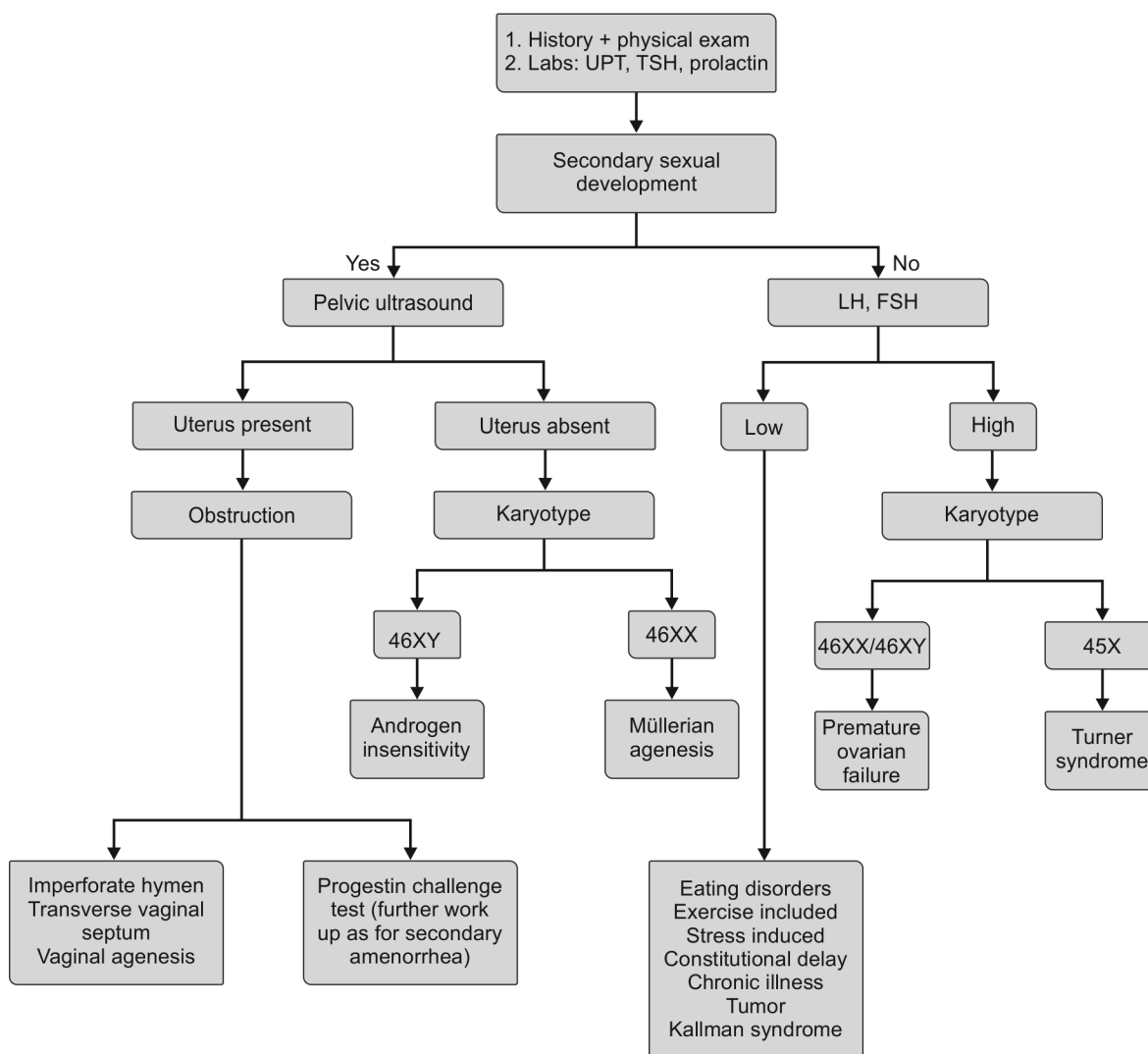
## Laboratory Evaluation

A sensitive pregnancy test must be part of the initial evaluation of any girl with amenorrhea, regardless of the reported sexual history. Thyroid-stimulating hormone (TSH) and prolactin (PRL) levels should be done in all patients, as amenorrhea may be the result of hyperprolactinemia or thyroid gland dysregulation which are readily correctable by treatment. Further evaluation of adolescents with primary amenorrhea depends upon the presence or absence of secondary sexual characteristics (**Flow chart 1**).

### Primary Amenorrhea and Absence of Secondary Sexual Characteristics

The assessment should begin with measurement of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Elevated gonadotropin levels imply that the cause of the delayed puberty lies within the gonads, while low or normal FSH and LH levels point to constitutional delay of puberty, pituitary dysfunction, or hypothalamic disorders. In patients with elevated gonadotropin levels, pelvic ultrasound imaging is done to see the presence of follicles in the ovaries, and the thickness of the endometrium. Absence of follicles in ovaries or small, streak gonads along with thin or atrophic endometrium suggests ovarian

**Flow chart 1** Diagnostic evaluation of primary amenorrhea



Abbreviations: UPT, urine pregnancy test; LH, luteinizing hormone; FSH, follicle stimulating hormone, TSH; thyroid stimulating hormone.



failure. Karyotype study will contribute in the differential diagnosis between ovarian failure, gonadal dysgenesis, Turner syndrome, and androgen insensitivity syndrome, as these are the commonest causes of primary amenorrhea with underlying chromosomal deficiencies. **Table 1** describes the various congenital syndromes leading to hypergonadotrophic hypogonadism.

### Primary Amenorrhea and Normal Pubertal Development

These girls should undergo rectoabdominal gynecologic examination and pelvic ultrasound to exclude the existence of a congenital anatomic defect of the outflow tract. Absence of uterus with absent or short vagina suggests Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome or testicular feminization syndrome, the differentiating features of which are given in **Table 2**. If the possibility of congenital malformations of the genital tract has been ruled out, further work up is similar to that for girls who experience secondary amenorrhea.

### Secondary Amenorrhea

The assessment of an adolescent patient should begin with pregnancy exclusion and be followed with search for signs of clinical hyperandrogenism (**Flow chart 2**). In the presence of clinical hyperandrogenism, FSH, LH, testosterone, and dehydroepiandrosterone sulfate (DHEA-S) should be measured and further investigations in the direction of PCOS or congenital adrenal hyperplasia are done. However, in patients with absence of clinical hyperandrogenism and in patients with clinical hyperandrogenism but with normal serum androgen levels, progesterone challenge test (PCT) should be performed with medroxyprogesterone 5–10 mg once daily or 200–300 mg daily micronized progesterone for 7–10 days to assess the levels of circulating estrogens and their effect on the endometrial function. If PCT is positive, indicates ovaries are normally producing estrogen and anovulation is the cause. The most likely diagnosis is either immaturity of the hypothalamic-pituitary-ovarian (HPO) axis if the patient is within 2–3 years of menarche. If PCT

is negative, challenge with sequential estrogen-progestin regime is given and if the patient does not bleed, endometrial dysfunction should be suspected. However, if the patient bleeds on estrogen-progestin, absence of estrogen is the cause which may be due to ovarian failure, pituitary failure or hypothalamic failure. Further measurement of FSH, LH is indicated.

If elevated FSH and LH levels are a persistent finding in several consecutive measurements, along with normal TSH and prolactin (PRL) levels, the most probable cause of the secondary amenorrhea is ovarian failure. When the above mentioned hormone levels are low or within the normal range, pituitary or hypothalamic causes are the probable etiologies.

### Management

While managing an adolescent patient with amenorrhea, the first and foremost thing is to alleviate anxiety by detailed counseling and reassurance. Therapy should be directed at treating the underlying cause of the amenorrhea, if possible. In girls with no pubertal development due to hypoenestrogenism either due to ovarian failure, hypopituitarism or hypothalamic disorders, estrogen therapy is given in three phases:

**Phase 1** For induction of breast development, generally lower doses are given (25 mcg estradiol patches, 0.3 mg of conjugated estrogens) and continued for 6–12 months. Oral contraceptives are not recommended for initial therapy, as they contain higher levels of estrogen, as well as progestin, throughout the cycle, which is not physiological.

**Phase 2** Establishment of normal menses, completion of breast development and acquisition of normal bone mass. The estrogen dose is increased (50 mcg estradiol patches, 0.625 mg of conjugated estrogens or 20 mcg ethinyl estradiol). A short course of progestin (5 or 10 mg medroxyprogesterone) may be added within 2–3 months of phase 2 for 5 days in a month along with continuous estrogen to give a predictable onset of menses. This dose of progestin is given only until breast development is completed (6–12 months) and then the progestin dose is increased to 10 days and ultimately to 12–14 days.

**Phase 3** Long term maintenance of a normal estrogen state, both estrogen and progestin are continued till the expected age of menopause. Estrogen (50–100 mcg estradiol patches, 0.625–1.25 mg of conjugated estrogens or 20 mcg ethinyl estradiol) daily plus progestin for 12–14 days each month or oral contraceptives are given. Most adolescents prefer monthly menses, and thus, progestin is prescribed monthly. Some adolescents like athletes prefer a minimum number of withdrawal menses and hence, can be prescribed daily estrogen cycled every 60–90 days with progestin for 14 days. If the girl is well estrogenized with anovulation as the cause of amenorrhea, menstrual cycles can be induced with cyclic progestins every 1–3 months.

In addition to hormone therapy, calcium and vitamin D supplementation daily should be advised. Exercise is also important for hypoenestrogenic adolescents to promote bone formation and cardiovascular fitness; however, it needs to be limited in girls with anorexia nervosa.

In anorexia nervosa, psychological and nutritional rehabilitation is associated with resumption of menses in approximately two-thirds of patients within one year. Administration of dopamine receptor agonists, like bromocriptine and cabergoline, is the treatment of choice for hyperprolactinemia.

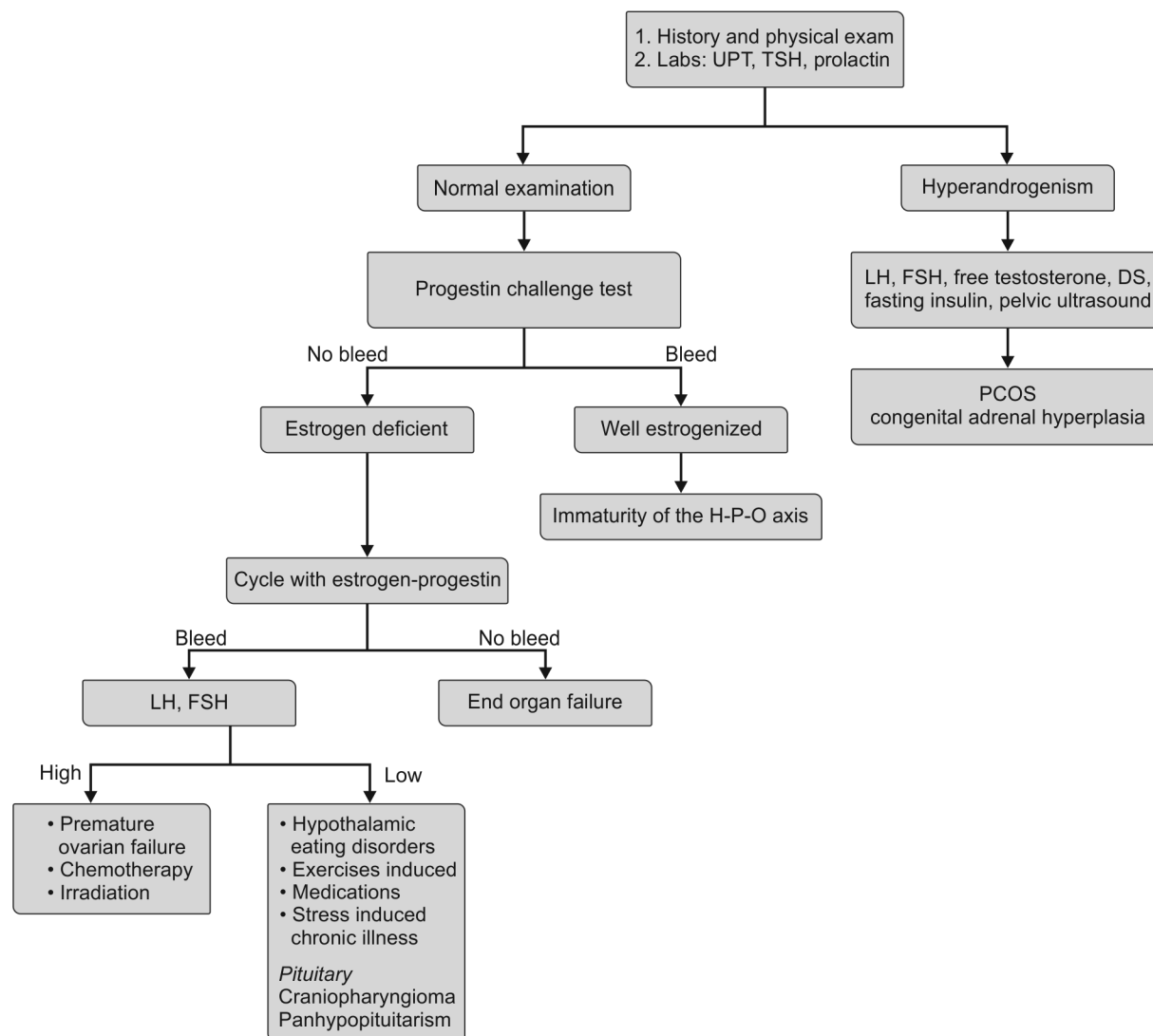
Surgical excision of the septum has to be done in cases of transverse vaginal septum. For patient with vaginal agenesis, use of manual dilators to create functional vagina can be done under supervision failing which, surgical creation of neovagina (vaginoplasty) is required so as to provide the girl the opportunity to have a normal sexual life. However, since patients of MRKH

**Table 1** Congenital syndromes of hypergonadotrophic hypogonadism

Syndrome	Karyotype	Clinical features
Turner syndrome	45 XO	Short stature, sexual infantilism, webbed neck, streak gonads
Swyer syndrome	46XY	Lack of sexual development, streak gonads, normal female testosterone
Pure gonadal dysgenesis	46XX	Premature menopause due to accelerated germ cell loss
Perrault syndrome	46XX	Neurosensory deafness
Mixed gonadal dysgenesis	45X/46XY	Streak gonad on one side, dysgenetic or normal testis on other side

**Table 2** Comparison of Mayer-Rokitansky-Küster-Hauser (MRKH) versus testicular feminization syndrome

Features	MRKH syndrome	Testicular feminization syndrome
Karyotype	46XX	46XY
Sexual hair	Normal female	Absent to sparse
Heredity	Not known	X-linked recessive
Testosterone levels	Normal female	Normal/slightly elevated
Other anomalies	Present	Rare
Risk of gonadal neoplasia	Not raised	Increased

**Flow chart 2** Diagnostic work-up of an adolescent with secondary amenorrhea

**Abbreviations:** HPO, hypothalamic-pituitary-ovarian axis; LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; PCOS, polycystic ovary syndrome.

syndrome have normal ovaries, they can have children by oocyte retrieval, fertilization of the egg in vitro, and a gestational carrier. Uterine transplantation is a viable option, but so far transplanted uterus has not delivered a viable fetus. The presence of Y chromosome in the karyotype requires gonadectomy as soon as the diagnosis is made because of the risk of development of neoplasia and the risk of virilization. However, in patients with testicular feminization, the surgery should be performed once puberty is achieved to allow for breast development and the attainment of the maximum expected adult stature. Estrogen replacement therapy should be given after gonadectomy.

## DYSMENORRHEA

Dysmenorrhea refers to recurrent, crampy lower abdominal pain that occurs during menstruation. Primary, or functional, dysmenorrhea is pain that occurs in the absence of pelvic disease and is more common as compared to secondary dysmenorrhea, which occurs secondary to a pathologic process.

## Etiology

The prevalence of dysmenorrhea among adolescent females ranges from 60% to 93%. Many adolescents report limitations of daily activities, such as missing school, sporting events, and other social activities, however, only 15% of females seek medical advice for menstrual pain, signifying the importance of screening all adolescent females for dysmenorrhea.

The symptoms are caused by prostaglandin E<sub>2</sub> and F<sub>2α</sub> (alpha) secretion or an elevated PGF<sub>2</sub> alpha: PGE<sub>2</sub> ratio. These compounds can cause dysrhythmic uterine contractions, hypercontractility, and increased uterine muscle tone leading to uterine ischemia.

## Clinical Features

### Primary Dysmenorrhea

It is usually associated with ovulatory cycles, hence presents in the second or third gynecologic year, however, it may occasionally accompany anovulatory cycles, especially if heavy bleeding and clots are present. The pain may be associated with headache,

nausea, vomiting, dizziness or diarrhea. The symptoms typically begin several hours prior to the onset of menstruation and continue for one to three days. The severity of the disorder depends upon the severity of menstrual pain, presence of systemic symptoms, and impact on daily activities.

### Secondary Dysmenorrhea

It usually develops years after menarche and can occur with anovulatory cycles and this may be associated with uterine and pelvic pathology such as intrauterine contraceptive device (IUCD), endometriosis, pelvic inflammatory disease (PID), cervical stenosis, a submucosal fibroid or an endometrial polyp. The pain often begins 1–2 weeks prior to menses and persists until a few days after the cessation of the bleeding.

### Approach to Diagnosis

#### History

A complete menstrual history, onset and duration of cramps, presence of nausea, vomiting, diarrhea, back pain, dizziness, or headache during menstruation, impact of symptoms on daily activities, medication taken for pain relief and their perceived effectiveness and sexual history should be taken.

In adolescents with dysmenorrhea from menarche that progresses steadily, obstructive genital tract abnormalities or endometriosis should be considered. Adolescents with history of pelvic infections may develop adhesions that result in pelvic pain, especially during menstruation.

#### Physical Examination

A pelvic examination is generally not required in adolescents presenting with typical symptoms of primary dysmenorrhea. However, if the history is suggestive of an organic disease or any congenital malformation of the genital tract, or if the patient does not respond to the conventional therapy of primary dysmenorrhea, a complete pelvic examination is indicated or a rectoabdominal examination is advised if the patient is virgin to exclude adnexal tenderness and masses. It is not uncommon to detect an abdominal lump in cases of Müllerian anomalies.

### Laboratory Investigations

Laboratory testing or imaging is not routinely required to make a diagnosis of primary dysmenorrhea. However, specific investigations may be ordered when secondary dysmenorrhea is suspected. For girls who suffer from dysmenorrhea refractory to first line therapy, or in whom pelvic examination is impossible or unsatisfactory, ultrasound may uncover a pelvic mass or an obstructing Müllerian malformation. Ultrasonography cannot detect subtle signs of organic diseases such as uterosacral ligament tenderness or nodules and cervical motion tenderness. MRI is a useful adjunct in diagnostic pelvic pathology in young girls.

### Treatment

Primary dysmenorrhea may result in significant school absence and lost productivity, so aggressive and evidence-based treatment is warranted. [Nonsteroidal anti-inflammatory drugs, (NSAIDs), mefenamic acid, ibuprofen, naproxen, etc.] are considered the first line of therapy. In randomized trials of NSAIDs, approximately 70–90% of patients have effective pain relief. NSAIDs should be started at the onset of menses and continued for the first one to two days of the menstrual cycle or for the usual duration of crampy pain. However, with severe symptoms, NSAIDs should be started one to two days prior to the onset of menses. Adequate rest, sleep, hot fomentation, acupuncture and regular exercise may help in some women.

If NSAIDs do not control symptoms after two to three cycles, a trial of oral contraceptive (OCPs) may be indicated. OCPs reduce menstrual pain by eliminating ovulation and by thinning the endometrial lining; leading to reduced synthesis of prostaglandins. In severe cases, extended cycle OCP regimens (e.g., 84 active pills, followed by 7 placebos) may be used to eliminate menses. In a sexually active female, OCPs may be considered the first line of therapy because they serve a dual purpose: prevention of both pregnancy and dysmenorrhea. If there is no relief with either NSAIDs or OCPs, both can be prescribed simultaneously.

In case of secondary dysmenorrhea, treatment of the underlying cause is very important. Dilation of a narrow cervical os may give 3–6 months of relief (and allows diagnostic curettage if needed). Other surgical measures (e.g., myomectomy, polypectomy, or dilation and curettage) may be needed in some patients. But these are usually not required for adolescent girls. Presacral neurectomy and division of the sacrouterine ligaments may help selected patients.

### ABNORMAL UTERINE BLEEDING

Abnormal uterine bleeding is reported commonly during adolescence. Pediatric practitioners must know what is normal in order to assess patients accurately. A normal period usually lasts 3–7 days. The normal interval between menses in adolescents may be between 21 and 45 days, although 21–35 days is more common. The median blood loss during each cycle is 30–40 mL which usually translates into 10–15 soaked tampons or pads per cycle; the upper limit of normal is 80 mL.

Menorrhagia or heavy menstrual bleeding (HMB) includes duration greater than eight days, flow greater than 80 mL/cycle or subjective impression of heavier-than-normal flow (i.e., more than six full pads or tampons per day, soaking through a pad within 1 hour, soaking through bedclothes or passage of clots); metrorrhagia means irregular bleeding, and menometrorrhagia means heavy and irregular bleeding; polymenorrhea is bleeding occurring at less than 21 days.

### Etiology

The differential diagnosis of abnormal vaginal bleeding is vast and is given in **Box 3**. The most common cause of abnormal uterine bleeding in adolescents is anovulatory cycles secondary to a delay in maturation of the negative feedback loop, whereby rising estrogen levels suppress FSH secretion. This results in a constantly proliferative endometrium with irregular shedding. In a study of hospitalized adolescents with heavy menstrual bleeding, 74%

#### BOX 3 Differential diagnosis of abnormal uterine bleeding in the adolescent girl

- *Anovulatory*
- *Bleeding disorders*: Thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, leukemia, aplastic anemia, chemotherapy)
- *Coagulation disorders*: von Willebrand disease, liver dysfunction, vitamin K deficiency
- *Hypothalamic cause*: Excessive exercise, psychological stress
- *Endocrine disorders*: Hypo- or hyperthyroidism, adrenal disease, hyperprolactinemia, PCOS, primary ovarian insufficiency
- *Systemic diseases*: Diabetes mellitus, renal disease, liver disorders
- *Pregnancy-related complications*: Abortion, ectopic pregnancy, gestational trophoblastic disease, complications of termination procedures
- *Structural defects*: Submucous myoma, congenital anomalies, Polyp
- *Infection*: Pelvic inflammatory disease, endometritis
- *Neoplasia*: Hormone secreting ovarian tumors, prolactinoma, adrenal tumors, endometrial cancer (rare)
- *Medications*: Hormonal contraceptives, anticoagulants, platelet inhibitors, androgens, spironolactone, antipsychotics

were diagnosed to have anovulatory dysfunctional bleeding, 19% had coagulation defects and rest 7% had other causes. Although most episodes of abnormal bleeding do not cause acute medical complications, bleeding can be traumatic for young patients and their families.

## Approach to Diagnosis

### History

In evaluation, the possibility of pregnancy should be kept first, because pregnancy complications presenting with bleeding, such as ectopic pregnancy, can be life threatening. All patients should be asked privately about the sexual history and in sexually active adolescents, it is important to enquire about contraceptive use and testing for gonorrhea and *Chlamydia trachomatis* should be performed.

Menstrual history should include detailed information about menarche; the timing, duration, and quantity of bleeding during recent menstrual cycles; and/or abnormal bleeding episodes. The history should include the number of pads used per day, passing blood clots, the need to change sanitary protection during the night. For patients with heavy regular, cyclic flow since menarche, a bleeding disorder such as von Willebrand disease is more likely. It is important to establish whether the bleeding is ovulatory or anovulatory. Regular cycles associated with premenstrual symptoms and dysmenorrhea usually imply ovulatory bleeding. Irregular cycles suggest anovulatory cycles, which may be due to an underlying endocrinopathy. Intermenstrual bleeding suggests anatomic disease (cervicitis), pregnancy related complications or breakthrough bleeding associated with use of hormonal contraception.

Questions about weight changes, exercise habits, acne, hirsutism, headaches, visual changes and chronic illness should be asked. Girls should be asked about bleeding from other sites and symptoms of acute or chronic anemia (e.g., epistaxis, gum bleeding, easy bruising, postoperative bleeding, lightheadedness, syncope, fatigue, weakness, headache).

Family history of bleeding tendencies (especially during childbirth and surgical procedures), endocrinopathies, and infertility should be elicited. Clinicians also should ask about antipsychotic and antiepileptic medications that may cause irregular bleeding, and aspirin and other anticoagulants, which may worsen bleeding.

### Physical Examination

Physical examination should include orthostatic vital signs for those with heavy bleeding. Sometimes resting tachycardia or orthostatic hypotension may be the only sign of severe anemia. The general examination should include measurement of height, weight, palpation of breast and thyroid, evaluation for signs of androgen excess (hirsutism; acne; male pattern balding), examination of the skin for presence of petechiae and/or bruising, acanthosis nigricans, examination of the optic fundi and visual field testing to evaluate the possibility of a pituitary tumor.

Palpation of the abdomen might diagnose an undetected pregnancy or an ovarian mass. Pelvic and bimanual examination is indicated for sexually active patients to screen for cervicitis and PID. In virginal patients who have longstanding ongoing bleeding, a rectoabdominal examination or transabdominal pelvic ultrasonography may be helpful.

### Laboratory Investigations

Laboratory testing should consist initially of a urine pregnancy test and a complete blood count, including platelet count to assess

the severity of bleeding. Other laboratory testing may be indicated depending upon the severity and the nature of the symptoms.

For severe bleeding or with hemorrhage since menarche, coagulation studies including prothrombin time/international normalized ratio, partial thromboplastin time, and Von Willebrand panel are indicated. For irregular bleeding, screening for endocrinopathies should be conducted by measuring FSH, LH, TSH, and prolactin, as well as androgen levels for girls with signs of hyperandrogenism on examination. Abdominal ultrasonography is warranted for girls presenting with a pelvic mass or if a uterine anomaly is suspected, or bimanual examination not possible in an adolescent with significant bleeding.

## Management

The goals of management include establishment and/or maintenance of hemodynamic stability, correction of acute or chronic anemia, return to a pattern of normal menstrual cycles, prevention of recurrence and prevention of long-term consequences of anovulation. The preferred treatment of abnormal uterine bleeding in adolescence is medical (**Table 3**); surgical intervention rarely is indicated. All treatment regimes must include iron replacement, although this therapy can be overlooked easily during the acute presentation and management.

Bleeding can be controlled with either combined OCPs or with progestins alone. OCPs reduce menstrual loss and establish a regular pattern of withdrawal bleeding. However, intravenous estrogen is required rarely in some patients who are actively bleeding and cannot tolerate oral medications in a dose of conjugated estrogens 25 mg every 4 hour for 2–3 doses followed by progestin.

A progesterone only preparation like **norethisterone** may be used if estrogen is contraindicated or if contraception is not desired. In our clinical experience, norethisterone controls bleeding in majority of patients. It is given in a dose of 10 mg thrice daily till the bleeding stops and then tapered off to 10 mg twice daily for 3 days followed by a dose of 5 mg twice daily for 21 days. Progestin-eluting intrauterine device (IUDs) may be an option in some cases.

Menstrual suppression using gonadotropin-releasing hormone (GnRH) analogs is generally avoided in adolescents because of their negative effects on bone mineralization. Antifibrinolytics such as tranexamic acid interfere with the breakdown of blood clots and thus stop or slow down bleeding; these agents may be used alone or along with OCPs.

If medical therapies fail to control bleeding within 24–36 hours in an ill patient, the possibility of pelvic pathology should be excluded by ultrasound, anesthesia examination, and rarely, dilation and curettage.

Once the acute episode of bleeding is controlled and the initial course of hormonal therapy is complete, further management depends upon the presence of persistent anemia and the desire for contraception. Low-dose combination OCP pills should be continued in girls who desire contraception and in those who required IV conjugated estrogen for initial control. Progesterone therapy may be used in girls with moderate or severe anovulatory uterine bleeding who were initially controlled with progestin-only regimens and do not desire contraception. As a general rule, hormonal therapy is continued for 3–6 months when possible either as 21 day cycle or extended cycle of 3 months or longer until the hematocrit returns to normal.

## POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy affecting up to 10% of women of reproductive age. The incidence is still increasing because of the change in lifestyle including sedentary habits, increasing intake of junk food and higher stress levels. Young women with PCOS present with amenorrhea



**Table 3** Management of abnormal uterine bleeding based on severity of bleeding

	<i>Mild bleeding</i>	<i>Moderate bleeding</i>	<i>Severe bleeding with moderate anemia</i>	<i>Severe bleeding with severe anemia</i>
Hb	> 11g/dL	10–11g/dL	8–10 g/dL	< 7 g/dL
Anemia correction	Oral iron	Oral iron	Oral iron	Blood transfusion
Treatment	Reassurance	Progestin/OCPs	Progestin/OCPs	OCPs/conjugated estrogen
OCPs dosage	1 pill daily for 21 days	1 pill BD till bleeding stops and then 1 OD × 21 days	1 pill QID × 2–4 days and then, 1 TDS × 3 days, then 1 BD × 2 weeks till Hb normal	1 pill 4–6 hourly till bleeding slows, then 1 QID × 2–4 days; 1 TDS × 3 days; 1 BD × 2 weeks till Hb normal
D & C	Never done	Not done	Not required	Required for recurrence or treatment failure
Follow-up	Monthly	Weekly, then monthly	Weekly, then monthly	Daily, then weekly

or oligomenorrhea and signs of hyperandrogenism, including hirsutism, acne, scalp hair loss, seborrhea, or hyperhidrosis. They are often, but not always, overweight. The diagnosis of PCOS has lifelong implications with increased risk for metabolic syndrome, type 2 diabetes mellitus, and possibly cardiovascular disease and endometrial carcinoma.

There are three sets of criteria for diagnosis of PCOS given in **Table 4**. Generally, the NIH criteria are preferred in adolescents which include patients with anovulatory cycles and clinical or biochemical evidence of hyperandrogenism, with or without polycystic ovaries on ultrasonography, in whom other diagnoses (e.g., late-onset congenital adrenal hyperplasia and thyroid disease) have been excluded. The Androgen Excess Society guidelines also include those patients with normal menses, but have biochemical or clinical hyperandrogenism and also polycystic ovaries on ultrasonography. New criteria, Amsterdam workshop (2010)—all these elements of Rotterdam criteria should be present in teenagers to make the diagnosis of PCOS.

### Pathogenesis

Patients with PCOS have an increased LH pulse frequency and amplitude which act on ovarian theca cells and increase androgen production. Intraovarian androgen excess appears to be responsible for both anovulation and the formation of multiple ovarian cysts (which are actually small ovarian follicles that are hindered in developing a dominant follicle). Majority of women with PCOS have insulin resistance and compensatory hyperinsulinemia; these abnormalities are independent of BMI. Insulin decreases serum hormone binding globulin (SHBG) and hence increases free testosterone levels. The so called HAIR-AN

syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans) is used to describe the severe end of spectrum.

### Approach to Diagnosis

#### History

Apart from a detailed menstrual history, history of premature pubarche, weight changes especially related to puberty, and duration, location and progression of unwanted hair growth should be sought. Drug history (valproate, anabolic steroids in athletes) and family history of hirsutism, PCOS, infertility, diabetes or hyperinsulinemia should be asked.

#### Physical Examination

Given the high prevalence of metabolic syndrome associated with PCOS, blood pressure, BMI and waist circumference should be measured. Evidence of androgen excess (hirsutism, acne, etc.), evidence of hypo or hyperthyroidism, presence of galactorrhea may help arrive at a diagnosis. Objective scoring of hair growth by Ferriman-Gallwey scoring system allows for measurement of the severity of hirsutism. Although a thorough pelvic examination is essential in older women; it is rarely needed in the adolescents, especially during the 5 years following menarche, except if there is contact bleeding or if the possibility of an STD cannot be excluded.

### Laboratory Investigations

As in all other menstrual complaints, a urine test to rule out pregnancy is mandatory. Other tests for evaluation for PCOS includes measuring LH, FSH, TSH, and prolactin levels to exclude other disorders, as well as obtaining serum levels of testosterone, free testosterone, and dehydroepiandrosterone (DHEAS). Most patients with PCOS have serum testosterone concentrations below 150 ng/dL.

The role of ultrasonography is to exclude the rare, but serious adrenal or ovarian tumor and ovarian pathology. The Rotterdam criteria define PCO as the presence of more than 12 follicles measuring 2–9 mm in diameter or ovarian volume more than 10 mL in at least one ovary. The classic peripheral pattern of a *string of pearls* is no longer necessary for making a diagnosis of PCOS.

Additional laboratory testing to detect metabolic abnormalities include fasting lipid profile and oral glucose tolerance test every 2 years.

### Management

Lifestyle modification including weight reduction by change in dietary habits and regular exercise should be advised in all obese patients with PCOS. **Table 5** summarizes the therapeutic options in PCOS, based on symptoms.

The endocrinologic therapy aims at reducing the excess production of androgens, reducing serum free androgen levels

**Table 4** Different diagnostic criteria for polycystic ovary syndrome (PCOS)

<i>Criteria</i>	<i>Hyperandrogenism</i>	<i>Oligo/anovulation</i>	<i>Polycystic ovaries</i>
National Institutes of Health (NIH)	+	+	±
Rotterdam criteria (if 2 of 3 present)	+	+	+
Androgen Excess Society criteria	+	± (either of two)	± (either of two)
Amsterdam criteria (all 3 should be present)	+	+	+

**Table 5** Therapeutic options in polycystic ovary syndrome (PCOS) based on symptoms

Chief complaint	First line therapy
Oligomenorrhea	Estrogen/progestin
Hirsutism, mild	Estrogen/progestin
Hirsutism, moderate to severe	Estrogen/progestin plus antiandrogen
Overweight	Exercise/nutrition plus metformin
Infertility	Ovulation induction

by increasing androgen binding to plasma-binding proteins and blocking androgen action at the level of target organs (e.g., hair follicle). The mainstay of treatment for PCOS includes three options: cyclic use of progestins to induce withdrawal bleeding; use of oral contraceptives pills to reduce ovarian androgen production and increase steroid hormone binding globulin; and use of metformin to lower circulating insulin levels and reduce ovarian steroid hormone production.

Oral contraceptive (OCPs) are the best option for sexually active young women who do not desire a pregnancy or who have menstrual irregularity and in those with hirsutism and acne; OCPs act by regularizing cycles, progestin inhibits endometrial proliferation, preventing hyperplasia, estrogen inhibits the activity of the hypothalamic-pituitary-gonadal axis, reducing ovarian androgen production as well as increasing sex hormone binding globulin (SHBG) levels. Unwanted hair growth improves in 50–70% of hirsute women.

In adolescent who is not sexually active and does not have significant hirsutism or acne, menses can be regulated with cyclic progestin only therapy. Metformin is particularly helpful for those with glucose intolerance. Metformin reduces insulin concentrations, promote ovulation, and lower androgen levels. Therapy is started with 500 mg daily before the evening meal, with an increase in the dose by 500 mg per week to the effective dose of 1500–2000 mg daily, as tolerated. Metformin promotes ovulation, so this drug should not be the sole therapy in sexually active teenagers.

Antiandrogenic therapy, which inhibits binding of androgen to its receptor, may be added in adolescents in whom hirsutism is the main problem. Antiandrogens including spironolactone, flutamide, finasteride, and cyproterone acetate inhibit the androgen-induced transformation of vellus to terminal hairs. Thus, the effects of these agents usually are not appreciated before 9–12 months because of the long growth cycles of sexual hair follicles. They should be prescribed with an OCP because they may cause menstrual disturbance and their potential teratogenic feminization of the male fetus.

If fertility is an issue, clomiphene citrate with and without metformin is the treatment of choice for ovulation induction.

Cutaneous hirsutism can be treated by cosmetic and dermatologic measures, and/or by medical endocrinologic therapy. Masking the presence of excess hair and physical hair removal are cornerstones to treat hirsutism; shaving, chemical depilatory agents, bleaching, and waxing techniques are effective but can cause skin irritation. Eflornithine hydrochloride cream inhibits hair growth and takes about 6–8 weeks for clinical effect. Laser therapy and electrolysis removes hair permanently by destruction of the dermal papilla.

Gonadotropin-releasing hormone analogs have been prescribed for patients not responding to the above therapeutic agents. GnRH analogs decrease gonadotropin secretions, lower androgen concentrations, lower hirsutism score and hair shaft diameter in patients with PCOS. However, add back therapy needs

to be added to prevent the long term consequences of estrogen deficiency.

### IN A NUTSHELL

1. Menstrual disturbance is the most common gynecological complaint of adolescent girls as the cycles are anovulatory in the first 2 years post menarche.
2. Patients who are pregnant can present with secondary amenorrhea, and rarely primary amenorrhea, irregular or heavy menstrual bleeding and hence, urine pregnancy test should be the first step in evaluating these adolescents, regardless of the stated sexual history.
3. A detailed and systematic work up is essential to find out the cause of primary amenorrhea. Adolescents with Müllerian abnormalities can have children even in the absence of uterus by oocyte retrieval, fertilization of the egg in vitro, and a gestational carrier.
4. In the hypoestrogenic causes of amenorrhea in adolescent, it is important to give estrogen replacement therapy for secondary sexual character development, maintenance and menses and acquisition of normal bone mass.
5. The detection of Y chromosome in the karyotype requires gonadectomy as soon as the diagnosis is made because of the risk of development of neoplasia and the risk of virilization.
6. Menstrual complaints like heavy bleeding and dysmenorrhea are a common cause of limitation of daily activities and school absenteeism, and a cause of anxiety for the patient and their families.
7. Coagulation disorders commonly present for the first time as puberty menorrhagia, therefore, every patient should have a coagulation screen.
8. Polycystic ovary syndrome is the most common endocrinopathy among young adults and is responsible for 70–85% of cases of androgen excess in adolescents.
9. Polycystic ovary syndrome is a syndrome and not a disease. It is characterized by menstrual disturbance, signs of hyperandrogenism, infertility and/or obesity.
10. It is important to recognize PCOS because it has metabolic and cardiovascular risks. Adolescent girls with PCOS are at increased risk for impaired glucose tolerance, type 2 diabetes, dyslipidemia, hypertension and myocardial infarction.

### MORE ON THIS TOPIC

- Agarwal N, Suneja A, eds. Paediatric and Adolescent Gynaecology. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2003.
- Deligeorgiou E, Athanasopoulos N, Tsimaris P, et al. Evaluation and management of adolescent amenorrhea. *Ann NY Acad Sci.* 2010;1205:23–32.
- Diaz A, Laufer MR, Breech LL American Academy of Pediatrics Committee on Adolescence; American College of Obstetricians and Gynecologists Committee on Adolescent Health Care. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Pediatrics.* 2006;118(5):2245–50.
- Emans SJ, Laufer MR, eds. Emans, Laufer, and Goldstein's Pediatric and Adolescent Gynecology. 6th edition. Philadelphia, PA: Lippincott, Williams, and Wilkins; 2011. pp. 159–67.
- Fritz MA, Speroff L, eds. Clinical Gynecologic, Endocrinology and Infertility, 8<sup>th</sup> edition. Philadelphia: Lippincott Williams & Wilkins; 2011.
- Golden NH, Carlson JL. The pathophysiology of amenorrhea in the adolescent. *Ann NY Acad Sci.* 2008;1135:163–78. Gray SH. Menstrual disorders. *Pediatr Rev.* 2013;34(1):6–17; quiz 17–8.
- Williams CE, Creighton SM. Menstrual disorders in adolescents: review of current practice. *Horm Res Paediatr.* 2012;78(3):135–43.

## Chapter 25.6

# Sexually Transmitted Infections

Newton Luiz

Sexually transmitted infections (STIs) occur more frequently in sexually-active adolescents than in adults. They are at least twice as common in girls as in boys and occur earlier in them. The incidence is believed to be on the rise. In 2003, more than 5% of the adult population in India suffered from STIs. There is no reliable data on the incidence of STIs in adolescents in India or other developing countries. In a study done in six representative states in India in 2006-2008, in which 50,848 adolescents and youth aged 15-24 were privately interviewed about their sexual experience by sensitive and trained young personnel, 12% of the males and 3% of the females admitted to premarital sex. In an older 1997 Indian study in adolescents aged 16-17 years, 8% of males and 1% of females admitted that they had experienced sex. In a college study in Nepal in 2006, 35% of adolescent males claimed to have had premarital sex. Adult data on STI in India suggests that chlamydia and gonorrhea are the commonest infections, while syphilis, chancroid and trichomoniasis are also frequent. Infection due to herpes simplex virus (HSV) and human papilloma virus (HPV) are probably under-reported due to lack of awareness.

### PHYSICAL FACTORS AFFECTING GIRLS

- The adolescent vagina is more prone to infection than the adult vagina. Early sexual debut is associated with a high incidence of STIs.
- After puberty, as a result of increasing estrogen levels, the simple columnar epithelium of the adolescent vagina changes over many years into stratified squamous epithelium, thus making it resistant to infection. But throughout adolescence 70% of females continue to have some columnar epithelium at the junction of the vagina with the uterine cervix, a condition called *cervical ectopy* that predisposes to cervical infection.
- The hormonal changes of puberty increase local mucus production and decrease the pH. This decreases susceptibility to chlamydia and gonorrhea but increases susceptibility to *Candida albicans* and *Trichomonas vaginalis*.
- The smaller introitus of the adolescent girl predisposes her to physical trauma during coitus.

### OTHER FACTORS

- Infection is usually asymptomatic in adolescents.
- There is low awareness about STI among adolescents. Education about STI is meager in the school syllabus, and a significant percentage of adolescents do not attend high school. Girls are often unable to differentiate normal from abnormal vaginal discharge.
- The sexually active girl is more concerned about the possibility of pregnancy or menstrual problems than STIs.
- Adolescents have inadequate concern about their future health, and indeed believe that they are physically invulnerable. A risk-taking attitude is common at this age.
- Even when concerned, adolescents have difficulty accessing sexual advice. There may be no special facilities for adolescents or they may be unaware of the facilities available. The facilities may be far away from home and school or may not be available outside school hours. Adolescents may not have the financial resources to visit a hospital, to do tests and to buy medicines.

The girl dislikes pelvic examinations and is reluctant to discuss her complaints if the doctor is a male. The boy is too embarrassed to ask about condoms.

- Adolescents fear disapproval of their sexual behavior. They worry that their parents or friends may come to know of their problem.
- The adolescent may be a victim of sexual abuse.

### MAJOR INFECTIONS

#### HIV/AIDS

This major STI presents predominantly with systemic rather than genital lesions and is discussed in detail in another chapter.

#### Gonorrhea

This is caused by *Neisseria gonorrhoeae*, a gram-negative intracellular diplococcus. Genital infection is symptomatic in 90% of infected men but only 20% of infected women. The incubation period is 2-5 days. It presents as urethritis in boys; if untreated, a urethra abscess or stricture may develop. In girls, it causes cervicitis and is a major cause of pelvic inflammatory disease (PID). About 20% of boys and 40% of girls with gonorrhea have associated chlamydial infection. A single dose of oral cefixime 400 mg is effective against gonorrhea. A single dose of injectable ceftriaxone 250 mg intramuscular (IM) is preferred and has the extra benefit of being effective against incubating syphilis and chancroid (but not against *Chlamydia*).

#### Chlamydia

This is the commonest of the STIs, but the majority of affected adult women is asymptomatic or only has a mucoid vaginal discharge. It often causes silent PID. It is more common and more severe in adolescents: 20% of adolescent girls with *Chlamydia trachomatis* infection will suffer from chronic pelvic pain, 10% will have an ectopic (tubal) pregnancy in the future and 20% will become infertile. Women with *C. trachomatis* infection have a four-fold increased risk for acquiring HIV infection. Asymptomatic urethral infection is common in men, but it is the commonest cause of nongonococcal urethritis (NGU) and is a major cause of epididymitis. Diagnostic tests are costly and unreliable. A single dose of azithromycin 1 g is effective; so is doxycycline 100 mg BD  $\times$  7 days.

#### Genital Herpes

It is characterized by multiple painful shallow ulcers that heal spontaneously within weeks, but more than 50% have lifelong intermittent episodes of viral shedding. It can also cause cervical ulcers. HSV-2 is the usual cause, while HSV-1 is an infrequent agent.

#### Chancroid

This is caused by *Haemophilus ducreyi*, a gram-negative coccobacillus. A papule occurs within a week of exposure and rapidly ulcerates. Without treatment the ulcer may last for weeks or months. There is unilateral tender inguinal lymphadenitis which may become fluctuant and a discharging sinus may develop. Effective regimens include ceftriaxone 250 mg IM stat, azithromycin 1 g orally stat, erythromycin 500 mg QID  $\times$  7 days or ciprofloxacin 500 mg BD  $\times$  3 days.

#### Syphilis

This great scourge of the past is now rare in developed countries, possibly because it is usually symptomatic and can be diagnosed by simple tests. But primary syphilis, an indolent infection caused by *Treponema pallidum* that presents as a genital ulcer, is not uncommon in developing countries. Secondary and late syphilis do not cause genital ulcers and are infrequent in adolescence.



## Trichomoniasis

*Trichomonas vaginalis* is a flagellated protozoan parasite that primarily causes vulvovaginitis in girls but infrequently causes PID in women and chronic prostatitis in men. Most men and up to 30% of women are asymptomatic.

## Lymphogranuloma Venereum

This disorder is caused by *C. trachomatis* (L1, L2 and L3 serovars). The characteristic feature is femoral or inguinal lymphadenitis with enlarging, painful buboes that break down to form multiple draining sinuses. As the disease progresses, the patient suffers from rectovaginal fistulas, rectal strictures and urethral damage. Doxycycline 100 mg BD  $\times$  21 days is the recommended treatment. Azithromycin 1 g weekly for 3 weeks is an effective alternative.

## Granuloma Inguinale (Donovanosis)

This STI is caused by *Klebsiella granulomatis* (formerly called *Calymmatobacterium granulomatis*). As it heals very slowly, treatment should be given for 3 weeks or until all lesions heal, whichever is longer. Thus, treatment requires doxycycline 100 mg BD  $\times$  21 days. Alternatives include azithromycin 1 g weekly or ciprofloxacin 750 mg BD for 3 weeks.

## Bacterial Vaginosis

This is very common. It is not a STI but is often mistaken for one. It occurs when *Lactobacillus*, which is the normal vaginal flora of the vagina, is replaced by an overgrowth of *Mobiluncus* (an anaerobe), often in association with *Gardnerella vaginalis*, *Ureaplasma urealyticum* and *Mycoplasma genitalium*.

## Candidiasis

Candidal vulvovaginitis is more common in adolescents who use oral contraceptives, after oral antibiotic therapy or when pregnant. There is vulvar pain or itching, dysuria, vulvar or vaginal erythema and an opaque white or cheesy exudate. A single dose of fluconazole is effective.

## DIAGNOSIS

Many STIs are curable and all are treatable. But the majority of STIs are asymptomatic and when symptomatic, the manifestations are variable and usually nonspecific. Hence, a syndromic approach to management is preferred in resource-poor settings, where the laboratory facilities and expertise required for diagnosis are either limited or unavailable or unaffordable. Case management goes beyond history taking, clinical examination, diagnosis and prompt management, and includes partner management, counseling to prevent recurrence and careful follow-up.

## History Taking

Adolescents are naturally anxious about visiting a clinic. This stress can be alleviated if the clinic has a bright, attractive waiting room with magazines that would attract adolescents, and/or a TV showing programs of interest to adolescents. Both male and female staff should be present, and should be friendly and patient. The consulting room should offer privacy for genital examination and one should ensure that conversations cannot be overheard. Adolescents should not be expected to visit an *STI Clinic*. The clinician should emphasize confidentiality right at the start. He should be nonjudgmental and reassuring even when he suspects the adolescent's honesty. Most adolescents are not frank or open initially and it may take time to gain their confidence. One should expect the adolescent to be unwilling or embarrassed to share information. A high degree of suspicion is required, as the

adolescent may only mention lesser or nonspecific complaints and hope that the clinician will find the right diagnosis.

History taking will initially focus on the presenting complaints. Next one should ask leading questions about symptoms that could possibly be due to an STI. Does the girl have normal and regular menstrual cycles, dysmenorrhea, dysuria or frequency micturition, vaginal discharge (and if so what is the amount, odor, color); does she have genital itch or rash or ulcers? Does the boy have dysuria or frequency of micturition, discharge of pus from the penis, genital itch or rash or ulcers, scrotal pain or swelling, or groin swelling? Have these symptoms occurred in the past and if so, was any treatment taken?

Finally one should take a sexual history. Is the adolescent having sex, and if so how often; is it with a person of the opposite or same sex; is it genital, oral or anal sex? Has he or she had sex earlier and with how many partners? Has the adolescent ever been tested for, diagnosed with or treated for STI? What about the partner? Is any protection against pregnancy or STI used, and if so what and how regularly?

## Clinical Examination

Before doing a genital examination, the clinician should explain what is to be done and why. If the patient is below 18 years, parental permission is needed. Ask the adolescents if they wish someone trusted to be present. If examining a member of the opposite sex, an assistant of the same sex as the patient should be present.

Start with a general examination including the vital signs, inspection of the skin and mucous membranes. Do a systematic search for enlarged lymph nodes and record their size, consistency, number and whether tender.

Use gloves during genital examination. When examining the male adolescent, look for penile rashes or ulcers. Retract the foreskin and systematically examine the glans penis, coronal sulcus, frenum and urethral meatus. If there is no obvious discharge, milk the urethra 3-4 times from the base toward the urethral meatus. Palpate the testis, epididymis and spermatic cord.

In the female, separate the labia majora with both hands and inspect the labia majora and minora, the Bartholin glands and the introitus. Pressing under the urethra with one finger might cause a drop of urethral discharge to come out. Holding the labia majora apart and pulling them toward the examiner permits internal examination. Palpate the abdomen, looking for a mass or pelvic tenderness. Separate the buttocks with two hands to visualize the area properly. Do a rectal examination and proctoscopy if there is rectal discharge or history of anal intercourse.

## Investigations

- All symptomatic patients should be tested for chlamydia and gonorrhea if possible, and an HIV rapid test, venereal disease research laboratory test (VDRL) and hepatitis B surface antigen (HBsAg) should be done
- Pregnancy test should be done to all with suspected PID as management differs, if pregnant
- Repeat tests after 3 months to confirm cure in chlamydia and gonorrhea
- Partners should be tested, if possible.

## Vaginal Discharge

Vaginal fluid is collected with a swab inserted deep into the lateral or posterior fornices of the vagina, or from the tip of the speculum after a speculum examination of the vagina. The use of jelly or disinfectant will interfere with the results. The tests described below will give us a diagnosis in up to 80% of cases of vaginal discharge.



## pH

Using pH paper of range 3.8–6.0, one can check the pH of the vaginal fluid. It is normally 4.0 and is usually more than 4.5 in bacterial vaginosis (BV) and trichomoniasis. A negative pH test makes a diagnosis of BV very unlikely, but a positive test may be due to *Trichomonas* or contamination with cervical mucus, semen or menstrual blood.

## Saline Microscopy

A fresh sample may reveal the darting motility of *Trichomonas* in 80% of symptomatic girls (but only 50% of asymptomatic girls), the yeast cells of *Candida* or the presence of *clue cells* in BV. Clue cells are epithelial cells that are covered with many small coccobacilli making their edges indistinct. Plenty of WBCs are seen in PID. The vaginal discharge has a foul odor in BV and if a drop of 10% KOH is added, the slide immediately emits a fishy odor. 70% of cases of candidiasis can be diagnosed by adding KOH which dissolves the other cells and makes the yeast cells and pseudohyphae more obvious.

## Gram Stain

In BV, the lactobacilli are replaced by a variety of other microbes; clue cells are seen more clearly than in saline microscopy. In gonorrhea, there may be WBCs with intracellular gram-negative diplococci. Though the yield is good in urethral pus, it is low in vaginal discharge and vaginal commensals often produce a similar picture. Culture usually grows only commensals.

## Urethral Discharge in Men

In gonorrhea, Gram stain will reveal WBCs with intracellular gram-negative diplococci. In NGU, there will be more than five neutrophils per oil immersion field and a first-void (NOT midstream) urine sample will show more than 10 neutrophils per high power field.

## Genital Ulcers

Rapid plasma reagin (RPR) and VDRL are excellent nontreponemal screening tests that pick up most cases of early syphilis, but occasional false positives are seen. Treponema pallidum hemagglutination test (TPHA) is a confirmatory test. In chancroid, *H. ducreyi* may be picked up by a Gram stain or culture. The Tzanck test is insensitive and not specific for HSV.

## Other Tests

Pelvic inflammatory disease can be diagnosed by a USG and more accurately by MRI or a laparoscopy, which will reveal thickened, fluid-filled tubes with or without free pelvic fluid, or a tubo-ovarian mass and help to rule out other causes of abdominal pain. HSV can be diagnosed by serology, PCR and culture, but these tests are costly and not easily available and have limited accuracy. Nucleic acid amplification tests (NAATs) are the most sensitive tests for chlamydia and gonorrhea and allow testing on self-collected vaginal swabs, or less sensitively on urine. They are costly and not easily available.

## PRINCIPLES OF TREATMENT AND COUNSELING

- The drug used should preferably be at least 95% effective, low-cost, single-dose, oral, with low toxicity and not contraindicated in pregnancy.
- One should explain to the patient how he got the infection and how it can be cured so that he understands why drugs are needed and how to avoid getting infected in future and how to prevent infection from spreading to others.
- The importance of treating the sex partner should be emphasized.

- The patient and partner should practice sexual abstinence until 7 days after completing treatment.
- There should be a return visit after 7 days to ensure treatment compliance, to see the reports of tests done and to confirm cure.
- Counseling should be tailored to the adolescent's unique life situation. It is important whenever possible to help the patients develop critical thinking skills, promote their self-esteem and encourage positive values.

## SYNDROMIC APPROACH TO SEXUALLY TRANSMITTED INFECTION

### Urethral Discharge or Burning Micturition in Boys

Urinary tract infection in an adolescent boy is due to an STI until proved otherwise. This is usually gonorrhea which presents as a mucopurulent urethral discharge. NGU is caused by *Chlamydia* in up to 50% of cases; the etiology is unknown in the rest, though *Trichomonas*, *M. genitalium* and *U. urealyticum* are sometimes implicated.

### Treatment

Treatment should cover both gonorrhea and chlamydia as dual infection is common:

- Ceftriaxone 250 mg IM (for *N. gonorrhoeae*) + oral azithromycin 1 g stat (for *Chlamydia*)
- If allergic to azithromycin, give erythromycin 500 mg QID × 7 days (50 mg/kg if <40 kg)
- If symptoms persist or recur, treat for *Trichomonas* with metronidazole 2 g stat orally.

### Scrotal Pain or Swelling

Both *Chlamydia* and the gonococcus can cause epididymo-orchitis which manifests as acute scrotal pain and swelling. Examination reveals a swollen and tender epididymis and testis, and there may be hydrocele and urethral discharge. Fever and malaise are present, and there may be associated dysuria. As orchitis can reduce fertility, it should be treated aggressively for both gonococcal and chlamydial infection.

### Treatment

Treatment consists of cefixime 400 mg BD × 7 days and doxycycline 100 mg BD × 14 days (2.2 mg/kg/day if <45 kg). Other causes of acute epididymo-orchitis include mumps, filaria and infection by coliform bacteria. Torsion of the testis is an important differential diagnosis.

### Inguinal Bubo

Chronic inguinal lymphadenitis (buboes) caused by STIs tend to break down and leave draining sinuses.

Lymphogranuloma venereum (LGV) starts with small painless papules on the external genitalia. Later the characteristic buboes appear which break down to form multiple fistulae. If untreated, the patient may develop lymphatic obstruction resulting in elephantiasis of the lower limbs or genitals. Granuloma inguinale (Donovanosis) presents with painless buboes that break down to form beefy red painless ulcers. Chancroid usually presents more acutely and has a single draining sinus.

### Treatment

Doxycycline 100 mg BD × 21 days at least (for LGV and Donovanosis) and azithromycin 1 g stat (for chancroid). Avoid local incision and drainage as this leads to chronic sinus formation. If fluctuant, aspirate.

The differential diagnosis includes local bacterial infections of the genitalia, groin, perineum, buttocks and lower limbs that can involve the inguinal glands and also chronic involvement due to *Mycobacterium tuberculosis* or filariasis.

### Genital Ulcers

Herpes simplex virus, syphilis and chancroid are the usual causes of penile and vulvar ulcers. Genital herpes is characterized by multiple vesicles or painful shallow ulcers. Acyclovir 400 mg TID  $\times$  7 days may be given. Chancroid presents with multiple painful ulcers with nonindurated and undermined borders and a purulent base. A painful bubo is occasionally seen. Primary syphilis manifests as a chancre, i.e., a single painless ulcer on the labia majora or penis with a well-demarcated indurated border and a clean base. The lymph nodes are enlarged, rubbery and nontender.

### Treatment

Benzathine penicillin 50,000 IU/kg (up to 2.4 million units) deep IM stat (for syphilis), given in two divided doses as the volume for injection is large and azithromycin 1 g stat orally (for chancroid). If allergic to penicillin, give doxycycline 100 mg BD  $\times$  14 days.

### Vaginal Discharge

Vaginitis in adolescence is usually due to BV, but *Trichomonas* and *Candida* can cause vaginitis. Cervicitis, caused by *N. gonorrhoeae*, *Chlamydia*, *Trichomonas* and HSV can result in a profuse cervical discharge which manifests externally as vaginal discharge. A speculum examination will differentiate between the two, but if the adolescent refuses one will need to treat for both. It is essential to rule out PID.

In BV, there is no vulvar itch or soreness. The vaginal discharge is sticky, grayish in color and has a foul odor. Gonorrhea presents with a vulvar itch, mild vaginal discharge, urethritis or cervicitis. Chlamydial cervicitis produces a red friable cervix which manifests with intermenstrual or postcoital bleeding, or a profuse mucopurulent discharge. Trichomoniasis causes a malodorous frothy yellow-green vaginal discharge with vulvar soreness and irritation. Candidiasis causes vulvar pruritus, pain, redness and excoriation, and a thick curdy white discharge. Candidal vaginitis increases during menstruation. HSV rarely causes an ulcerative cervicitis.

### Treatment

If vaginitis is diagnosed, give metronidazole 2 g stat orally (for BV and *Trichomonas*) and fluconazole 150 mg stat or clotrimazole 500 mg intravaginally as a single dose (for *Candida*). If cervicitis is suspected, give ceftriaxone 250 mg IM (for *N. gonorrhoeae*) and azithromycin 1 g stat (for *Chlamydia*).

### Lower Abdominal Pain

Lower abdominal pain in girls may indicate PID. It is rare for the infection to be sharply localized, especially in adolescent girls. An ascending infection of the internal genitalia can affect the uterus, fallopian tubes, ovaries, the pelvic peritoneum, the vascular tissues and/or connective tissue. There may be endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. The infecting agent is usually gonococcus or *Chlamydia*; other causes include anaerobes like *Mobiluncus*, *Gardnerella*, enteric gram-negative bacilli, *M. genitalium* and *U. urealyticum*.

Pelvic inflammatory disease may be asymptomatic (silent PID), especially in chlamydial infection, or it may present with chronic pelvic pain. There may be vaginal discharge, menorrhagia, dysmenorrhea, dyspareunia, dysuria, tenesmus or low backache. On examination, some girls have high fever, tenderness and guarding of the lower abdomen, a pelvic mass, or tenderness of the adnexa or cervical motion. The erythrocyte sedimentation rate

(ESR) is raised. The differential diagnosis includes twisted ovarian cyst, ovarian tumor, endometriosis, ectopic pregnancy, threatened or septic abortion, tubo-ovarian abscess, UTI and gastrointestinal tract (GI) disorders like appendicitis and inflammatory bowel disease.

### Treatment

Treatment consists of cefixime 400 mg BD  $\times$  7 days and doxycycline 100 mg BD  $\times$  14 days and metronidazole 400 mg BD  $\times$  10 days. Careful follow-up is essential to confirm cure.

### Genital Skin Lesions

Human papilloma virus causes genital warts (condyloma acuminata) which consist of multiple soft painless pink cauliflower-shaped growths on the external genitalia, around the anus or in the perineum. Apply 20% podophyllin on the wart and wash it off after 3 hours. The surrounding areas should be protected with vaseline before applying it. Do this weekly till the lesions resolve. Cervical lesions cannot be treated with podophyllin, and cryotherapy is needed. Other causes of warts are HPV-6 and HPV-11 (which cause benign genital warts), molluscum contagiosum and syphilis (which cause condylomata lata).

### Oral and Anal Sexually Transmitted Infections

A high degree of suspicion is required to diagnose them. There is a history of oral or anal sex. Orally, there may be ulcers or pharyngeal inflammation. Anal STI can cause anal discharge, tenesmus, diarrhea, blood in stool, abdominal cramps and local ulcers or vesicles. *N. gonorrhoeae*, *Chlamydia*, HSV, *T. pallidum* and *H. ducreyi* are the usual agents.

### Sexually Transmitted Infection and Pregnancy

Adolescents are more likely when pregnant to have a miscarriage than adult women and this is partly due to their higher incidence of STIs.

### PARTNER THERAPY

Partner therapy is important to cure the partner (who may be asymptomatic and so does not seek treatment), to prevent the primary patient from being reinfected and to prevent other persons from being infected by the partner. The patient should be convinced of the importance of partner management and he or she should be asked to bring the partner along. Both of them should be treated for any STIs found in either of them. If it is not possible to examine the partner, a prescription is given for empirical treatment of the partner without evaluation and this is known as *expedited partner therapy*.

There is always a risk of wrongly labeling a patient as having a STI as the symptoms of many STIs are nonspecific, e.g., vaginal discharge. The result is that one unnecessarily treats the sexual partner. Nevertheless, when one suspects PID, the danger of undertreatment is greater and it better to counsel them that there is an infection that could possibly reduce fertility if untreated and advise both to take treatment.

### PREVENTION

#### Educate the Adolescent about Sexually Transmitted Infections

This is most practical in schools. Where school enrolment is low other sources of information could be youth clubs, youth magazines, libraries and churches. The importance of this was emphasized by a cross-sectional survey in 2006-2007 of urban girls studying in the 11th and 12th grades in Delhi: 53% had never

attended a class on STI, HIV or safe sex; 22% agreed that premarital sex was acceptable between loving couples; 30% believed that HIV was curable and 44% had not heard of gonorrhea.

### Make Available Adolescent Friendly Health Services

Early diagnosis and treatment will prevent further spread of disease. These services should be exclusive to adolescents, should be open soon after or before school hours and should be situated close to schools. They should preferably offer multiple activities such as evening classes and sports facilities so that the adolescent who wishes to visit them can do so without drawing attention to himself or herself. *Do routine screening* to detect cases early. This implies a sexual history that is appropriate to the adolescent's developmental level and culture.

### Routine Screening Tests

While simple low-cost screening tests are available for HIV and syphilis, they are not available for common organisms like *Chlamydia* and *gonorrhoeae*. All patients who come in with complaints suggestive of STI, or are found to have STI, should be routinely tested for HIV and syphilis. Ideally, all sexually active adolescents should be screened confidentially for chlamydia and gonorrhea every year.

### Promote Condom Use among Sexually Active Adolescents

Condoms are highly effective for prevention of HIV and quite effective for the other STIs, though less so for genital ulcers and HPV. Ignorance about condoms, nonuse, wrong use and repeated use of the same condom are all common. Many adolescents believe that if they are in a regular relationship with a single partner the risk of STI is negligible, yet US data shows that 19.7% of adolescents with STI had only one sex partner.

### Immunization

Human papilloma virus is vaccine preventable in theory. The vaccines available have 70% efficacy in American whites, but their efficacy is lower in American blacks and their efficacy in Asian populations is unknown. There is also inadequate data on what percentage of the population is already seropositive at any given age. Hepatitis B can be transmitted as a STI and hepatitis B vaccine is highly effective when given at 0, 1 and 6 months.

### GOVERNMENT PROGRAMS TO CONTROL SEXUALLY TRANSMITTED INFECTIONS

The prevention, management and control of STIs are mainly under the Reproductive Child Health-II (RCH-II) program. The National AIDS Control Program-III (NACP-III) includes STI management services as a major program for prevention of HIV. It aims to provide services to the general population and simultaneously to focus on certain high risk behavior groups. The main objectives are to: enhance access to services, especially for adolescents and to high-risk groups; standardize treatment protocols and emphasize

treatment compliance; focus on prevention including partner management and condom use; bring about behavior change by enhancing knowledge; and provide counseling and testing services for HIV or AIDS.

#### IN A NUTSHELL

1. STIs are common in sexually active adolescents, especially in females.
2. They are often asymptomatic, yet cause considerable immediate and long-term morbidity and also predispose the adolescents to HIV.
3. STIs are more common in adolescents than in adults due to genital immaturity in girls, low awareness of STI, poor access to health services, inadequate concern for their health and the normal risk-taking attitude of this age.
4. The common causes are *C. trachomatis*, *N. gonococcus*, HSV, *Trichomonas*, HPV, *H. ducreyi* and *T. pallidum*. Multiple infections are common.
5. The usual presentations are urethral discharge, scrotal pain and swelling, inguinal bubo, genital ulcer, vaginal discharge or low abdominal pain.
6. A syndromic approach to management is preferred as sensitive low-cost diagnostic tools are not available.
7. The drugs used should preferably be at least 95% effective, low-cost, single-dose, oral, with low toxicity and not contraindicated in pregnancy.
8. Case management should include treatment of the patient and partner, counseling to prevent recurrence and careful follow-up.
9. There is a need for adolescent friendly, accessible, low-cost health facilities.
10. There is an urgent need for providing Family Life Education to adolescents including awareness of STI and HIV.

#### MORE ON THIS TOPIC

- Burstein GR. Sexually transmitted infections. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE. Nelson Textbook of Pediatrics, 19<sup>th</sup> ed. Philadelphia: Elsevier; 2011. pp. 705-14.
- Government of India. National Guidelines on Prevention, Management and Control of Reproductive Tract Infections (RTIs) including Sexually Transmitted Infections (STI's). New Delhi: Ministry of Health and Family Welfare, Government of India; 2007.
- McManus A, Dhar L. Study of Knowledge, Perception and Attitude of Adolescent Girls towards STIs/HIV, Safer Sex and Sex Education: (A Cross Sectional Survey of Urban Adolescent School Girls in South Delhi, India). BMC Women's Health; 2008;8:12.
- Santhya KG, Acharya R, Jejeebhoy SJ. Condom use before Marriage and Its Correlates: Evidence from India. International Perspectives on Sexual and Reproductive Health; 2011. pp. 170-80.
- Shekhar M, Ghosh S, Panda P. Exploring Safe Sex Awareness and Sexual Experiences of Adolescents in Patna. Economic & Political Weekly; 2007. pp. 48-55.
- WHO. Sexually Transmitted Infections in Adolescence. Geneva: World Health Organization; 2004.

## Chapter 25.7

# Teenage Pregnancy

Amita Suneja, Richa Aggarwal

Teenage pregnancy is high risk pregnancy with medical and social problems. It is of concern to pediatric health care givers during discussions of sexual activity, contraception or during diagnostic evaluation of problems such as menstrual irregularities, gastrointestinal complaints or pelvic mass.

In developed countries, teenage pregnancies are often associated with social issues including lower educational levels, poverty and other poor life outcomes in children of teenage mothers. Teenage pregnancy in developed countries is usually outside of marriage and carries a social stigma in many communities and cultures.

By contrast, teenage parents in developing countries are often married and their pregnancies welcomed by family and society. However, in these societies, early pregnancy may combine with malnutrition and poor health care to cause medical problems.

## MAGNITUDE OF THE PROBLEM

About 16 million girls aged 15-19 years and 2 million girls under the age of 15 give birth every year. Worldwide, one in five girls has given birth by the age of 18. In the poor regions of the world, this figure rises to over one in three girls. Pakistan and Sri Lanka show much lower rates of pregnancies among women aged 15-19 than India and Bangladesh according to the report titled *Motherhood in Childhood*. For every 1,000 girls aged 15-19, there were 76 adolescent births in India in 2010 compared to 49 worldwide and 53 in less developed regions.

## FACTORS CONTRIBUTING TO TEENAGE PREGNANCY

### Early Marriage

India and Bangladesh remain among the countries where a girl is extremely likely to be married before she is 18 and have a child while still a teenager. The expectation in the sociocultural milieu that after marriage a woman will become pregnant as soon as possible encourages early onset of maternity.

### Poverty

Almost all adolescent births—about 95% occur in low- and middle-income countries. Within countries, adolescent births are more likely to occur among poor, less educated and rural populations. At least one-third of teenagers who become pregnant are themselves product of teenage pregnancy.

### Early Puberty

The average age of menarche is decreasing and as a result of early menarche and changing sexual pattern, a marked increase in the number of young pregnant girls has been witnessed. The youngest mother reported in literature is Lina Medina who was around 5 years old when she was delivered by cesarean section in Lima, Peru in 1939.

## Increasing Sexual Activity among Teenagers

The increased sexual activity among adolescents is manifested as increased teenage pregnancies and an increase in sexually transmitted diseases. In a 2005, Kaiser Family Foundation study of

US teenagers, 29% of teens reported feeling pressure to have sex, 33% of sexually active teens reported *being in a relationship where they felt things were moving too fast sexually*, and 24% had *done something sexual they didn't really want to do*. Several polls have indicated peer pressure as a factor in encouraging both girls and boys to have sex. Younger teenagers are especially vulnerable to coercive and nonconsensual sex.

## Childhood Sexual Abuse

Subsequent teenage pregnancy in industrialized countries up to 70% of women who gave birth in their teens were molested as young girls; by contrast, 25% of women who did not give birth as teens were molested.

## Lack of Contraception

Adolescents may lack knowledge of or access to conventional methods of preventing pregnancy as they may be too embarrassed or frightened to seek such information. Contraception for teenagers presents a huge challenge for the clinician. Young women often think of contraception either as *the pill* or condoms and have little knowledge about other methods. They are heavily influenced by negative, second-hand stories about methods of contraception from their friends and the media. Prejudices are extremely difficult to overcome. Over concern about side-effects, for example weight gain and acne, often affect choice. Missing up to three pills a month is common, and in this age group the figure is likely to be higher. Restarting after the pill-free week, having to hide pills, drug interactions and difficulty getting repeat prescriptions can all lead to method failure.

In other cases, contraception is used but proves to be inadequate. Inexperienced adolescents may use condoms incorrectly, forget to take oral contraceptives or fail to use the contraceptives they had previously chosen. Contraceptive failure rates are higher for teenagers, long-acting contraceptives, such as intrauterine devices, subcutaneous contraceptive implants and contraceptive injections (such as Depo-Provera and combined injectable contraceptive), which prevent pregnancy for months or years at a time are more effective in women who have trouble remembering to take pills or using barrier methods consistently.

According to The Encyclopedia of Women's Health, published in 2004, there has been an increased effort to provide contraception to adolescents via family planning services and school-based health such as HIV prevention education.

## RISKS OF TEENAGE PREGNANCY

Teenage pregnancy is primarily a sociological problem with medical consequences. Rather than maternal age itself as the sole factor, the obstetric risks for older teenagers are more related to poverty, inadequate nutrition, poor health before pregnancy, unmarried status and poor education and lack of antenatal care. The common problems are listed in **Box 1**.

## PREVENTION

WHO published guidelines on how to prevent early pregnancies and poor reproductive outcomes among adolescents in low- and middle-income countries. These include legalization of minimum age for marriage, creating understanding and support to reduce pregnancy before the age of 20, introducing sex education in schools, increasing the use of contraception by adolescents at risk of unintended pregnancy, reducing coerced sex among adolescents, reducing unsafe abortion among adolescents and increasing the use of skilled antenatal, childbirth and postnatal care among adolescents.



**BOX 1 Problems of teenage pregnancy**

- *Increased maternal morbidity and mortality due to:*
  - More likelihood of unsafe abortions
  - Less likely than adults to obtain skilled care before, during and after childbirth
  - Pregnancy related complications: preterm labor, pre-eclampsia, anemia
  - Teenagers are more likely to have sexually transmitted infections (STIs): chlamydia, syphilis and HIV
  - Teenagers are more likely to smoke and take drugs: placental problems
  - More complications of childbirth due to fetopelvic disproportion
- *Fetal risk*
  - Low birth weight (LBW) babies
  - Still births, newborn and infant deaths: Stillbirths and newborn deaths are 50% higher among infants born to adolescent mothers than among those born to mothers aged 20–29 years
  - Fetal effects because of STI and substance abuse: LBW, sudden infant death syndrome
- *Other consequences*
  - Dropouts from school
  - Lack of job skills
  - Financial dependence

**MORE ON THIS TOPIC**

WHO. Adolescent Pregnancy. Fact sheet. Geneva: WHO; 2012. From: [www.who.int/mediacentre/factsheets/fs364/en/](http://www.who.int/mediacentre/factsheets/fs364/en/). Accessed November 5, 2008.

**IN A NUTSHELL**

1. Teenage pregnancy is high-risk pregnancy with medical and social problems.
2. In developing countries, practice of early marriage while in developed countries, liberal society and early initiation of sexual activity are major contributing factors for teenage pregnancy.
3. Teenage pregnancy is associated with increased perinatal and maternal morbidity and mortality.
4. To prevent teenage pregnancies, sex education, easy availability of contraceptives and strict enforcement of law for minimum age of marriage are essential.

# Section 26 CARE OF ADOLESCENTS

**Section Editor** MKC Nair

## Chapter 26.1

### Promoting Health of Adolescents

*Harish K Pemde, Kamlesh Harish*

Youth (10–24 years) are nearly one-third of India's population and adolescents (10–19 years) constitute over one-fifth of India's population, i.e., 253 million. Social and economic fortunes of this country depend heavily on the health and well-being of this population. We need to leverage this demographic advantage to the benefits of country and its people. We need to invest in promotion of health of adolescents to achieve India's health goals including country targets for Millennium Development Goals. A large number of adolescents face many challenges in healthy development and transition to adult life. A variety of factors influence this transition and these include structural poverty, inadequate school education, negative social norms, early marriage and child bearing, and social discrimination. To respond to these factors we need to view adolescence in a life span perspective within dynamic sociological, cultural and economic realities. Thus, sectors like education, social justice, youth empowerment, sports and legislation need to join health sector in promoting health of adolescents. Pediatricians are placed uniquely in this system and they are expected to make a delicate balance between these sectors for promoting health of adolescent client(s). This chapter describes principles of promotion of health of adolescents, risk and protective factors, prevention interventions including life skills education, family life education (FLE), adolescent education program (AEP) and adolescent vaccination.

#### ELEMENTS OF HEALTHY DEVELOPMENT

Adolescence is a critical phase of the life of an individual as achievements and deficiencies during this phase determine, to a large extent, the future adult life. The achievements in social functioning, personal interactions and relationships, and health-care are interrelated and go together. Health is influenced by all these factors. What matters the most is healthy development of an adolescent. Following eight elements have been identified as fundamental requirements for healthy development of adolescents:

1. Participate as citizen, household member, worker, and as responsible member of society
2. Gain experience in decision making
3. Interact with peers, and acquire a sense of belonging
4. Reflect on self in relation with others, and to discover self by looking outward as well as inward
5. Discuss conflicting values and formulate one's own value system

6. Experiment with one's own identity, with relationship to other people, and with ideas to try out various roles without having to commit oneself irrevocably
7. Develop a feeling of accountability in the context of a relationship among equals
8. Cultivate a capacity to enjoy life.

The family, society, government and medical practitioners have to incorporate these elements of adolescent development for prevention and reduction of specific risk behaviors such as substance use, violence, physical inactivity, unhealthy diets, and unprotected sex and its consequences.

#### GENERAL HEALTH SCREENING

Adolescence is a stage of life where individuals remain more or less healthy. But, one should never forget that certain behaviors like smoking or inadequate physical exercise very often begin during this period which can lead to ill health during adult life. Some adolescents may carry some risk factors too which if left unattended may lead to diseases after few years when they become adults.

Screening adolescents for risk factors is important and is different than that in adult as in adults we look for existing diseases but in adolescents we look for risk factors in addition to existing conditions.

#### Identification of the Risk Factors in Adolescents

This is of paramount importance that we look for risk factors in adolescence in our clinical encounters with them. If one or more risk factors are found then *selective screening* by some blood tests can be added to clinical screening.

#### History

Include some questions related to unhealthy diet, physical activity or inactivity, smoking and substance (including tobacco and alcohol) use/misuse in your history. Ask for family history of diabetes, hypertension, coronary heart diseases, stroke or early (< 45 years of age) death or disability due to acquired heart disease or stroke in parents or grandparents. Some questions are given below:

1. Do you exercise or participate in outdoor games at least 5 days a week?
2. Do you watch television (TV)/computer or spend time on mobile for more than 2 hours per day?
3. Do you consume fruits, fruit juices or green leafy vegetables in your routine diet at least 5 days a week?
4. Does anybody in your family (parents, siblings, grandparents or maternal grandparents, etc.) have high blood pressure, diabetes or any heart disease?
5. Do you consume any kind of tobacco (bidi, cigarette, hookah, gutkha, etc.)?
6. Do you consume any kind of alcohol (beer, whiskey, vodka, etc.) or drugs (*ganja*, *charas*, etc.)?

### Physical Examination

Perform a thorough physical examination including assessment of weight and body mass index (BMI), blood pressure, and systemic examination. Find whether unhealthy diets, overweight or obesity, hypertension, inadequate physical activity or sedentary behaviors are present. Adolescents having one or more risk factors should be considered for targeted screening blood tests. Clear guidelines are not available for adolescents; however, whenever one or more risk factors are identified especially family history as above then in such cases screening for risk factors for atherosclerosis may be advised. Serum cholesterol and very low-density lipoprotein estimation along with fasting blood sugar level should be done. Some studies have used hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) as screening for diabetes. Other tests may be required depending on the history and examination of an individual adolescent.

### Adolescent Immunization

Vaccines and immunizations are regarded as one of the most successful public health promoting interventions. Vaccines have saved millions of lives and have resulted in elimination of polio after eradication of smallpox. Vaccines are traditionally used in young children and children up to 5 years of age are the focus of national immunization program. Adolescents do need vaccines for certain reasons. Certain vaccines (e.g., pertussis) do not provide long-term immunity and protection provided by childhood vaccines wane by adolescence. Reinforcement is needed for these diseases including diphtheria, pertussis and tetanus. Adolescents have increased risk of acquiring some new infections in this age. Human papillomavirus is one such infection. Some adolescents might have not developed adequate immunity against certain infections (e.g., hepatitis A or B, chicken pox, mumps and rubella). Adolescents may find themselves in certain new situations promoting some infectious diseases like living in dormitories promote spread of meningococcal infections and hence they need to be protected against these infections. Some adolescents might have missed one or other childhood vaccines or some vaccines were probably not available during their childhood. Catch-up vaccinations are needed for such adolescents. Some students travel abroad and this necessitates administration of certain vaccines as required by travelers. Indian Academy of Pediatrics (IAP) recommendations for vaccination of adolescents are given in **Table 1**.

### Other Vaccines

Pneumococcal conjugate vaccine or pneumococcal polysaccharide vaccine can be given in special circumstances like immune compromised status [human immunodeficiency virus (HIV), etc.], preparing for splenectomy or functional or anatomical asplenia, cochlear implant or cerebrospinal fluid leak. Single dose of either

vaccine is needed. Polysaccharide vaccine can be repeated every 3 years. *Haemophilus influenzae* type b (Hib) vaccine may also be given while preparing for splenectomy.

### LIFE SKILLS EDUCATION

In today's world information is readily available to all including adolescents. However, it becomes more important to learn how to manage this for adolescent whose brains are still maturing and they have a limited capacity to perceive consequences of current acts. The adolescents need skills to use the vast information in their benefit to remain healthy. Out of several life skills the following skills are more important—self-awareness, critical thinking, empathy, coping with stress and emotions, and interpersonal relationship and effective communication. Principles of life skills include the following:

- That, certain life skills are inherently present in all individuals and we need to recognize and to practice to polish them
- That, life skills can be learned and be mastered
- That, life skills are for self
- That, self-awareness is mother of all life skills so one should know his/her strengths and weaknesses
- That, life skills are interdependent, they assist each other, they often work in pairs and are used in combinations
- That, life skills can be used both positively and negatively
- That, in a similar situation different people would use different combinations of life skills
- That, one need to learn and practice them to acquire the life skills
- That, life skills are not the solution of any problem but one of the ways to tackle the problem
- That, life skills are better learned by *learning by doing*; mere talking about life skills is not beneficial.

### Core Life Skills

The World Health Organization (WHO) has identified ten core life skills for adolescents. These skills can be taught to adolescents using various methods like discussion, brainstorming, demonstration and guided practice, role plays, small group discussion, educational games and simulations, case studies, storytelling, debates, discussing use of life skills in a particular situation, using videos and short films, through art, music, and theatre, and decision mapping and problem trees. A combination of these methods can be used depending on available resources, expertise and time. These core life skills are:

- *Self-awareness* This is the ability to identify both our strengths and weaknesses or desires and dislikes. This is required for effective communication and useful interpersonal relationships. This skill is also needed for developing empathy towards others.

**Table 1** Indian Academy of Pediatrics recommendations for vaccination of adolescents

Tetanus toxoid	Booster at 10 and 16 years. It is better to use one dose of Tdap after 10 years and subsequently Td (at 16 years)
Rubella	As part of MMR vaccine or monovalent vaccine, one dose to girls at 12–13 years of age if not given earlier
MMR	One dose at 12–13 years of age if given earlier or two doses at 4–8 weeks interval
Hepatitis B	Three doses (0, 1 and 6 months) if not given earlier
Typhoid	One dose every 3 years (Vi vaccine)
Varicella	One dose up to 12–13 years and two doses (at 4–8 weeks interval) thereafter, if not given earlier
Hepatitis A	Two doses (0 and 6 months), if not given earlier (prior checking anti-HAV IgG may be cost effective)
HPV vaccine	In females up to 15 years 2 doses (0 and 6 months) and >15 years, three doses 0, 1 or 2 (depending on the vaccines) and 6 months

*Abbreviations:* MMR, measles-mumps-rubella; HAV, hepatitis A virus; IgG, immunoglobulin G; HPV, human papillomavirus.

- *Empathy* This is the ability to understand other's real situation or to put ourselves in others' shoes and try to learn the difficulties (or ease) of being in that particular situation. Empathy helps us in understanding people who may be in a very different situation than us or people who are in very different ethnic or cultural diversity. This skill leads us to help people who need help from others like those who have some physical or mental illness or subnormality.
- *Critical thinking* This is objective analysis of situations and information and certainly keeping bias aside. Often writing pros and cons of a situation or likely decision helps in objective analysis. Critical thinking helps us in choosing healthy and useful options and in avoiding harmful situations. It influences our attitude and behavior in dealing with media, peer pressure, and potentially harmful influences.
- *Creative thinking* This skill is related to exploring the alternatives and options available in a particular situation or at a particular point of time. Learning this process helps us in problem solving and decision making. This skill enables us to look beyond our personal experiences, to learn from experiences of others, and to learn responding favorably by adapting our actions. This skill also makes us flexible which is very important as all have to face different circumstances.
- *Problem solving* This is a very important skill and can be learned. One has to use several skills to effectively solve problems. Analysis of various aspects of a problem (or issue) and the available options is the first step in problem solving. Choosing an option based on one's abilities or situation at that point of time is the next step. Implementing the chosen option is the final step in problem solving. Unresolved problems often lead to stress which can in turn have somatic symptoms of anxiety.
- *Decision making* This is a very important skill as it is needed everyday! Adolescents have to make lots of decisions which have lifelong impacts. These decisions may include not choosing friends, opting for particular course or carrier, selecting food items, selecting lifestyle, etc.

Decision-making process includes defining problem(s), identifying consequences of unresolved problem(s), finding solutions and consequences of adopting a solution, choosing a solution and implementing the decision. Writing these steps on a paper helps a lot especially when one is learning the process of decision making. Later this becomes a habit.

- *Interpersonal relationship* We are social beings and interpersonal relationships are integral part of our life. We need to learn to retain useful relationships and to learn ending the relationship amicably if needed. This skill helps us to relate positively with people whom we respect, value and love. These may be our parents, siblings, relatives, teachers and friends. Respecting others as they are and selfless expectations build this skill.

This ability to make and keep friends is a big support for our social and mental well-being. At times, not having good friends or unhappy and failed relationships can prove to be major cause of adolescent anxiety, depression and suicide.

- *Effective communication* Communication is a two-way process and includes the ability to express and also the ability to listen and understand. This skill is expressing oneself verbally and nonverbally directly or indirectly through various means including through social media (Facebook, Twitter, YouTube, etc.) and public media like radio, TV. Mobile phone has become a mode of choice for communication through voice or video calls or short message service or video communications, and group calls. Nevertheless, direct face-to-face communication will never lose its charm and

importance. This skill let us express our opinions, desires, needs and also the fears. This also includes the ability to ask for help, for advice and for providing help in time of need.

- *Coping with emotions* This life skill is the ability to recognize emotions in ourselves as well as in others too. This also includes the ability to be aware that how extreme emotions can influence our attitude and behaviors.

Extreme emotions blunt our skill to appropriate behaviors and decision making. It is advised not to take big decisions [like accepting a job or resigning from it; accepting proposals (or not accepting) for long-term relationships, etc.] when one is under the influence of extreme emotions like happiness or sadness. It is also advised not write letters (or email) during extremes of emotions. Inability to handle appropriately the strong emotions like anger and sorrow can lead to inappropriate or antisocial behavior. This may lead to soar relationships and can also potentially affect mental and physical health.

- *Coping with stress* Stress is integral part of our life. Mild or healthy stress can improve our behavior and timely completion of assignments whereas inappropriate or excessive stress (inadequate handling of mild stress) can be harmful to our health. This skill includes recognizing the source and triggering factors for stress in our life, identifying its effects on our routines in daily life, and finding the ways of controlling the stress and its effects on us. When stress in unremovable then certain modifications in our lifestyle helps. Stress-busting methods include avoidance of factors leading to stress, meditation, yoga, laughter clubs, participating in group activities, physical exercises, etc.

## FAMILY LIFE EDUCATION

Family life education aims to improve quality of life of individuals in family by providing adequate age-appropriate information, imparting values, and providing skills to use the gained knowledge. In the context of adolescents, this term of FLE has a very useful purpose. There are some aspects of adolescent growth and development which need to be communicated correctly to adolescents. Such efforts have drawn criticism from various individuals and organizations mainly because of its nomenclature. Adolescence education has been termed as sex education or sexuality education and this caused problems in various parts of India. So, adolescence education has been termed FLE.

Family life education sessions are organized where a physician well versed with adolescence issues take these interactive sessions with adolescents, parents and teachers. The topics are chosen depending on the needs of adolescents of the area/school. Generally, session begins with growth and development during adolescence. Physiological growth including puberty and development of secondary sexual characteristics are described in simple age-appropriate terms in a scientific manner. The psychosocial issues are taken up in some details as this is the most frequent less understood subject. Personal hygiene issues are embedded in the discussion. Emphasis is given on keeping oneself clean during menstrual periods, hand washing and taking care of own body. Nutritional issues are discussed in detail including nutritional needs, undernutrition and overnutrition.

Depending upon the interest of the audience topics related to substance use, stress, anxiety and depression are taken up. Routine adolescence issues like friendships, relationships, and participation in group activities and sports are also taken up. Issues related to abuse including sexual abuse are very sensitive and should be raised. Adolescents are encouraged to raise voice against abuse and share it with parents, teachers or other significant adults in their life. Life skills are also discussed and attempts are made to



empower the adolescents to use these life skills. Emphasis is given on assertive skills, saying no, and empathy.

Family life education helps adolescents in preparing for responsible adult roles. It helps parents and teachers in understanding adolescent growth and development and behavior in a better way. It also prepares parents and teachers to negotiate better with adolescents on various contentious issues. FLE helps the whole family and improves quality of life of not only of adolescents but also of parents and others in family.

## PREVENTIVE INTERVENTIONS

For healthy adolescent development, we need to understand and apply certain preventive interventions. These are expected to reduce risk factors and to enhance the protective factors and thus make healthy development more probable. Preventive interventions may be universal, selective and indicated. *Universal preventive interventions* are applied to all population irrespective of existing risk, e.g., media interventions for prevention of use of tobacco; encouraging youth to have physically active life; and avoiding driving vehicles after drinking alcoholic beverages, etc. *Selective interventions* target groups with some enhanced risks, e.g., screening for hyperlipidemia in obese adolescents or in adolescents with family history of hyperlipidemia or coronary artery disease or stroke. *Intended interventions* are for those individuals who already have some features of a disorder or disease or problem behavior, e.g., working with adolescents under detention in juvenile care homes to prevent further involvement in antisocial activities.

Several studies have proven the efficacy of policy interventions like providing contraceptives without parental consent, counseling and sexuality education lead to reduction in adolescent pregnancy, and increasing minimum legal age for drinking reduces drinking and traffic accidents. Randomized controlled trials (RCTs) have found interventions like parent training programs, computer based interventions for parents and adolescents, and family therapy through various means including home visits very useful in reducing smoking, drinking alcohol, and less involvement in crimes. Similarly RCTs showing school based life skills training interventions on decision making, goal setting, anger management, communication, stress reduction, drugs misuse and its consequences reduced smoking and use of alcohol and drugs. Including emotional literacy, self-control, social competence, peer relations, and problem solving skills in school curriculum led to better positive development (e.g., psychological competencies and positive self-identity) and lower level of risk behaviors (e.g., substance misuse and delinquency). These interventions promote interpersonal skills, positive peer relationship and skills to face negative peer influences. These programs lead to development of individual skills and competencies.

These programs demonstrated that targeting reduction in risk factors and enhancement of protective factors lead to healthy developments. Some of the health promoting interventions during adolescence are described here.

## Role of Media

Media influences almost all aspects of adolescence including diet and eating disorders, physical activity and overweight/obesity, behaviors like sex, drugs, violence, suicide, school problem and even sleep. History of media use and media influence is very important and it should be elicited in all adolescent clinical encounters. Two questions should always be asked: How much time do you spend daily on all media (newspaper/magazines/novels, TV, mobile phone and computer)? Is there a TV set and a computer (or smart mobile phone) with access to internet in your bed room? Response to these questions will give a very fair idea of media use by adolescent.

Media has become ubiquitous and newer media in form of internet-enabled mobile phones and handheld computers are in common use. The challenge is to promote use of media in education and promotion of health and values and at the same time avoiding the negative influence and misuse of these interactive media.

Media certainly influences adolescent psychosocial development and behaviors including behaviors related to drugs, sex, food habits and physical activity patterns. Conventional and modern media can be judiciously used to promote various aspects of health promotion in adolescents. Some TV serials have been made based on various health education messages. In clinical practice too counseling process becomes more effective when it is supplemented by showing video or interactive computer program. Video-based programs and smartphone-based interactive apps/softwares are available for various health-related uses. One can find such programs which are useful in delivering intended health promoting messages.

The practitioners need to ask about media use and to advise parents about how to control media use (e.g., keeping TV sets in common place and avoiding TV/computer with internet in adolescent's room), how to use media wisely (e.g., watching TV or other media together and discussing about talking points like drug use, sex and physical activity, etc.) and how to implement media education programs. Even briefly discussing media can be very useful.

## ADOLESCENT EDUCATION PROGRAM IN INDIA

This program was developed by several government agencies and National Council of Education Research and Training coordinated the development of this program and its implementation in schools. The AEP considers adolescence as a positive phase of life, full of possibilities and potentials. It also recognizes that adolescents in India are very heterogeneous group with diversity in terms of urban/rural, caste, class, religion, cultural beliefs, etc.

This program aims to empower young people with accurate, age-appropriate and culturally relevant information, promote healthy attitudes and develop skills to enable them to respond to real life situations in positive and responsible ways.

It prescribes to make adolescents understand their growing body and physical and psychosocial needs learn core life skills in a scientific and culture sensitive manner, to understand and negotiate existing and constantly changing life realities. AEP also makes them aware about various issues related to substance abuse and HIV. AEP is implemented in various government run schools mainly the *Kendriya Vidyalayas*. It is prescribed to influence the entire school curriculum and ethos rather than being an isolated and stand-alone component. The AEP should be introduced in a process which is participatory, process oriented, nonjudgmental, nonprescriptive, nonstigmatizing and not fear inducing. It has inbuilt flexibility in contents and process so as to make it sensitive to the needs of adolescents of a particular school and according to local cultural sensitivities. It is strongly oriented towards transformational potential of education based on principles of social justice and equity.

A concept of *Teen Clubs* is also incorporated in AEP. This includes formation of group of adolescents which meet a prefixed frequency and where adolescents can express themselves freely. These clubs are run by adolescents themselves and are supported by school authorities. Certain issues relevant to member adolescents and society are identified and are taken up in the activities of Teen Clubs. This becomes an informal way of giving messages related to good health for avoiding risks like tobacco consumptions, unhealthy relationships, unprotected sex, etc. In new adolescent health program (*Rashtriya Kishor Swasthya Karyakram*), similar activities have been planned where Peer Educators will be identified and Peer Educators Meet will be organized at least once every 2-3 months. Relevant issues will be dealt with in these meetings. This is an extension of the concept of Teen Clubs.

**IN A NUTSHELL**

1. We need to invest in promotion of health of adolescents to achieve India's health goals including country targets for Millennium Development Goals.
2. General health screening should include identification of risk factors and immunization for the adolescents.
3. Adolescence should be viewed in a life span perspective within dynamic sociological, cultural and economic realities.
4. Sectors like education, social justice, youth empowerment, sports and legislation need to join health sector in promoting health of adolescents.
5. Adolescents need to learn and master the following life skills: self-awareness, critical thinking, empathy, coping with stress and emotions, and interpersonal relationship and effective communication.
6. Adolescent Education Program in India aims to empower young people with accurate, age-appropriate and culturally relevant information, promote healthy attitudes and develop skills to enable them to respond to real life situations in positive and responsible ways.

**MORE ON THIS TOPIC**

Adolescent Education Program. From: [http://mhrd.gov.in/adolescence\\_education](http://mhrd.gov.in/adolescence_education). Accessed November 5, 2014.

Bhave SY, Gupta PK, Jain TS, Nair MKC. Course Manual for Adolescent Health. Part-II: Indian Perspective. IAP International Training Programme on Adolescent Health, IAP Sub-chapter on Adolescent Health 2002.

Fisher MM, Alderman EM, Kreipe RE, Rosenfeld WD. Textbook of Adolescent Health Care. 3<sup>rd</sup> ed. Elk Grove Village, IL: American Academy of Pediatrics; 2011.

Resource Manuals: Handouts for Medical Officers under Rashtriya Kishore Swasthya Karyakram, Ministry of Health and Family Welfare, Government of India, 2014.

## Chapter 26.2

# Adolescent Counseling

Atul M Kanikar

Counseling psychology is one of the largest subfields in psychology that is centered on offering therapy and aiding clients who suffer from mental illness and psychological distress. Some amount of depression, thought distractions, anxiety, phobias, tendency to experiment and even blues (sadness) are normal for teenager. Intervention is needed only when these troubles augment to an extent of causing emotional disturbance and hindering the mental growth and potential of the individual. The purpose of intervention counseling is prevention, remediation, learning new skills (behavior modification), growth and personality development.

Various thinkers, theories, languages and cultures have given different meanings to the word *counseling*. However, all psychologists agree on the ultimate purpose or aim of counseling, i.e., to help individuals overcome future problems. The Oxford dictionary defines counseling as *the provision of professional assistance and guidance in resolving personal or psychological problems*.

Pérez (1965) gave a popular definition of counseling as an interactive process conjoining the counselee who needs assistance and the counselor who is trained and educated to offer this assistance. This interactive process needs to be initiated, facilitated and maintained by the counselor through feelings of spontaneity, warmth, tolerance, respect and sincerity. Carl Rogers in his book *"Counseling and Psychotherapy"*, has defined counseling as a process consisting of a definitely structured permissive relationship which allows the client to gain an understanding of self to a degree which enables the client to take positive steps in the light of his/her new orientation. Most of the definitions proposed by renowned scholars maintain that counseling is a process which involves bringing about sequential changes over a period of time, leading to a set goal. Over the years, due to exponential growth of various old and new stressors, the scope of counseling has evolved into multiple fields of human life and at all ages (**Fig. 1**).

For the benefit of practitioners, researchers and theoreticians, the Western Interstate Commission for Higher Education (WICHE) led by Parker (1974) has proposed a three dimensional model for the functions or roles of a counselor. This further elaborates and specifies the scope of counseling in the modern world (**Fig. 2**). Laypeople equate counseling to guidance or education or giving advice but the meaning differs in psychology (**Table 1**). Mental health professionals employ various theories of counseling in dealing with their clients with an approach that keeps the *best benefit of client's growth in focus* (eclectic approach). A detailed discussion is beyond the scope of this chapter.

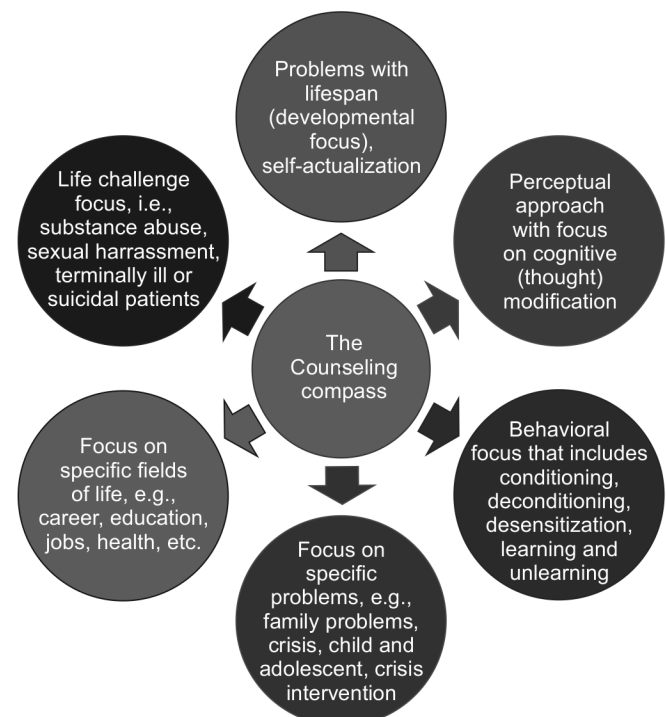
## SPECIAL ISSUES IN COUNSELING ADOLESCENTS

The obvious challenges in counseling adolescents are unwillingness towards therapy, unfriendly attitudes of the therapist, not accepting the problem leading to resistance, tendency to blame the caretakers, social stigma, poor compliance leading to drop outs, peer influence and a feeling of being victimized by parents or teachers. However, many adolescents are quite receptive to the process if the counselor exhibits a skillful and adolescent friendly interview. Further, because adolescence is a stressful period, adolescents need someone who will understand, respect and accept them unconditionally. The counselor must remember that adolescence is a period when basic life philosophies take shape and hence interventions during this period will have a long-term benefit.

## PRINCIPLES OF COUNSELING

Counseling is more of an art than science. Reading about the skills and techniques is easy, understanding them is easier but practicing them consistently is very difficult, if not impossible (**Fig. 3**). The core skills essential for the successful process of counseling are discussed below:

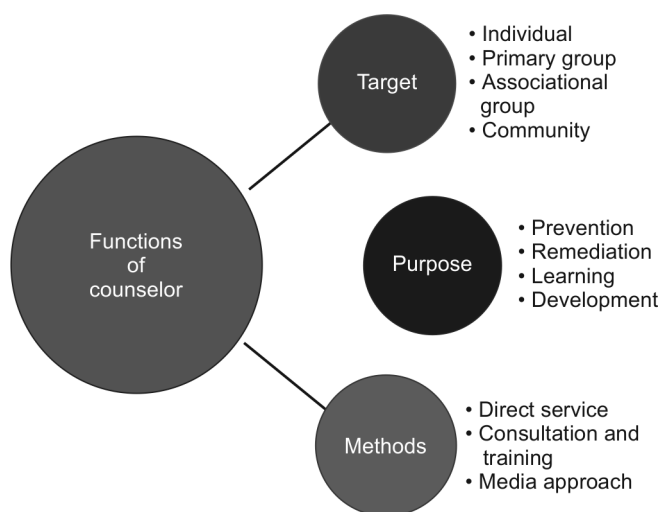
- **Active listening** (see also the subsection on parenting) Most adolescents want and need to be heard and understood, not advised or preached. The counselor must not make interpretations of the client's problems or offer any premature suggestions as to how to deal with or solve the issues presented.
- **Empathy** Empathy is a communicated understanding of the other person's intended emotional message (Martin, 1983). Empathy is also described as putting yourself in the client's shoes without removing your socks and looking at the situation from the client's perspective. Empathy requires listening to and understanding the feelings and perspective of the client and positive regard is an aspect of respect (Carl Rogers). Empathy is not imitation. Dymond (1949) mentions empathy as imaginative transposing of oneself into the thinking, feeling and acting of the client and so structuring the world as the client does.
- **Leading** Also called as *moving the client*. There are several ways to lead the client forward in a session. The counselor needs to be aware of how and in which direction, the discussion is proceeding. Working on the client's issues (and not the counselor's issues) should be prioritized. Responding to the client could be affective (focusing on feelings), cognitive (focusing on thoughts) or behavioral (focusing on the actions and behavior).
- **Self-disclosure** Counselor's self-disclosure is necessary as it relates to the therapeutic process. Too much self-disclosure hinders the counseling process, whereas not enough may inhibit the client from forming a bond with the counselor. For example, at the beginning of adolescent counseling



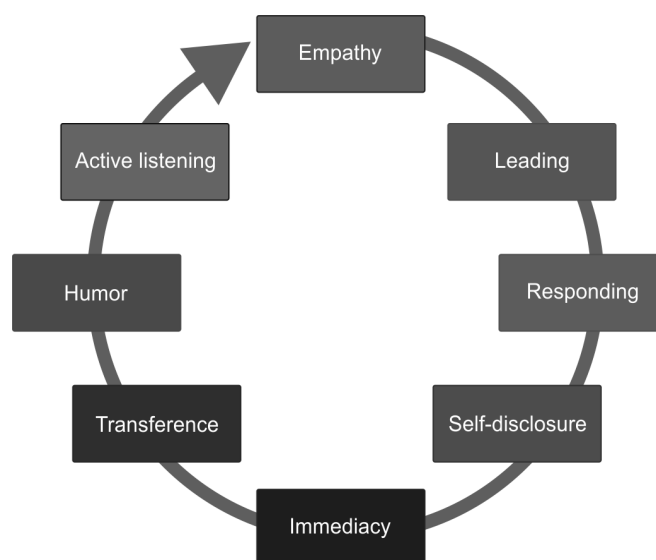
**Figure 1** The scope of counseling

session, the adolescent should know about the type of cases the counselor handles. This helps to break the ice, relieve the client's nervousness and develop rapport.

- *Using humor* Humor must be used with sensitivity and timing. It should never humiliate or ridicule the client.
- *Immediacy (closeness)* Although counseling can take place anywhere, it is better to have a quiet, comfortable and cozy room without any distractions to ensure effectiveness. All the nonverbal tools of communication (see later) should be employed. Proper distance should be maintained so that both the client and counselor feel safe yet secluded during the process.
- *Transference and countertransference* This is a process wherein the client feels and has perceptions of the therapist that rightly belong to other people in the client's life, either past or present. It is a process somewhat related to *projection*. Understanding transference reactions can help the client gain understanding of important aspects of their emotional life. Countertransference refers to the emotional and perceptual reactions the therapist



**Figure 2** Three dimensional model for counselor's role



**Figure 3** Principles and basic skills of counseling

has towards the client that rightly belong to other significant people in the therapist's life. Sigmund Freud has employed transference and countertransference during psychoanalysis and has mentioned it as an important tool. Transference is the client's projection of past or present feelings, attitudes or desires onto the counselor. It can be direct or indirect and will cause the client to react to the counselor as he/she would in the past or present relationship. Countertransference is the counselor's projected emotional reaction to or behavior towards the client. It can take on many forms, from a desire to please the client, to wanting to develop a social or sexual relationship with the client. When this happens, supervision or counseling for the counselor is necessary.

The counselor should be genuine, interested in helping people, having perceptual sensitivity, normally adjusted in his/her personal life and well trained with good emotional control. A lot of importance is given by Carl Rogers to the term *Acceptance*. He defined acceptance as *a warm regard for the client as a person*

**Table 1** Comparison between guidance, counseling and psychotherapy

	Guidance	Counseling	Psychotherapy
Aim	Making choices/decisions in future for otherwise normal individuals in <i>difficulties</i>	Focus on the present problem in a <i>disturbed</i> individual who is capable of changing into a "fully functioning individual"	Restructuring of personality with focus on the root causes/conflicts originating due to past experiences or mental trauma in mentally <i>disordered</i> individuals
Role of the director/professional	As guide, information provider, supervisor or assistant for short-term only (1–3 sessions)	Purely mental with communicator's and facilitator's role for dealing with the deranged triad of thinking, feeling and behaving. May take 1–15 sessions	Long-term intervention as trained and sometimes dominant authority in exploration and resolution of conflicts or unconscious processes that resulted in severe emotional disturbances in the client/counselee
Problem in the patient/client	Confusion in choices and unclear vocational ideas/concepts	Stress-related situation/crisis which could be due to intra/interpersonal disturbances	Severe mental health disorder (psychosis, severe anxiety, phobias, severe depression, etc.) usually needing pharmacotherapy/electroconvulsive therapy (ECT) in addition
Process	Quantitative analysis, problem-solving techniques and listing of possibilities using information pool	Qualitative as well as quantitative tools and specialty skills which may be cognitive, emotive or behavioral	Mostly qualitative, directive and interpretative due to severity of disorders. Psychoanalysis including dream therapy or cognitive behavior therapy in conjunction with ECT and drugs
Objectives	Educational/vocational/career improvement	Positive self-esteem, capacity building and autonomy for becoming a fully functional and responsible human	Empowerment for adjustment, functionality and improved mental health



of unconditional self-worth and of value under any condition, behavior or feeling. Acceptance implies helping an individual and not controlling him/her.

A counselor must avoid advice giving, lecturing, excessive questioning, storytelling, etc. which may take away the client's interest in the process.

## PROCESS AND STEPS OF COUNSELING (BOX 1)

### BOX 1 The counseling process

- Stage 1: Awareness of need for help
- Stage 2: Development of relationship
- Stage 3: Catharsis and clarification of problems
- Stage 4: Exploration of deeper feelings
- Stage 5: The integration process
- Stage 6: Orientation of time
- Stage 7: Developing awareness or insight
- Stage 8: Termination of contract or referral.

### Stage 1: Awareness of Need for Help

In the Indian context, this is the most crucial step especially in adolescent counseling due to lot of lethargy and wishful ignorance about the extent and severity of mental health problems amongst teenagers and the gatekeepers. Pediatricians, school authorities, media and the administrators have a role to play in creating awareness for the early detection of children and youth with mental health problems.

### Stage 2: Development of Relationship

This is a bridge between personalities of the client and the counselor. The emotionally warm relationship is characterized by mutual trust, liking and respect. The defense may manifest either as the helpless attitude of the client giving all the tasks to the counselor or evoking excessive sympathy and seeking undue attention from the counselor to avoid unpleasant tasks. By exhibiting such defense mechanisms, the adolescent may successfully ward off the counseling relationship especially when brought to counselor's office against will.

### Stage 3: Catharsis and Clarification of Problems

The ventilation of feelings is crucial and the client experiences a sense of relief due to release of tension. This process may further aid in clarification of the problems. However, sometimes the client may have a false sense of resolution of tension, leading to incomplete therapy.

### Stage 4: Exploration of Deeper Feelings

This is a step of *analysis* wherein, the counselor, without remaining satisfied with the superficial view of client's feelings (revealed in stage 3), tries to explore the deeper feelings and conflicting situations which the client was unable to bring to the surface initially.

### Stage 5: The Integration Process

During this stage which evolves smoothly out of stage 4, the client appreciates the feelings and underlying polarities objectively without undue fear, withdrawal or lack of concern. This being a very important step, the counselor has to apply all the necessary skills to help the client to see the feelings from a new perspective. During this process, the counselor can synthesize the needs and potential of the client to direct him/her towards appropriate goals.

### Stage 6: Orientation of Time

Adolescents are usually confused about their time perspective. The counselor helps the adolescent to understand that the present arises logically from the past and has significant influence on the future.

### Stage 7: Developing Awareness or Insight

During this process, the counselor helps the client to gain a new look at self and the world. During psychoanalysis, the counselor aims at providing insight into one's conflicts, repressions and inhibitions and once these are seen from a new perspective by the client, they cease to be painful. Albert Ellis in rational emotive behavior therapy mentions that rational understanding is a prelude for emotional insight.

### Stage 8: Termination of Contract or Referral

The counseling session should start and end on time. It is better to leave 5 minutes for summarizing, assigning homework and setting up next appointment. Termination is the end of the professional relationship with the client when the session goals have been met. A formal termination serves three functions:

1. Counseling is finished and it is time for the client to face his/her life challenges.
2. Changes taken place have generalized into the normal behavior of the client.
3. The client has matured and thinks and acts more effectively and independently.

If the counselor feels that the adolescent has achieved behavioral, cognitive or affective goals; termination is indicated. At times, the clients and counselor may not want the sessions of counseling to end. In many cases, this may be the result of grief or insecurity about losing the relationship. For the client, this is something to process, for the counselor; this is an issue for supervision. For all practical purposes, when pediatricians as counselors suspect a thought disorder, stage 3 substance abuse, severe depression with suicidal ideation, relapse of symptoms with increasing severity or unresponsiveness to their treatment; the adolescent must be referred as early as possible to higher center, clinical psychologist or psychiatrist for further management. In this process, it is the pediatrician's task to convince the parents about the need for referral. The pediatrician can act as a guide and reliable source who can keep the client's follow-ups. In certain instances, adolescents consider the pediatrician as an intermediary to inform their parents about sensitive issues, e.g., pregnancy or love affair and in such circumstances, the pediatrician must ensure the importance of such disclosure to the adolescent in trouble and inform the parents about the situation at hand in the presence of the teenager.

## PARENTING OF ADOLESCENTS

Parenting by definition means an art of bringing up children. It is a bilateral process where both parents and children learn from each other mostly through mistakes. This art is more learnt than inherited. Principal components of parenting are outlined in Table 2.

The factors affecting parenting are educational background of the parents, sociocultural backgrounds, economic well-being, influence of guests/visitors, size and type of the family, mother's profession and her status in the family, methods of family enjoyment and grandparent's role in raising children. Parenting comprises of various tasks, emotions, responsibilities, difficulties and rewards involved in the process of bringing up children (Table 3). It is an ongoing process and will remain so. However, the situation worsens as parent reach middle age when the children enter the stressful period of adolescence and the grandparents face aging disasters. The parents struggling with their careers thus get sandwiched between these two highly sensitive and at times stubborn generations. There is a significant difference in parenting a younger child and an adolescent. Even during adolescence, the early phase, i.e., between 10 years and 14 years, is described as the most difficult to handle by many parents due to unexpected

**Table 2** Principal components of parenting

<i>Important parental task</i>		<i>Methods</i>
1.	Responding to the needs	<ul style="list-style-type: none"> <li>• Caring for children</li> <li>• Spending time and energy for them</li> </ul>
2.	Establishing closeness	<ul style="list-style-type: none"> <li>• Hugging, giving a pat on the back</li> <li>• Holding hands</li> </ul>
3.	Helping to be independent	<ul style="list-style-type: none"> <li>• Giving household responsibilities</li> <li>• Avoiding unnecessary interference</li> <li>• Encouraging them to do tasks independently</li> </ul>
4.	Accepting the individuality	<ul style="list-style-type: none"> <li>• Respecting what a teenager has to say</li> <li>• Considering their point of view especially in family discussions</li> </ul>
5.	Nurturing self-esteem	<ul style="list-style-type: none"> <li>• Avoiding empty praise</li> <li>• Avoiding excessive criticism</li> <li>• Having realistic expectations of what he/she can do</li> </ul>
6.	Accepting our own limitations	<ul style="list-style-type: none"> <li>• Spending quality time together</li> <li>• Having realistic expectations from others</li> <li>• Understanding the ever changing outside world</li> <li>• Knowing our physical and economic constraints</li> </ul>

**Table 3** Parenting responsibilities

1.	Unconditional love	Being on teenager's side, no matter what Separating the teenager from the misdeed Not giving incentives Not bribing them for better results
2.	Keep a close vigil	Monitoring their daily routine Knowing their whereabouts and peer groups Encouraging supervised group activities Interaction with parents of peers Regular visits to the parent-teacher's meetings
3.	Discipline	Maximum use of nonverbal communication Explaining family rules clearly Using time-appropriate rewards Using punishment in proper dose Maintaining consistency and uniformity
4.	Introspection	Parents need to be good role models Accepting teenagers with all their limitations
5.	Crossing the boundaries	Thinking beyond our own family Forming parents' self-help groups Taking professional help if necessary

rebelliousness shown by the teenager. Parental anxiety is also at its peak resulting in strict disciplinary methods, extreme restrictions on the teenager, especially girls, since most parents are not prepared for the changes of menarche that occur usually in early adolescence. A teenager is also very clumsy (due to disproportionate growth) in this period giving rise to many clashes with the family. A teenager is treated simultaneously as a child and an adult, which adds to further confusion. Although technically, parents may not function as ideal counselors, it is the warm, nurturing and safe

home environment which shapes the core personality and yields the desired responsible behavior of an adolescent. If the parents are receptive, exhibit warmth and are good listeners, adolescents in trouble are likely to call them in difficulties. Thus, parents are the first and foremost counselors for children.

## COMMUNICATION SKILLS

Communication by definition is the sharing of feelings, thoughts and information with another person or people through speech, writing, gestures or symbols. Communication has three essential components:

1. Nonverbal
  2. Verbal
  3. Active listening.
- *Nonverbal communication* This major component alone is sufficient many times when dealing with teenagers. Major components are shown in **Table 4**.
  - *Verbal communication* The most traumatizing hurdle of the process of productive communication is improper use of words, initially by parents and then boomeranged by teenagers. However, the task may become easier if parents practice the tips outlined in **Table 5**.
  - *Active listening* Listening includes understanding the feelings and emotions and not merely the spoken words. The four important components of active listening are outlined in **Table 6**. Sometimes crowding of emotions disables the teenager or parents from expressing their feelings. Proper use of pauses and sensible silence helps the communication to become smoother, productive and purposeful. It also gives breathing space for restructuring words, putting thoughts sequentially and understanding exact flow of emotions. Silence can thus be called paradoxically, the most useful tool in interpersonal communication.

**Table 4** Components of nonverbal communication

1.	Eye contact	Ensures confidence, trust and avoids distractions
2.	Facial expressions	Smiling shows that you are interested and even enjoying the process
3.	Position of hands and legs	Open hands and flexed knees reflect openness whereas crossed arms and stretched legs reflect domination
4.	Body movement	Minimum movements avoid distractions
5.	Physical proximity	Holding hands, keeping hand on shoulder, fluffing hair, patting the back, etc. show love, affection and warmth. Touch melts away the fear, uncertainty and chaos in teenagers mind

**Table 5** Tips for good verbal communication

1. Proper use of language	Using the language which if used by the teenager will be tolerated. Parents should be respectful and civil their language
2. Instructions given clearly and assertively	Conveying expectations and values vividly. Making him/her repeat these if necessary without any scope for conflicts due to misunderstandings
3. The KISS principle	"Keep it short and sweet". Avoiding lectures which the teenager learns by heart if repeated often. Short and simple commands are nonirritating and bring out desired effect
4. Use teachable moments	Newspaper articles, advertisements, stories, etc. can be used to initiate discussions. Let the teenager speak out first. Understand what he/she knows, poke his/her eagerness to know further and imbibe values at the end
5. Using "I" statements	"I" statements help the parents convey their feelings and expectations to children. "You statements" sound accusatory and create a resentful feeling. For example, saying, "I am disappointed with the mess in your room and I will be happy to see it clean" is better than saying "you are lazy, careless, lousy, shameless and untidy and you intentionally make me suffer a lot"
6. Open-ended questions for timid teenagers	Questions that begin with how, why, can you describe are likely to get descriptive and elaborate answers, allowing the teenager to open up better. For example, instead of saying "Sex before marriage is bad, isn't it", ask "what do you think about sex before marriage?"
7. Proper use of humor	Not too much but just a dash of humor in a nonhurting way can be very helpful. For example, if the teenager is wearing a short skirt which you do not approve, try saying "Now mosquitoes can really have a great feast"
8. Written notes and chits	Smiling face, dislikes, list of tasks on hand, reminder notes, schedule for the day and sharing feelings and thoughts through letters or chits can help parents and teenagers to effectively and efficiently get their message across

**Table 6** Components of active listening

1. Paying attention	Facing the teenager, minimizing ambient distractions
2. Use of minimal responses	Responses like Ah-ha, Oh, Yes, OK, Right, I understand, Mmm, Hummm enhance continual talk
3. Use of reflection	Helping the teenager to express himself better by paraphrasing what he is saying or trying to say
4. Summarizing	Picking up the key points in the teenager's description of events and emotions and reflecting these back

Because the presenting problem in almost all the child and adolescent clients seen at counseling center is *scholastic*, the adolescent care pediatricians are slowly merging their expertise in the field of educational and career counseling.

## IMPROVING SCHOLASTIC PERFORMANCE

Scholastic achievement is an important developmental task of adolescence. Before one concludes the problem to be purely study related, pediatrician has to rule out certain other possibilities (**Box 2**). Once the cause for scholastic deterioration is sought, the action plan can be formulated with the involvement of parents, teachers and the adolescent client. Patience and consistency must be assured to obtain good results. The key to learning is motivation and it is the counselor's job to work on the adolescent's belief system which acts as a link between thinking and behavior. The task of learning can lead to distress or eustress as illustrated in **Flow chart 1**.

Poor study habits remain the most common cause of scholastic deterioration. The counselor along with a genuinely interested teacher can teach productive study skills to an adolescent. Various tests for assessing intelligence, personality, interests and aptitudes are available and may be employed to gain further knowledge about the etiology and prognosis of scholastic deterioration. Other tests to assess mental health problems like anxiety or depression may also be employed if indicated. Thus, the three areas of intervention can be grouped as given in **Figure 4**.

## Role of Teachers

A teacher counselor is more effective than a teacher and a counselor. A well-trained educational counselor has the following roles to play:

- The counseling role to deal with emotional, educational and vocational planning along with basic life skills education.

He/she is well trained to use various test devices for specific diagnosis of scholastic deterioration.

- The consulting role in collaboration with teachers, parents, educationists, school administrators and pediatricians towards understanding and managing and sometimes referring students. Thus, a well-trained teacher multitasks as an educator, facilitator, consultant and booster for bringing out the best in students.

Different forms of motivation are:

- *Intrinsic motivation* This is motivation from within. For example, I enjoy learning new things; I will be better equipped to obtain a degree.
- *Extrinsic motivation* This is motivation from external forces. For example, my parents will be disappointed if I do not succeed, I will get a pay rise if I finish my degree.
- *Positive motivation* This is nothing but a positive attitude towards the task. For example, I have the ability to get a degree and know that if I do the work, my future income will be much greater when I graduate.
- *Negative motivation* A negative attitude towards the task. For example, My parents will cut off my allowance if I do not study, my friends will think I am stupid if I fail, my family will be disappointed if I drop out.

The most effective forms of motivation are intrinsic and positive. The crowding of emotions, discomfort with self and others, inferiority complexes, etc. all add to the need a counselor in fixing goals. The counselor may categorize goals into the following groups.

**Long-term goals (3–5 years)** Outcomes which an adolescent would like to achieve after completing studies.

**Short-term goals** Outcomes which a student would like to achieve over the next year and up to the completion of the course. These are the stepping stones towards the long-term goals.

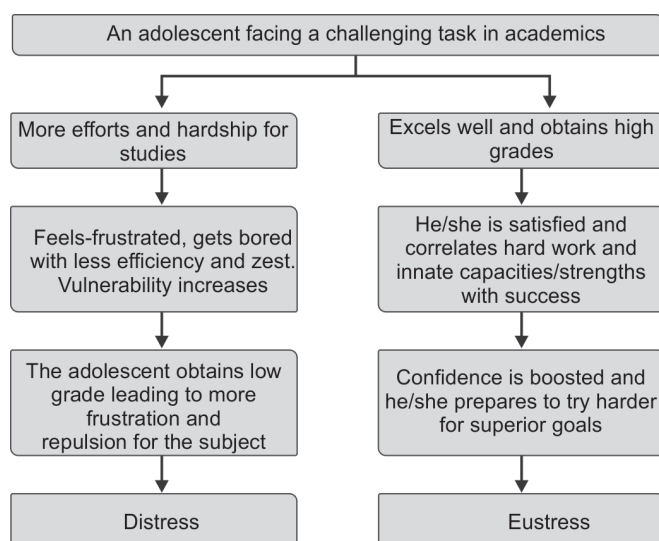
### Why Communication Fails?

- F Fear of the topic (e.g., sexuality or drugs) and being afraid of parental reactions due to authoritarian or very strict parenting style.
- A Assumption about sequence details of discussion due to bilateral prejudices and prototypes.
- I Interruptions. Not allowing the teenager to complete what he/she wants to say. Giving opinions/alternatives without being asked.
- L Labeling the teenager. Calling names and overgeneralization of past mistakes. Not separating the teenager or parents from their misdeeds.
- U Uncertainty about individual abilities to communicate, cooperation from other members and the outcome of dialogue leading to anxiety and chaos.
- R Resentment mainly due to past bitter experiences. Teenagers are touchy about certain issues, e.g., bad company or high-risk behaviors.
- E Ego for both parents and teenager without any empathy. Teenager may feel offended when parents still regard him/her as a child.

### BOX 2 Causes of scholastic deterioration

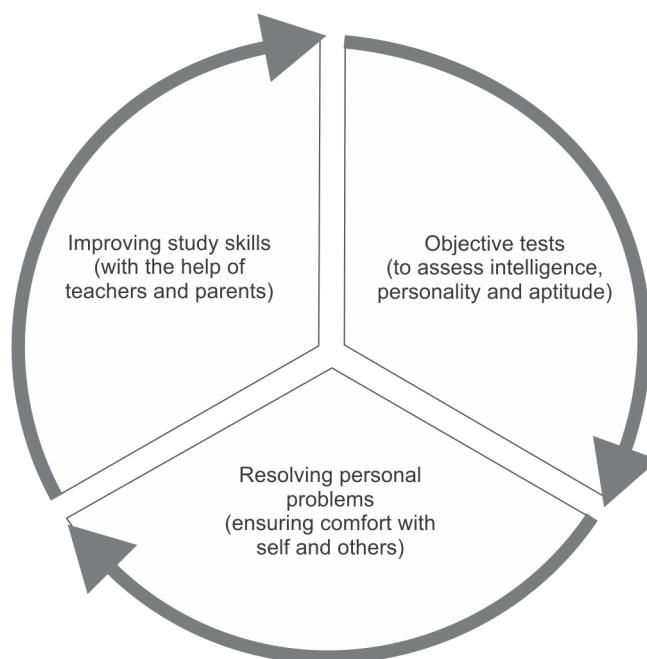
- Physical health-related problems (anemia, refractive error, migraine, infections, delayed puberty, body image concerns, etc.)
- Maladjustment with peers or school teachers (a sense of being victimized, new school)
- Study-related stresses (e.g., poor study skills, learning disabilities and dislike for specific subject, with procrastination tendencies)
- Peer influence (bad company compelling the adolescent to drift away from school work) and desire to identify with peers
- Easily available pocket money which boosts and nurtures various temptations of adolescence
- Broken heart (today's adolescents are maturing early and crushes or intimacies are blooming prematurely)
- Sexual urges and concerns (e.g., masturbation anxiety), drugs and sexual experimentations
- Cyber addictions and excessive, inadvertent and unsupervised use of electronic media including mobile phones
- Poor family communication and other issues at home (abuse, alcoholic parent, financial restraints, terminal illnesses, etc.)
- Depression, anxiety and other mental health disorders.

**Flow chart 1** Consequences of facing an academic challenge



**Mini-goals** Outcomes to achieve by the next day, week or term end. These are stepping stones towards short-term goals. Breaking up larger goals into smaller tasks helps provide a sense of achievement.

BF Skinner has given a very useful therapeutic tool of *homework assignments, practice sessions and shaping techniques*



**Figure 4** Areas of educational counseling

for improving study skills and behavior. AT Beck mentions the role of *solution focused techniques* in scholastic improvement.

The ideas that help sustain motivation are summarized in **Box 3**.

### Preventing Procrastination

The tendency to postpone tasks is almost universal. However, making this a lifestyle can adversely hinder the achievement

### BOX 3 Ideas for motivation

- Affirm and feel that *you can do it!*
- Identify your previous achievements
- Devise a list of all the reasons you originally decided to study. Ensure they are positive and display them in your home and workplace
- Identify your long-term, short-term and mini-goals. Write them down together with your objectives and display these in your home and work place. If you are struggling with motivation, place more emphasis on mini-goals as these tend to be easier to achieve and will help lead to the completion of larger goals
- Construct a realistic study plan and follow it
- Evaluate your time management and decide if you need to develop a more realistic plan to managing your time
- Ensure that your study environment is comfortable and conducive to effective study
- Seek support and encouragement from teachers, family, friends or professionals.



of goals. In reality, thinking about the difficulty in starting or continuing a task is worse than the task itself. Often getting started is the hardest part and so the best way to counter procrastination is to take the first step. Reasons for procrastination are depicted in **Figure 5**.

Fear of failure can be managed by focusing on goal setting and reframing thoughts more positively (I can do it and I should do it). Anxiety about the task can be managed by breaking the task into mini-goals. An adolescent may need assistance to understand the task properly. Time management is crucial for which the tasks will have to be prioritized. Making doable and realistic daily, weekly and semester plans will help. Management of personal issues may need professional intervention and a lot of support from family and peers. Concentration skills can be enhanced by ensuring minimum distractions. The most difficult tasks should be completed when alertness is more. Cooperation from family members and friends is mandatory to minimize distractions and disturbances. Praise for improved efforts boost confidence and self-esteem to make the task achievable and to maintain futuristic thinking.

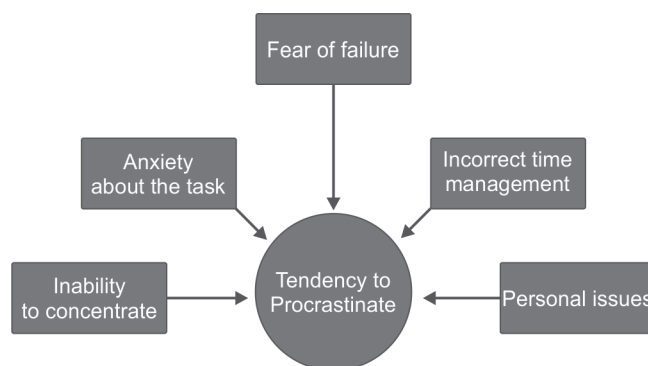
## CAREER GUIDANCE

In recent times, career guidance has evolved into a specialty and as primary caretakers of adolescents; pediatricians are expected to understand key ideas and referral services for guiding teenagers. Preference for a specific career starts in early adolescence but there is a tendency to shift. By late adolescence, a teenager has a fair idea about his/her career ambitions. The choices are made on subjective factors (values), occupational opportunities, societal acceptability and satisfaction level. Familial and cultural factors also add to these. Vocational development is influenced by physiological, psychological and environmental conditions.

The principal focus of vocational counseling is to plan career options and build motivation to achieve these options by working on specific scholastic tasks and learning new skills. Thus, it is an amalgamation of educational and career counseling. The counselor must have a nonauthoritarian approach and should help the client adopt more positive attitudes and be more realistic in assessing his/her assets and liabilities and gain insight about self. Many teenagers are apprehensive and anxious while making career choices. The counselor should be in a position to provide the latest and complete information about career choices with details of time, money and job opportunities involved. This step is done only after establishing rapport, relieving anxiety, helping him/her gain insights and self-assessment. Vocational guidance gives occupational information while vocational counseling helps the client to self-actualize and be a fully functioning individual in pursuit of his/her occupation. The career counselor has the following functions:

- Assessing the adolescent's abilities, interests, personality features and aptitude
- Facilitating development of specific skills needed for a particular career
- Managing negative emotions like anxiety, helplessness and hopelessness
- Discussing the means to get well adjusted to the new job
- Helping the adolescent in formatting resume and content.

Many times parents and peers govern the type of career that a teenager chooses. Further, in the Indian context, an adolescent girl prefers to give priority to marriage over career. Societal expectations, gender discrimination, poverty, unrealistic expectations of parents and family responsibilities compel many teenagers to choose a career which is easy to obtain and offers substantial financial resource for the family.



**Figure 5** The reasons for procrastination

## PREMARITAL COUNSELING

Family life of a couple many times differs from what it appears to the society. In India, most marriages are arranged and the partners are many times strangers to each other. A period of courtship is not sanctioned by society and the couple interacts with each other freely, few days after the wedlock. The main reason for strained marital relationships is the lack of understanding between partners and little or no empathy. Further, there is no effort to cultivate such empathy by either of the partners. The counselor helps them to gain better understanding of each other as the base for a happy marriage.

Premarital counseling for graduate college students is parallel to family life education in high schools. Today, an individual client is less likely to take help but the counselor can certainly offer group counseling sessions in educational institutions and youth gatherings. Sexual in competency is a very vital area causing conflicts between partners; however in India, nothing can be done in this regard before marriage. An orientation can be given to the couple about family life and various dimensions of human sexuality which are not just aimed at the physical act of sex, but can go up to love, belonging, security, self-esteem and mutual fulfillment. Respect for the opposite gender and willingness to have patience, commitment and active contribution has to be ensured. **Box 4** illustrates the various contributory factors for a happy marriage.

The principal aim of premarital counseling is to avail an opportunity to reevaluate and confirm that a particular partner is the right choice for evolving a stable, reliable and satisfactory married life. The counseling process aims at providing healthy attitudes, delivering scientific information including sexuality education and relieving various anxieties. A battery of laboratory tests recommended before marriage is blood group, enzyme-linked immunosorbent assays (ELISA) for human immunodeficiency virus (HIV), Venereal Disease Research Laboratory (VDRL), hemoglobin electrophoresis, ultrasound of the abdomen and pelvis (in girls). Special tests like metabolic screening and chromosomal studies may be indicated if there is a relevant reason.

### BOX 4 Factors contributing to happiness in marriage

- Freedom with responsibility
- Financial security
- Optimum socialization
- Religious and cultural values
- Interference by relatives
- Occupational choices
- Mutual trust and fulfillment
- Empathy and conflict resolution skills.

**IN A NUTSHELL**

1. Guidance, counseling and psychotherapy are different entities.
2. In spite of rising numbers of mental health problems in India, comprehensive adolescent mental health programs hardly exist and as primary health mentor of adolescents, pediatricians need to take this responsibility.
3. Adolescent counseling encompasses almost all the vital areas including scholastics, life skills, career guidance, premarital issues, mental health disorders, stress management and families. Counseling aims at prevention, remediation, learning and development.
4. Although parents often are not suitable counselors to their adolescents, they should inculcate effective communication skills to enhance adolescent's compliance and growth.
5. Pediatricians must learn the basic skills and steps of counseling with practical and supervised training before taking up the role of counselors.

**MORE ON THIS TOPIC**

- Corey G. Theory and Practice of Counseling and Psychotherapy. 9<sup>th</sup> ed. Cengage Learning.
- Galagali PM, Bhavé SY, Motivation. Bhavé's Textbook of Adolescent Medicine. New Delhi, India: Jaypee Brothers Medical Publications; 2010. pp. 897-906.
- Hurlock EB. Developmental Psychology. 7<sup>th</sup> ed. New York: McGraw Hill Companies; 1980.
- Kanikar A, Bhavé SY. Positive discipline. Bhavé's Textbook of Adolescent Medicine. New Delhi, India: Jaypee Brothers Medical Publishers; 2010. pp. 854-9.
- Mission Kishore Uday, Trainer's Manual on Comprehensive Adolescent Care. Indian Academy of Pediatrics; 2013.
- World Health Organization. Life skills education program in schools, Program on Mental Health. WHO/MNH/PSF/93.7A.Rev.2. Geneva: WHO; 1993.

## Chapter 26.3

# Adolescent Friendly Health Services

Rajesh Mehta, Neena Raina, Patanjali Dev Nayar

Among the people and institutions (government and nongovernment) that have the responsibility of ensuring healthy development of adolescents, health services have a specific role to play. Health-care providers have the direct responsibility of helping adolescents to prevent health problems and provide services, if and when they require, to diagnose and help address their health problems. They must help such adolescents to quickly restore their health by providing appropriate information, advice, counseling and treatment. In addition, health sector must proactively engage with parents, communities, teachers, nutrition programs and social sector for building their capacity to provide accurate and age-appropriate health information and life skills education to, and refer them to health services when needed.

It is a common observation that adolescent girls and boys do not utilize the existing health services even when suffering from one or more health problems or for health concerns. This happens because of several reasons. Many of the adolescents are not even aware of their health problems or that they can seek help from health services. They consider some of the health issues as personal and private (like concerns about penile erection, nocturnal ejaculation or masturbation in case of boys; and vaginal discharge or menstrual problems in case of girls) and do not want their parents to know about. They may be shy and embarrassed that they have such concerns and symptoms related to *private matters*. They are generally hesitant or even scared to contact health-care providers—*Oh, they ask too many questions and do not understand us*. Sometimes the health-care providers are perceived by adolescents to be unkind, judgmental or nonwelcoming. Many adolescents may not know where and how to access the health services; and may not have skills or experience to use health services on their own. They have no financial or social independence to seek health services even when they want to without anyone else coming to know. They do not want to be seen at health facilities from where adults and children also receive services. Sometimes the available services may be too distant.

Knowledge about such barriers for adolescents in utilizing existing health services must be used to design health services that are found welcoming and friendly by adolescent girls and boys.

## ADOLESCENT FRIENDLY ATTRIBUTES OF HEALTH SERVICES

Several attributes of friendly health services have been well identified in global literature. These are described below. Core characteristics are listed in **Box 1**.

### BOX 1 Core characteristics of adolescent friendly health services

- Services are to be readily accessible by adolescents
- Services are to be delivered in an equitable manner to all adolescents, regardless of gender, caste, age and marital status
- Services are to meet expectations and needs of adolescents
- Services are to cover the continuum of prevention and treatment
- Focus on quality of care.

## Provider Attributes

**Staff with appropriate skills** Health-care workers must be trained to acquire skills including clinical competence, interpersonal skills and a positive attitude towards adolescents.

**Privacy and confidentiality** Need for privacy and confidentiality rank very high among the adolescents. Privacy during consultation must be ensured so that no one can see or hear the interaction. Adolescents must feel confident that the health staff (doctor, nurse, counselor or support staff at the clinic) would not reveal their details to their parents or other persons.

**Adequate time for client-provider interaction** Adolescent-provider interactions need more time than adult clients since adolescents need time to open up and to reveal their *personal* concerns. Time is needed to uncover the actual problem, bring myths to the surface, to discuss and dispel them. Therefore, an adequate time should be allotted for each adolescent client.

## Health Facility Attributes

**Separate designated area** Earmarking a designated space for providing services only for adolescents is reassuring for some clients.

**Convenient timings** Adolescents may prefer timings after school hours to utilize health services so that they do not have to miss school or take permission from teachers.

**Safe and convenient location of the clinic** The clinic should be easily accessible and in safe surroundings.

**Privacy during consultation** This ideally requires separate room with doors for consultation and policies that support minimal interruptions and intrusions by other patients or health staff.

**Comfortable surroundings** In general, adolescents prefer a setting that is comfortable, bright, have posters or display material that relates to their taste and interests, and does not present an overly sanitized, hospital like environment.

## Clinic Policies

**Easy registration policies** The clinic registration should be quick and provide option for not having to reveal name or address. The person manning the counter should be friendly and respectful. Need to fill up lengthy forms puts many adolescents off.

**Consultation by drop-in as well as by appointment** Drop-in client's arrangement, which does not need prior appointments help to *seize the opportunity* whenever the adolescent clients show up. However, when requested an early appointment should be made available.

**No or short waiting times** Having to wait for a long time for the doctor dissuades adolescent clients. They have less patience in comparison to adults.

**Free of cost services or affordable fees** Most adolescents are financially dependent on their parents. If they need to pay clinic fees, they would be compelled to reveal the reason to parents for visiting clinic. This is likely to compromise their confidentiality.

**Publicity** The clinic should be widely publicized so that prospective adolescent clients are well informed about the existence of the clinic and services available for them. They must be reassured that they are welcome and will be served respectfully and confidentially.

**Onsite services** The clinic should provide most needed services at the clinic itself as *one-stop shopping* so that most needs are met at one place and they do not need to go from one place to another.

**Necessary referrals available** When essential, the adolescent clients should be referred to expert and clinic that are equally friendly.



Most of the literature on adolescent friendly service emphasizes that changing the attitudes of health-care providers and building their competencies for dealing with adolescent clients should be the first priority. In a large scale, population-based survey among youth in Kenya and Zimbabwe adolescents rated confidentiality, short waiting time, low cost, friendly staff and availability of most services at the same place (minimum need for referral) as most important characteristics for *friendliness*. In Mongolia, the strongest determinant to client satisfaction was reported to be related to acceptability of services; adequate physical environment at the health facility, receiving adequate information about the facility, and if the facility offered privacy.

## BUILDING CAPACITY OF HEALTH-CARE PROVIDERS

It is clear that the knowledge, attitude and skills of a health-care provider are the most critical factor for making adolescent health services friendly. Two main types of skills that are required include the clinical skills and more importantly, interpersonal skills of communication and counseling. The necessary knowledge and skills must be provided to health-care providers during preservice education and training programs (while they are still in medical colleges, nursing and paramedic schools as well as through in-service training while they are already in employment). The World Health Organization (WHO) and other agencies have developed appropriate training materials.

*WHO orientation program (Fig. 1)* is a package that prepares the health-care providers in dealing with adolescent clients differently through interactive participatory training. This builds their knowledge, attitudes and interpersonal communication and

counseling skills to design and provide adolescent friendly health services (AFHS).

*WHO adolescent job aid (Fig. 2)* is an excellent resource to build clinical skills to manage common adolescent conditions as well as reinforce skills in screening adolescents at risk and communicating with parents. It provides algorithms to address most common conditions with adolescent boys and girls present to health services to enable management of such conditions in a standard evidence-based manner. The Part-1 of the Job Aid provides guidelines for the following:

- The special contribution that you could make to health and development of your adolescent patients.
- Establishing rapport with your adolescent patients
- Taking a history of the presenting problem or concern
- Going beyond the presenting problem or concern—HEADSS screening
- Doing a physical examination
- Communicating the classification (possible diagnosis of the condition), explaining its implications, and discussing the management options
- Dealing with laws and policies that affect your work with your adolescent patients.

Part-2 of the Job Aid describes common adolescent health and development issues in algorithms and flow charts, communication tips, information to be given to adolescents and parents, and frequently asked questions. Part-3 of the Job Aid provides guidance on information to be provided to the adolescent and their parents on important topics including: healthy eating, physical activity, sexual activity, emotional well-being, the use of tobacco, alcohol and other substances, unintended injuries, and violence and abuse. Overall,

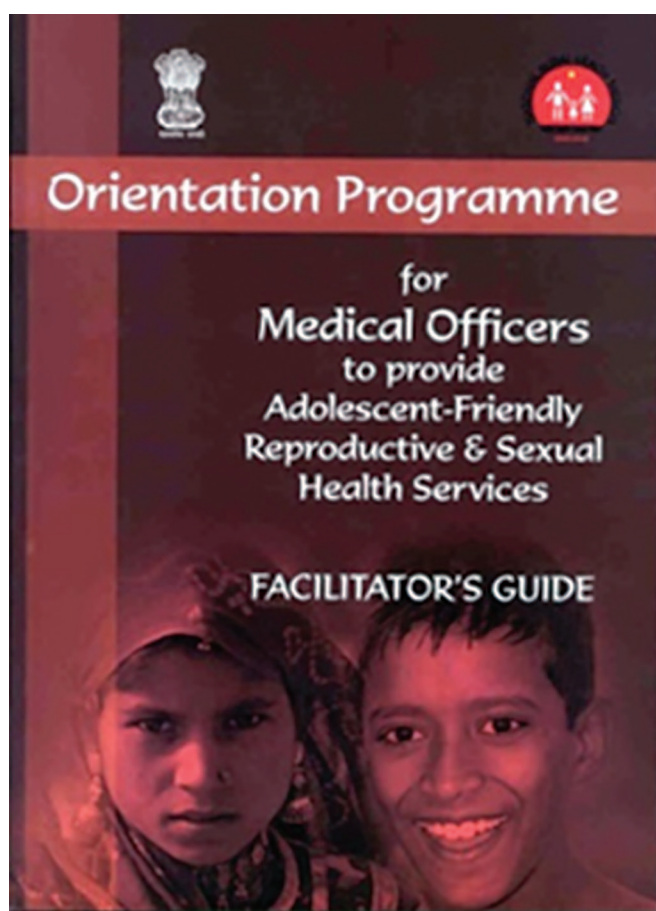


Figure 1 India adaptation of WHO orientation program

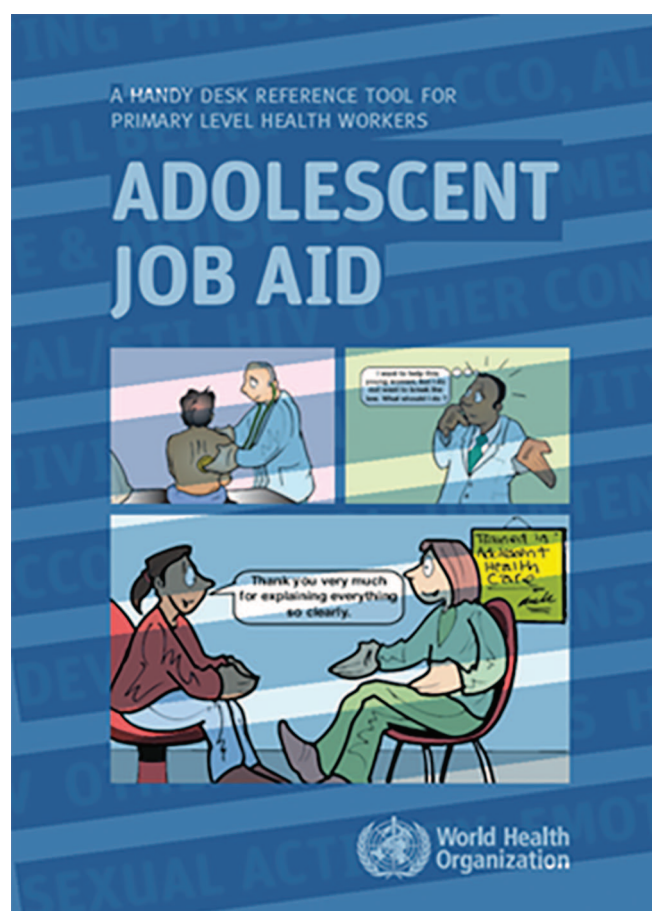


Figure 2 WHO adolescent job aid tool



Adolescent Job Aid is a ready desk reference to enable the trained health-care provider to provide evidence-based management to adolescents for common medical and health conditions.

## NATIONAL HEALTH PROGRAMS IN INDIA FOR ADOLESCENT HEALTH

### National Reproductive and Child Health Program: Adolescent Reproductive and Sexual Health Strategy (2006)

In India, during the National Reproductive and Child Health Program phase 1 (RCH-I), the health-care providers in the public health sector were oriented to the importance and special health needs of adolescents but there were no guidelines on the service provision. Progressing from there, the RCH-II program under the National Rural Health Mission (NRHM) positioned adolescent reproductive and sexual health (ARSH) strategy as one of the key technical strategies besides maternal health, family planning, child health and immunization to meet the overall RCH-II goals of reducing infant mortality rate to 30/1,000 live births by 2012; reducing maternal mortality ratio to 100/100,000 live births by 2012; and reducing total fertility rate to 2.1 by 2012 through: reducing teenage pregnancies, meeting unmet contraceptive needs, reducing number of teenage maternal deaths, reducing incidence of sexually transmitted infections (STIs) and reducing proportion of human immunodeficiency virus (HIV) positive in 10–19 years age group.

The RCH-II ARSH strategy focuses on reorganizing the existing public health system in order to meet the service needs of adolescents. It committed to provide AFHS at the existing health facilities and through outreach activities including preventive, promotive, curative and counseling services. The strategy also emphasizes creation of enabling and adolescent friendly environment in the community for improving accessibility to services and create demand for AFHS. Additional steps are listed below:

- Incorporate adolescent issues in all RCH training programs and all RCH materials developed for behavior change communication
- Identify appropriate indicators related to adolescent health services within the existing health management information system (HMIS) to monitor AFHS
- Intersectoral linkages with National AIDS Control Program and NRHM interventions.

### Implementation of RCH-II ARSH Strategy

All the states in India were supported by the national government to implement the ARSH strategy in selected districts by using the Implementation Guide to implement the seven national standards. Trainings of medical officers were carried out using the national adolescent health training package and rooms identified for running fixed time designated clinics in the health facilities. States used several innovative models like peer-led approaches, community-based and school-based approaches. Thousands of adolescent health clinics were operationalized in existing health facilities with variable utilization of services. Members of professional associations of pediatricians, obstetric-gynecologists and preventive medicine were trained in adolescent health to develop a national pool of trainers for training government and private sector health-care providers. Based on the National Standards for AFHS, the national body of obstetrics-gynecology, the Federation of Obstetric and Gynaecological Societies of India (FOGSI) developed their guidelines for establishing adolescent friendly clinics in the existing practice of their members.

## National Adolescent Health Program under RMNCH+A Strategy (2014)

Based on the experience of implementing RCH-II ARSH strategy in the country and realizing the importance to address the health needs of adolescents beyond sexual and reproductive health the Ministry of Health and Family Welfare has developed a comprehensive adolescent health strategy. The renewed strategy articulates the principles of participation, rights, inclusion, gender equity, and strategic partnerships that would guide its implementation. The vision is stated as: All adolescents in India are able to realize their full potential by making informed and responsible decisions related to their health and well-being.

The strategy identifies seven critical components: (1) coverage, (2) content, (3) communities, (4) clinics (health facilities), (5) counseling, (6) communication and (7) convergence. The interventions and approaches are expected to work towards building protective factors at four major levels: (1) individual, (2) family, (3) school and (4) community. Such protective factors would help adolescents and young people develop *resiliency* to resist negative behaviors and adopt healthy behaviors.

Alongside, the health system would strengthen effective communication in the community, capacity building of service providers and monitoring and evaluation systems. The implementation of such an approach would require a concerted effort by all stakeholder ministries and other institutions including health, education, women and child development, labor, social justice, as well as adolescents, their families and communities.

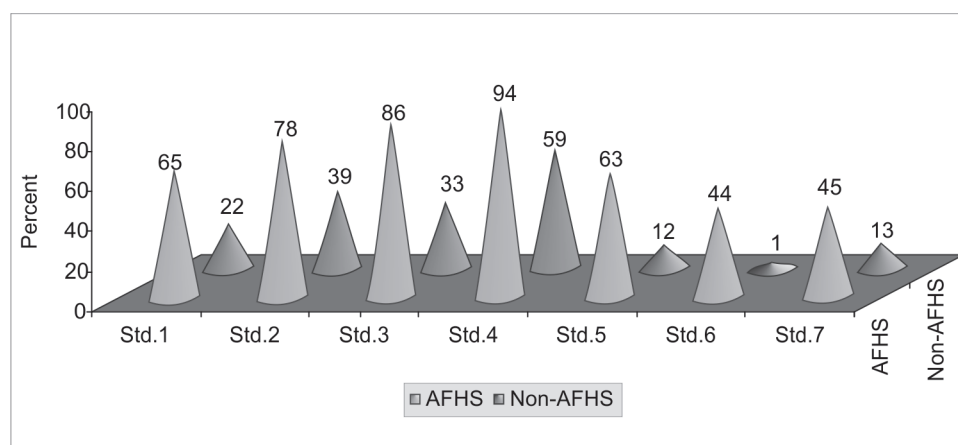
## MAINTAINING QUALITY OF AFHS

As described above, certain characteristics of health services are critical for attracting the adolescents to seek services and retain them as clients after the first visit. An ongoing monitoring of quality of AFHS would ensure that such adolescent friendly characteristics are actually practiced at the health service delivery points. National standards articulated by Ministry of Health enable assessment of quality of services being delivered from the health facilities. Such standards can be adopted by the private clinic as well. The main purposes of quality improvement process include:

- Measuring the level of performance of health facilities in implementing the AFHS based on the predesigned standards
- Helps identify the gaps and deficiencies of the health-care system and services provided
- Helps identify corrective measures to further improve the quality of AFHS
- Helps strengthen health information system and generating useful information on AFHS.

The World Health Organization has supported assessment of quality of AFHS in India in identified facilities by using a set of assessment tools including observation of health facilities, interview of provider and clients. For example, in Haryana (Fig. 3) and Maharashtra, government health facilities implementing AFHS were found to have higher compliance to the national standards as compared to control health facilities that were not implementing AFHS. Supervisory check lists have also been tried to measure and monitor the quality in an ongoing manner within the system leading to continuous improvement of quality based on the findings of each supervisory visit.

*Disclaimer* The authors are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this Chapter and they do not necessarily represent the decisions, policy or views of the World Health Organization.



**Figure 3** AFHS standards: comparison with control sites in Haryana primary health center  
*Abbreviation:* AFHS, adolescent friendly health services

### IN A NUTSHELL

1. Adolescents are a large proportion of population and are a crucial resource for national development.
2. Contrary to prevalent view that they are healthy, adolescents face specific public health problems that can be prevented and need to be treated urgently.
3. To keep them healthy they need AFHS that they find welcoming and easily accessible.
4. It is important to maintain good quality of the AFHS to sustain utilization by adolescents.

### MORE ON THIS TOPIC

World Health Organization. Adolescent Job Aid: A handy desk reference tool for primary level health workers. Geneva: WHO; 2010.

World Health Organization. Adolescent friendly health services: an agenda for change. WHO 2002. From: [http://www.who.int/maternal\\_child\\_adolescent/documents/fch\\_cah\\_02\\_14/en/](http://www.who.int/maternal_child_adolescent/documents/fch_cah_02_14/en/). Accessed November 5, 2014.

World Health Organization. Growing in confidence: lessons from eight countries in successful scaling up of adolescent health and development programming. WHO 2002. From: [http://www.who.int/maternal\\_child\\_adolescent/documents/fch\\_cah\\_02\\_13/en/](http://www.who.int/maternal_child_adolescent/documents/fch_cah_02_13/en/). Accessed November 5, 2014.

World Health Organization. Making health services adolescent friendly: developing national quality standards for adolescent friendly health services. WHO 2012. From: [http://www.who.int/maternal\\_child\\_adolescent/documents/adolescent\\_friendly\\_services/en/](http://www.who.int/maternal_child_adolescent/documents/adolescent_friendly_services/en/). Accessed November 5, 2014.

World Health Organization. Orientation programme on adolescent health for health-care providers. WHO 2006. From: [http://www.who.int/maternal\\_child\\_adolescent/documents/9241591269/en/](http://www.who.int/maternal_child_adolescent/documents/9241591269/en/). Accessed November 5, 2014.

World Health Organization. Programming for Adolescent Health and Development. Geneva: WHO; 1999.

WHO. Strengthening the health sector response to adolescent health and development. WHO 2010. From: [http://www.who.int/maternal\\_child\\_adolescent/documents/cah\\_adh\\_flyer\\_2010/en/](http://www.who.int/maternal_child_adolescent/documents/cah_adh_flyer_2010/en/). Accessed November 5, 2014.